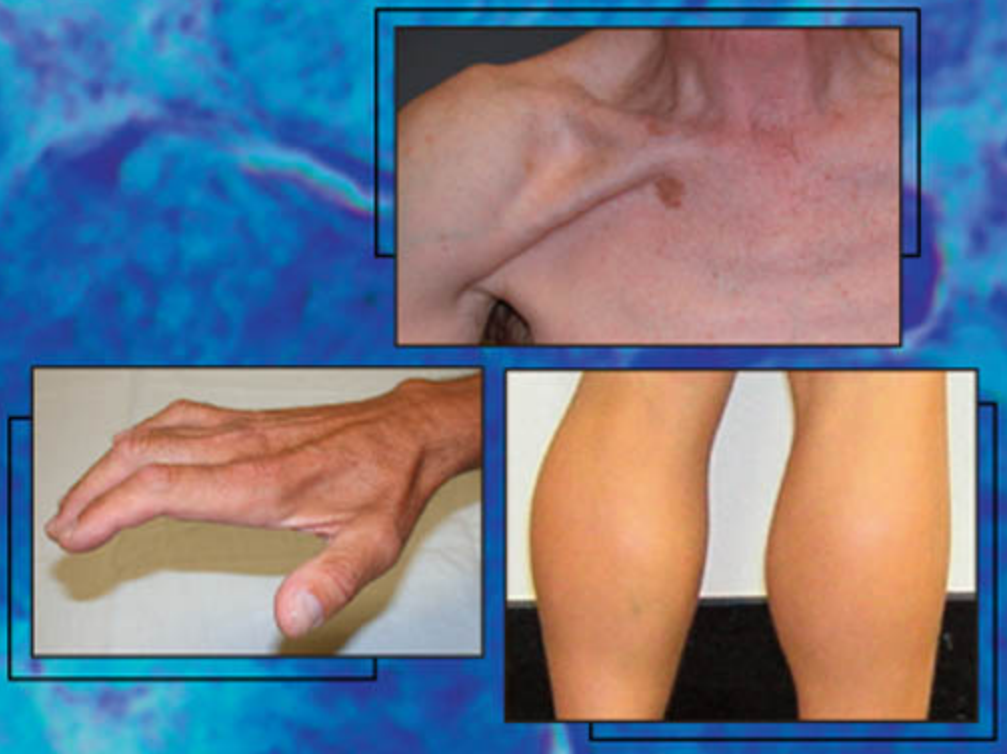

Neuromuscular Disorders

ANTHONY A. AMATO • JAMES A. RUSSELL

Neuromuscular Disorders

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Neuromuscular Disorders

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I want to express my gratitude to my mentors and colleagues who have taught me the art of neuromuscular medicine and continue to do so. I would be remiss if I did not thank all the patients whom I have had the honor to learn from all these years. Most of all I would like to thank and dedicate this book to my wife, Mary, and my children, Joseph, Erin, Michael, and Katie, for their unconditional love and support over the years.

— Anthony A. Amato, MD —

For me, neuromuscular medicine has been as much an avocation as a vocation. I owe much to many in my professional life, to my many friends in the neuromuscular community, but in particular to H. Royden Jones, Jr., Paul T. Gross, and David Chad who have cultivated and mentored my neuromuscular interests. But most of all, I am indebted to my wife, Michele, and our sons, Andy and Peter, for their love and for years of tolerance for the time spent in undertakings such as this.

— James A. Russell, DO —

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FOREWORD

This new book provides a scholarly, comprehensive, and practical account of neuromuscular disorders that will appeal to specialists and trainees in neuromuscular medicine as well as to general neurologists and other physicians. Neuromuscular diseases are among the more common neurological disorders, and gratifying advances in our understanding of them have occurred in recent years. In particular, advances in genetics, immunology, epidemiology, neurophysiology, imaging, histopathology, and pharmacology have led to new approaches to diagnosis and treatment. There is now a greater understanding, for example, of the molecular biology of many neuromuscular diseases, the basis of various channelopathies, and the response cascades that together lead to inflammatory reactions. Many disorders once considered distinct entities are now recognized to be heterogeneous, with different subgroups having different prognostic implications and requiring different therapeutic strategies. Dr. Anthony Amato and Dr. James Russell have provided a detailed, thoughtful, and critical appraisal of developments in these fields while, at the same time, defining the limits of our knowledge and providing a thorough clinical account of the various neuromuscular disorders. They describe an approach to diagnosis, management, treatment, and prognostication that is practical but is based on their extensive clinical experience and wide knowledge of the literature.

This volume is unusual in that it is written in its entirety by these two eminent and respected physicians, both of whom are recognized authorities in the field and have well-deserved reputations as clinicians, scholars, and teachers. Because they are the sole authors of this book, the text flows well, with a uniformity of style that is pleasing, and the various chapters and sections of the book are integrated seamlessly, without excessive overlap between chapters. Scientific advances are placed into their clinical context and described in a manner that will enable clinicians to grasp more easily the significance of these advances.

I have little doubt that this book will become an indispensable resource for clinicians involved in the diagnosis and management of patients with neuromuscular diseases, as well as for scientists working on the nature and pathogenesis of these disorders. It is a much-needed and welcome addition to the neurological literature and will rapidly gain acceptance as a standard work of reference. I welcome its publication and congratulate Dr. Amato and Dr. Russell for producing such an outstanding volume.

Michael J. Aminoff, MD, DSc, FRCP

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PREFACE

The field of *neuromuscular medicine* is a now a subspecialty recognized by the Accreditation Council for Graduate Medical Education. Our knowledge regarding the various neuromuscular disorders, their pathogenic bases, and treatment options has rapidly expanded over the past decade, thus making the practice more challenging. There are several outstanding reference textbooks devoted to myology, neuropathies, electrodiagnostic medicine, or neuromuscular pathology and this book is not meant to replace any one of these classic texts. However, our experience as mentors to medical students, residents, and fellows in the neuromuscular clinic and hospital wards as well as referrals from practicing clinicians suggested to us the need for a neuromuscular textbook that was all inclusive and practical in regards to how to approach and treat individuals with the broad range of neuromuscular diseases. There is no standard approach or treatment for most of these disorders and experienced clinicians may disagree with our recommendations. Nevertheless, we hope this book lays the groundwork for how to evaluate and manage patients with all types of neuromuscular disease.

Anthony A. Amato, MD

James A. Russell, DO

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SECTION I

APPROACH TO PATIENTS WITH NEUROMUSCULAR DISEASE

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CHAPTER 1

Approach to the Patient with Neuromuscular Disease

Despite technological advances, the neurologic evaluation of patients remains first and foremost a bedside exercise. Accurate diagnosis requires consideration of individual patient and disease differences. Confounding variables that are part of the human experience may be missed or overemphasized by testing algorithms. This textbook will repeatedly emphasize the strongly felt philosophy of its authors, i.e., patient assessment strategies are most effective when based on clinical hypotheses. These hypotheses should be formulated based on the principles of neurological localization, the chronological course of symptom development, and application of risk factor analysis. Ideally, the tests described in the subsequent two chapters and throughout the text would be ordered with the primary intent of resolving a clinically established differential diagnosis or, if possible, in an attempt to prove a working diagnosis. As all tests are potentially fallible, the credibility of their results diminishes when they are used as screening procedures. A laboratory abnormality, occurring without the context of clinical correlation, fails to establish the desired confidence in a cause and effect relationship with the patient's complaint(s). Metaphorically, laboratory tests are analogous to a carpenter's tools. They are of great value when placed in the hands of a skillful artisan, but are potentially damaging if used injudiciously.

In this textbook, a neuromuscular disorder will refer to any condition that affects the structure and/or function of any component of the peripheral motor or sensory nerves. The differential diagnosis of disorders of the neuromuscular system neuromuscular varies to a certain extent with age. Infants, children, and adolescents share both similarities and differences in their differential diagnosis with their adult counterparts (Tables 1–1 to 1–3).[1,2] The applied diagnostic principles are similar. Specifically, this text will address disorders that affect the peripheral motor system between anterior horn and the muscles they innervate, including ventral root, plexus, peripheral nerve, and neuromuscular junction. The neuromuscular system will also be considered to include the sensory nerves at or distal to the dorsal root ganglion. In essence, with the exception of disorders affecting small, poorly, or unmyelinated nerve fibers such as the small fiber or pure autonomic neuropathies, a neuromuscular disorder may alternatively be defined as one that can be potentially detected by electromyography and nerve conduction studies. Disorders affecting the peripheral autonomic system or cranial nerves will be discussed only as necessary to better understand diseases affecting their somatic and spinal counterparts.

There is another key point in history taking that will be repeatedly emphasized in this text. Many patients with heritable disorders will not recognize the hereditary nature of their disease. This may be due to a recessive inheritance pattern, spontaneous mutation, false paternity, or incomplete or delayed penetrance. Frequently, it is due to a lack of familiarity with the medical issues of other family members. In suspected hereditary disease, acquisition of family history, particularly if done in a cursory fashion, may be insufficient. Examination of other family members, even if only briefly, is strongly recommended.

In the pediatric population, parents must be questioned with great care and sensitivity. The heightened concern of the parents may cause them to unconsciously omit important details of the patient's status or assume a benign attribution as the cause of the symptom. Parents may also bring a considerable amount of guilt to the examination, which may limit their willingness to share information. The parents' fears and associated guilt should be dealt with and not ignored. If necessary, professional counseling should be offered in addition to treating the patient. Often, when a child is ill, the entire family is affected, which can in turn have profound repercussions on more than just the patient from both a physical and a psychological standpoint.

▶ STRATEGIC APPROACH

The nature of neurologic practice is such that many patients evaluated by a neurologist will have complaints that are attributable neither to a specific neuromuscular disorder nor to the nervous system in general. The strategies outlined in this chapter are based on the general principle that diagnostic accuracy is enhanced by correlation of the patient's signs and symptoms, with knowledge of the natural history and behavior of the

▶ TABLE 1–1. DIAGNOSIS OF THE FLOPPY INFANT

Central nervous system disorders (most common etiology)

Anterior horn cell
- Spinal muscular atrophy type 1 and 2

Peripheral neuropathy
- Congenital hypomyelinating/amyelinating neuropathy
- CMT III (Dejerine–Sottas)
- CMT I and CMT II—rare
- Giant axonal neuropathy

Neuromuscular junction
- Infantile botulism
- Transient neonatal myasthenia gravis
- Congenital myasthenic syndromes

Myopathy
- Congenital myopathies (all of them can present in infancy)
- Muscular dystrophies
  - Congenital muscular dystrophies
  - Dystrophinopathy/sarcoglycanopathy (rare)
  - Congenital myotonic dystrophy
- Metabolic myopathies
  - Glycogen storage defects
    - Acid maltase deficiency
    - Debrancher deficiency
    - Branching enzyme deficiency
    - Myophosphorylase deficiency (rare)
  - Disorders of lipid metabolism
    - Carnitine deficiency
    - Fatty acid-acyl-CoA dehydrogenase deficiencies
- Mitochondrial myopathies
  - Benign and fatal infantile myopathy
  - Leigh's syndrome
- Endocrine myopathies (e.g., hypothyroidism)

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ever-expanding menu of neuromuscular diseases. In our opinion, adherence to these principles will improve the diagnostic accuracy of both the neurologist and the referring physician. This chapter will attempt to focus on information that is important to elicit, and also on an organizational framework to interpret it accurately.

▶ DOES THE PATIENT HAVE A NEUROMUSCULAR PROBLEM?

HISTORY TAKING

Neuromuscular diseases manifest themselves primarily through some combination of symptoms attributable to the dysfunction of lower motor and sensory nerves. Motor symptoms are typically expressed in a "negative" fashion (weakness or atrophy). Occasionally, "positive"

▶ TABLE 1–2. WEAKNESS PRESENTING IN CHILDHOOD OR EARLY ADULTHOOD

Anterior horn cell
- Spinal muscular atrophy type 3
- Poliomyelitis
- Amyotrophic lateral sclerosis

Peripheral neuropathy
- Acute or chronic inflammatory demyelinating polyneuropathy
- Hereditary neuropathies

Neuromuscular junction
- Botulism
- Myasthenia gravis
- Congenital myasthenic syndromes
- Lambert–Eaton syndrome

Myopathy
- Congenital myopathies
  - Central core
  - Multicore
  - Centronuclear
  - Nemaline
- Muscular dystrophies
  - Dystrophinopathy (Duchenne or Becker)
  - Limb girdle muscular dystrophies
  - Myofibrillar myopathy
  - Myotonic dystrophy
  - Other dystrophies (e.g., FSHD and EDMD)
- Metabolic myopathies
  - Glycogen storage defects
    - Acid maltase deficiency
    - Debrancher and branching enzyme deficiency
  - Disorders of lipid metabolism
    - Carnitine deficiency
    - Fatty acid-acyl-CoA dehydrogenase deficiencies
- Mitochondrial myopathies
- Periodic paralysis
- Electrolyte imbalance
  - Hyperkalemia
  - Hypokalemia
  - Hypophosphatemia
  - Hypercalcemia
- Endocrine myopathies
- Toxic myopathies
- Inflammatory myopathies
  - Dermatomyositis
  - Polymyositis (after the age of 20 years)
  - Infectious myositis

FSHD, facioscapulohumeral muscular dystrophy; EDMD, Emery–Dreifuss muscular dystrophy.
Modified with permission from Dumitru D, Amato AA. Introduction to myopathies and muscle tissue's reaction to injury. In Dumitru D, Amato AA, Swartz MJ (eds). Electrodiagnostic Medicine, 2nd edn. Philadelphia: Hanley & Belfus, 2002, pp. 1230, Fig. 26–2.

symptoms referable to overactivity (e.g., muscle cramps, stiffness, fasciculations, or other abnormal muscle movements) may dominate the clinical presentation. Sensory symptoms may also manifest in either a positive (e.g.,

▶ TABLE 1–3. WEAKNESS PRESENTING IN MIDDLE TO LATE ADULTHOOD

Anterior horn cell
- Spinal muscular atrophy type 3
- Kennedy's disease
- Poliomyelitis
- Amyotrophic lateral sclerosis

Peripheral neuropathy
- Hereditary neuropathies
- Acute or chronic inflammatory demyelinating polyneuropathy
- Drug-induced or toxic neuropathies
- Diabetic neuropathy
- Amyloid
- Vasculitis

Neuromuscular junction
- Botulism
- Myasthenia gravis
- Lambert–Eaton syndrome

Myopathy
- Muscular dystrophies
  - Dystrophinopathy (Becker)
  - Limb girdle muscular dystrophies
  - Myofibrillar myopathy
  - Oculopharyngeal dystrophy
  - Bent spine/dropped head syndrome
- Metabolic myopathies
  - Glycogen storage defects
    - Acid maltase deficiency
    - Debrancher deficiency
  - Disorders of lipid metabolism (rare)
- Mitochondrial myopathies
- Periodic paralysis
  - Familial hypo-KPP manifest within the first three decades
  - Familial hyper-KPP usually manifests in the first decade
- Electrolyte imbalance
  - Hyperkalemia
  - Hypokalemia
  - Hypophosphatemia
  - Hypercalcemia
- Endocrine myopathies
- Toxic myopathies
- Myopathy associated with systemic disease (e.g., cancer), poor nutrition, and disuse
- Amyloid myopathy
- Inflammatory myopathies
  - Inclusion body myositis (most common inflammatory myopathy after the age of 50 years)
  - Dermatomyositis
  - Polymyositis (after the age of 20 years)
  - Infectious myositis

hypo-KPP, hypokalemic periodic paralysis; hyper-KPP, hyperkalemic periodic paralysis.
Modified with permission from Dumitru D, Amato AA. Introduction to myopathies and muscle tissue's reaction to injury. In Dumitru D, Amato AA, Swartz MJ (eds). Electrodiagnostic Medicine, 2nd edn. Philadelphia: Hanley & Belfus, 2002, pp. 1231, Fig. 26–3.

paresthesia or pain) or a negative (e.g., numbness or sensory ataxia) manner. During history acquisition, there is considerable value in identifying both the location and the nature of the initial symptom(s), including the circumstances during which that symptom developed. The subsequent evolution of symptoms should then be developed in a chronological fashion. The value of this approach can best be illustrated in the setting of patients with multifocal neuropathy. By the time they see a neurologist, their deficits may have become confluent and indistinguishable from a length-dependent neuropathy and its far more extensive differential diagnosis. Identifying that the initial symptom occurred in a focal nerve distribution may be a key element in diagnostic success.

As muscle weakness is usually the most objective manifestation of neuromuscular disease, emphasis is often placed not only on its existence but on its type and pattern as well. The existence of weakness may be apparent either through history taking or, more commonly, by examination. Even though muscle weakness is the hallmark of neuromuscular disease, patients uncommonly use the word weakness in their symptom description. The complaint of weakness is more commonly used by patients as a synonym for asthenia—a more pervasive, generalized complaint due to a number of different pathologies. Patients with true muscular weakness more commonly speak in terms of the sequelae of their weakness, i.e., the problems that result with activities of daily living. History taking pertaining to muscle weakness should focus on the identification of specific functions or activities that the patient finds difficult. If a patient who claims to be weak cannot describe a specific activity that is problematic for them, the existence of true muscle weakness remains suspect until it is subsequently corroborated by the physical examination. Muscle pain is also a common complaint brought to the attention of the neuromuscular clinician. Along similar lines, myalgia without a definable trigger, weakness, or some other objective finding is unlikely to be of neuromuscular causation.

For example, patients with weakness of hip flexion will have difficulty getting in and out of a car without lifting their legs and will have more difficulty going upstairs than going down. Patients with weakness of hip abductors will waddle as a compensatory maneuver to maintain their center of gravity and balance. Patients with chronic weakness of hip extension will tend to have exaggerated lumbar lordosis resulting from posterior displacement of the shoulders for the same compensatory reasons. Knee extension weakness will result in difficulty getting up from a squat or out of deep chairs and commonly results in falls due to buckling of one or both knees. These patients may hyperextend their knees in order to prevent this while standing or walking, i.e., genu recurvatum. Ankle dorsiflexion weakness often results in tripping. Ankle plantar flexion weakness affects

efficiency of walking as well as depriving individuals from the ability to stand on their toes.

In the upper extremity, people with weakness of the shoulder girdle will have difficulty with antigravity movements such as washing their hair, getting their arms into sleeves of clothing, and retrieving objects from shelves. Weakness of elbow flexion and extension often goes unnoticed until fairly severe but may be recognized while attempting to open doors that require pull and push, respectively. Wrist and digit weaknesses interfere with grip and dexterity, which may impair multiple activities of daily living, including opening of bottles and cans, turning ignition keys, or buttoning buttons.

Neuromuscular disorders often affect the motor and to a lesser extent sensory functions of cranial nerves. Extraocular muscle involvement is a key discriminating factor in working through the differential diagnosis of neuromuscular disorders. For example, the extraocular muscles are rarely affected in motor neuron disease or the acquired inflammatory myopathies. Conversely, they may represent prominent manifestations of the inflammatory demyelinating polyneuropathies, disorders of neuromuscular transmission, and a finite list of muscle diseases, typically heritable and/or mitochondrial in nature.

Patients typically become aware of ptosis by personal or family observation (Table 1–4). Occasionally, they first become aware when their vision is impaired by the drooping eyelid. Extraocular muscle involvement is typically expressed as diplopia, although patients with slowly progressive, symmetric involvement of the extraocular muscles such as in chronic progressive external ophthalmoplegia may be amazingly asymptomatic.

Patients with the acute onset of unilateral facial weakness are usually very aware of the existence and nature of their problem. Again, this is commonly due to their appearance in a mirror prompted by an abnormal feeling that they may describe as numbness. They may be bothered by the saliva that drains from their drooping mouth, the tears that drain from their sagging lower eyelid, or an initial tendency to be slightly dysarthric. Patients with chronic, particularly symmetric facial weakness may not recognize either the existence or the significance of their problem. Questions pertaining to a tendency to sleep with their eyes open and their ability to blow up balloons or whistle may help to estimate the duration of a problem that may be first detected on neurological examination. Symptomatic jaw weakness is infrequent in most neuromuscular disease. When present, it is often overshadowed by symptoms referable to muscles concomitantly affecting speech, swallowing, and breathing. Difficulty with chewing should nonetheless be inquired about, as it may sometimes be the initial or key symptom in a limited number of disorders such as myasthenia or Kennedy's disease.

Symptoms referable to tongue weakness are common in many neuromuscular disorders. Patients may become aware of it with the development of dysarthria or through their inability to manipulate food properly. They may have difficulty pushing it to the back of their throat during swallowing or dislodging food stuck between their cheek and teeth. This kind of detail is rarely volunteered by the patient and is more commonly elucidated by detailed questioning. Weakness of the neck muscles may be noticed by patients or their families with the development of head drop. This is often accompanied by nuchal discomfort, presumably due to the constant and unaccustomed traction on posterior cervical ligamentous structures. It is possible that this same head drop may contribute to dysphagia as well. Trapezius weakness is most commonly symptomatic when acute and unilateral and is usually a result of a mononeuropathy of the accessory nerve. These are usually painful disorders, due again presumably to the shoulder drop and resultant traction on pain-sensitive structures. These can be easily missed unless the patient is viewed from the rear, with the shoulders exposed.

Symptoms of ventilatory muscle weakness represent a fairly common, ominous, and occasionally initial manifestation of a selective group of neuromuscular disorders.[3] In this text, ventilation will refer to the mechanical act of air exchange in and out of the lungs as

▶ TABLE 1–4. NEUROMUSCULAR CAUSES OF PTOSIS OR OPHTHALMOPLEGIA

Peripheral neuropathy
Guillain–Barré syndrome
Miller–Fisher syndrome
Neuromuscular junction
Botulism
Lambert–Eaton syndrome
Myasthenia gravis
Congenital myasthenia
Myopathy
Mitochondrial myopathies
Kearn–Sayres syndrome
Progressive external ophthalmoplegia
Oculopharyngeal and oculopharyngodistal muscular dystrophy
Myotonic dystrophy (ptosis only)
Congenital myopathy
Myotubular
Nemaline (ptosis only)
Hyperthyroidism/Graves disease (ophthalmoplegia without ptosis)
Hereditary inclusion body myopathy type III

Modified with permission from Dumitru D, Amato AA. Introduction to myopathies and muscle tissue's reaction to injury. In Dumitru D, Amato AA, Swartz MJ (eds). Electrodiagnostic Medicine, 2nd edn. Philadelphia: Hanley & Belfus, 2002, pp. 1233, Fig. 26–7.

opposed to respiration, the act of gas exchange within the lungs themselves. Dyspnea on exertion is the typical symptom of hypoventilation. Because of the frequently limited ability of patients with neuromuscular disease to exert themselves, hypoventilation in these disorders often presents in a more protean fashion with nonspecific and frequently unrecognized symptoms.[4] Hypoventilation in neuromuscular disease is often worse nocturnally. It may result in airway collapse, obstruction, and snoring, with resultant excessive daytime fatigue and sleepiness. Nocturnal hypercarbia may also interrupt normal sleep cycling and promote nocturnal restlessness. Early morning headache due to carbon dioxide retention is usually a late symptom but one that should be inquired about. If the diaphragms are preferentially involved in the disorder, orthopnea may be a prominent and even initial symptom.

Other organ systems may be affected in neuromuscular disorders, and a careful system review is important in an attempt not only to achieve a diagnosis but also to fully anticipate the scope of its potential morbidity. Symptoms referable to cardiomyopathy or cardiac conduction defects, impaired GI motility, cutaneous change, and discolored urine from myoglobinuria or porphyria may provide valuable insight.

Upper motor neuron (UMN) involvement needs to be considered in patients with neuromuscular disease as well, either as an alternative or as an additional explanation for the patient's complaints. As the final common pathway, lower motor neuron disorders can express themselves in only a limited number of ways, typically through the effects of weakness perhaps limited to a select group of muscles. Less commonly, the patient's initial complaints may reflect awareness of atrophy, fasciculations, or cramps. UMN involvement is usually noted at an earlier stage in the illness in comparison to its lower motor neuron counterpart, as it interferes with the synergistic functions of multiple muscle groups simultaneously. As a result, coordinated activities are impaired early in the course and positive motor symptoms (that are more readily recognized) are more likely to occur. Patients with UMN lesions will lose the ability to run early in the course if their legs are affected. They may complain of stiffness or a tendency to drag one or both lower extremities. They may notice an impaired ability to perform many activities that require rapid coordinated movements in the upper extremities. If the corticobulbar tracts are affected, swallowing and articulation are affected early and prominently, as these functions are dependent on the coordinated interplay of many muscle groups. The speech pattern that results is often halting, effortful, and "strangled" in its characteristics. Patients may lose their ability to effectively sniff or blow their nose. Patients with corticobulbar tract involvement may also develop lability of affect known as pseudobulbar palsy.

Detecting the existence and pattern of sensory involvement is of key importance in the deductive reasoning process of differential diagnosis. In the motor system, one could argue that it is the examination rather than the history that produces the most useful information in the majority of cases. Inquiry regarding the existence of sensory symptoms on the other hand is frequently far more rewarding than the sensory examination. The character of sensory complaints does not distinguish peripheral from central nervous system disease. The pattern of sensory complaints is extremely important in establishing not only their credibility but also in the localization process. For example, a complaint of paresthesia confined to one or two contiguous digits would, in the vast majority of cases, indicate a disorder of the neuromuscular system as opposed to a central nervous system, metabolic, or factitious disorder. The other major value in the determination of sensory involvement is to further localize the pathological process. For example, pure motor disorders almost always indicate a disorder of anterior horn cell, the neuromuscular junction, muscle, or rarely motor nerve itself.

Disorders that affect sensory neurons may lead to a variety of perceived sensations that may in part be related to the size of the sensory axons affected and the chronologic course of the illness. Paresthesias may be described as tingling, prickly, burning, or shooting electrical sensations, often with an unpleasant or overtly painful characteristic. The latter two sensations are thought to indicate preferential involvement of small unmyelinated sensory nerve endings. Other abnormal although probably less specific perceptions include coldness as well as itching. If large myelinated sensory fibers are affected, the patient often describes a band-like, wrapped, swollen, or wooden sensation. They may feel as though they have cotton stuffed between their toes or that their body parts are encased in plastic, dried glue, or skin that is foreign to them. Pain associated with large diameter nerve fibers is often deep, dull, and aching in characteristic.

As with the motor history, it is important to explore the functional consequences of sensory loss although these may be less specific. In the authors' experience, the complaint of "dropping things" from the hands has poor discriminating value in the separation of definable from nondefinable neurologic disease. Conversely, impaired balance from large fiber sensory loss, i.e. sensory ataxia, is an important symptom associated with significant morbidity. Inquiries should be made regarding nocturnal balance, the use of a night-light, and balance in the shower while hair washing.

Patients with autonomic neuropathy may complain of palpitations, orthostatic intolerance, constipation, diarrhea, urinary retention, incontinence, erectile dysfunction, sweating abnormalities, early satiety, blurred vision, dry eyes, or dry mouth. The symptoms referable to

disordered function of the autonomic system are covered in greater detail in the section on autonomic nervous system testing in Chapter 2.

THE EXAMINATION

The strategy of the examination is to determine the presence of motor and/or sensory impairment, and the pattern as well as type of involvement. With the motor system, deficits are identified as indicating pathology of either UMN or lower motor neuron systems (or both). In the sensory domain, an attempt is made to distinguish, if possible, characteristics that suggest preferential involvement of small or large fiber modalities.

Time constraints are part of the reality of medicine. Examining clothed patients seems to increasingly represent a response to this inconvenience. In neuromuscular medicine, this short cut is not a viable option. Recognition of muscle atrophy and hypertrophy, fasciculations and myokymia, deformities such as pes cavus and kyphoscoliosis, abnormal postures due to hyperlordosis, shoulder drop or scapular winging, cutaneous findings such as the rash of dermatomyositis or café-au-lait spots, and gynecomastia represent just a fraction of potential diagnostic clues integral to accurate diagnosis and elicitable only by direct observation of exposed body parts.

Arguably, atrophy and fasciculations are more readily detected in the genioglossus than in any other cranial-nerve-innervated muscle. This finding is often a key diagnostic feature and should be actively sought for. It is important to examine the muscle in the mouth in a relaxed state rather than protruded, as muscle movement in the latter position may be misinterpreted. It is also important to distinguish a generalized tremulousness of the tongue, which occurs frequently from the random twitching of individual motor units that represent fasciculations.

Muscle strength is typically assessed in two ways: isometric manual muscle resistance and functional testing. Ideally, suspected weakness identified by the first method, e.g., reduced resistance of foot dorsiflexors, would be confirmed by the latter, i.e., the inability to stand on that heel alone. There is an art to manual muscle testing, which is undoubtedly improved upon by experience. Muscles are typically tested against gravity in their fully contracted position. For example, elbow flexors are tested with the patient's fist resting against his or her shoulder. The patient is held by the examiner in such a way that the muscle(s) to be tested is isolated to the extent possible. Again, in the case of the elbow flexors, the examiner would place the hand that delivers the force just proximal to the wrist to produce the greatest mechanical advantage, while at the same time removing wrist movement from consideration. The other hand, which serves to stabilize, is placed on the under surface of the elbow.

True weakness is manifested by a consistent effort and a smooth resistance pattern. Variable resistance due to UMN disease, pain, or lack of volitional effort would be recognized by a delayed, jerky, or "give way" pattern. True weakness can be difficult to identify in the very frail, in the very strong, or in those with potentially brittle bones from osteoporosis or metastatic cancer. In this situation, corroboration with patients' ability to use that muscle(s) functionally, e.g., getting up from a squat, stand, hop on one foot, or other aspects of their examination, e.g., their reflex status, and their history become the basis by which conclusions are drawn. Diminished or absent deep tendon reflexes, focally, multifocally, or diffusely, occur commonly but not universally with neuromuscular disease.

Once weakness is recognized, two other characteristics are of paramount importance: its pattern and its severity. The primary importance of the former is in the formulation of the initial diagnosis. The latter may help in initial diagnosis by serving to define the natural history of the disorder by defining a progressive, nonprogressive, or variable course. The degree of weakness is also important in monitoring an objective response to treatment. It is beyond the scope of this chapter to review the anatomy of muscle innervation or topical sensation. A working knowledge of this is however mandatory for a neuromuscular clinician to be effective. Pattern recognition as a diagnostic tool will be described in detail in the subsequent section of this chapter.

Historically, the Medical Research Council (MRC) scale has been used to quantitatively assess muscle strength. This scale uses a 0–5 scale, with 5 representing normal strength and 0 representing no discernable muscle movement. Three represents limited resistance with a preserved ability to move the joint through a full range of motion against gravity. Two represents movement through a complete range of motion with gravity eliminated. One represents observed muscle contraction with little or no limb or digit movement. With the MRC scale, the majority of weak muscles will fall into the four (modest weakness) range.

Clinicians often examine patients exclusively in the sitting position. This may be inadequate for testing certain muscle groups. Ideally, the tested muscle should move against gravity, particularly if the tested muscle is stronger than the force the examiner can deliver. In order to detect subtle weakness in neck flexion, abdominal muscles, and hip flexors, the patient should be tested in the supine position. Hip abduction is ideally assessed with the patients on their side. The prone position is ideal for testing the neck extensors, hip extensors, knee flexors, and ankle plantar flexors.

The MRC scale may be problematic to use, as it may be insensitive, ordinal, qualitative, and subjective.[5] The

potential exists for considerable interexaminer variability. It has been documented that patients may lose 80% or more of their motor units in a given muscle before they receive a 3 or less MRC rating.[5] In the opinion of the author', it is a poor tool to measure motor deficits in UMN disease. Increasingly in clinical trials, and to some extent in clinical practice, tools such as hand-held dynamometry are used in an attempt to measure strength in a more objective, linear, and reproducible manner.

The presence of scapular winging is an important and easily overlooked diagnostic clue in the assessment of neuromuscular disease. The patients will be unable to raise their hand over their head effectively. On observation, these patients may appear to have overly developed trapezius muscles (when viewed from the front). What is actually being seen is the superior margin of the scapula, which is elevated due to weakness of the scapular support muscles. Other observations may include a crease in the anterior axillary fold and an abnormal hand position where the dorsum of the hand rather than the thumb faces forward, producing a simian arm position while standing. These are both the result of abnormal positioning of the scapula with rotation of the entire shoulder joint anteriorly. Scapular winging may be evident by simply looking at the patient from the rear. It may be accentuated by a number of maneuvers depending on the pattern of affected muscles that are weak. Scapular winging due to weakness of the serratus anterior causes the inferior tip of the scapula to be preferentially elevated off the ribcage and is deviated medially toward the spine. It can be accentuated by having the patient push against a wall or slowly flex the arm at the shoulder anteriorly against resistance. With scapular winging resulting from trapezius weakness, the entire medial border is elevated and is accentuated by attempted abduction of the arm at the shoulder against resistance. The dynamics of scapular winging resulting from the more diffuse myopathic and motor neuron disorders are more complex.

Testing cranial nerve function in suspected neuromuscular disease is in part observational. Eyelid position can offer significant insight. The upper lid normally covers the upper limbus by a few millimeters or less, whereas the lower lid typically intersects the lower limbus. This relationship might change with diseases that produce either ex- or endophthalmos or symmetrically on the basis of age-related loss of tissue tone. Alteration of lid position may also be of a neuromuscular consequence. For example, a sagging (ptotic) upper lid combined by a sagging lower lid exposing sclera below the lower limbus suggests concomitant weakness of muscles that both open and close the eye lids. As these muscles have different innervations, this observation by itself may be a clue that the diagnosis is one capable of causing multifocal weakness with a predilection for cranial muscles, e.g., myasthenia gravis. Another observation of importance is the position of the eyebrow and the state of frontalis contraction. With ptosis, the eyebrow should be elevated and the ipsilateral frontalis contracted (if possible) in an attempt to compensate for the drooping lid. If the patient is squinting, which may be confused with ptosis, the eyebrow descends and the frontalis is not activated.

The pupils should be examined, preferably, at least initially, in a dimly lit room to assess for the possibility of Horner's syndrome.

The lack of pupillary reactivity may represent an autonomic component of the patient's disorder. Perhaps, the greatest value of the pupil examination in neuromuscular disease is to distinguish neuromuscular disorders causing ophthalmoparesis that spare the pupil from those that do not. Myasthenia, diabetic third nerve palsies, and myopathic causes of ophthalmoparesis fit into the former category. Ophthalmoparesis with pupillary involvement may occur as a consequence of Guillain–Barré syndrome and its variants and also due to presynaptic disorders of neuromuscular transmission such as botulism.

Jaw weakness is uncommonly detected. Weakness of jaw closing can be tested by having the patient close his or her mouth while the examiner attempts to force it open with the thumbs. The index and middle fingers are placed on the side of the face and the fourth and fifth digits on the side of the neck, in an attempt to stabilize the neck. Testing the strength of jaw opening needs to be done cautiously, as both the patient's teeth and tongue may be injured if patient's effort or resistance is diminished. Typically, the examiner places one hand on the back of the head to stabilize while force is delivered with the palm of the other hand on the under surface of the chin. The examiner must be sensitive to any "give" on the part of the patient so as to stop pushing before the jaw potentially snaps shut in order to avert injury.

Facial strength can be assessed as previously mentioned by observation, either by a drooping lower lid or by patients' inability to bury their eyelashes when asked to close their eyes forcibly. The latter can be corroborated in a more objective fashion by using the index finger and thumb in an attempt to pry the eyelids open while the patient is rendering full effort. Patient effort can be assessed by the presence or absence of Bell's phenomenon (upward deviation of the globe) if the eyelids can be effectively separated.

Tongue strength is typically tested by having patients thrust their tongue in either cheek, i.e., "pocketing" or against a tongue blade. The examiner attempts to push it back to the midline by applying pressure to the tongue. Sternocleidomastoid strength can be tested by rotating the head and applying isometric pressure to the chin. To test neck flexion, the patient is placed in either supine or sitting position, depending on the strength of the patient and the examiner, and asked to place the chin on the chest while the examiner pushes down on

the forehead. The neck extensors are assessed with the patient in either prone or sitting position. One should be careful in checking neck strength in frail patient or one with possibility of instability of the cervical spine. As in testing the strength of jaw opening, applied force should be rapidly released once patient resistance is overcome.

Ventilation can be assessed at the bedside by a number of techniques. There is value in observing the patient generate a forceful sniff, cough, or attempt to clear his or her throat. It is estimated that the vital capacity can be estimated in the cooperative patients by having them inspire fully and then count out loud at the rate of one per second until that one breath is exhausted. That number multiplied by a hundred will estimate their vital capacity measured in cubic centimeters. There may be value as well in examining the patient in the supine position to assess for paradoxical abdominal movements (outward abdominal movement in response to inspiration) as an indicator of diaphragmatic weakness.

Impaired motor function of central nervous system origin may include weakness, particularly if acute in onset, but is often dominated by impaired coordination or function with limited and at times absent weakness. As mentioned previously, patients with UMN weakness are usually aware of impaired use of their extremity at an earlier stage of their illness. This is due in large part to increased muscle tone and incoordination between agonist and antagonist muscle groups, thus leading to a delay in activation and impaired rhythm of repetitive movements. This phenomenon has been referred to as "UMN stickiness." Clumsiness disproportionate to the degree of weakness is a hallmark of UMN disease, as is the presence of exaggerated and pathological reflexes. UMN weakness may also be suspected on the basis of topographic pattern of involvement. A hemiparetic pattern is rarely neuromuscular. A paraparetic or quadriparetic pattern often occurs as a result of corticospinal involvement of the spinal cord but may just as easily occur in a neuromuscular disorder as well. UMN weakness when limited in distribution is often more distal than proximal, particularly in the upper extremity. Often, UMN weakness can be implicated when flexors are stronger than extensors in the upper limbs and the opposite in the lower extremities. Impaired motor function of central nervous system origin can often be deduced by observation, i.e., the reduced spontaneous use of a body part such as diminished gesturing of an arm during talking. UMN disease is implied as well when there are other signs and symptoms of central nervous system disease.

Like its motor counterpart, the results of the sensory examination are most credible when they are concordant with both the history and the functional tests of sensation when available. There are many sensory examination strategies. In the authors' experience, the application of sensory stimuli in a random fashion with subsequent attempts to identify the boundaries of the sensory loss produces many false-positive results and is often difficult to interpret. An alternative technique is a hypothesis-driven approach. The examiners identify a pattern of sensory loss that they are seeking, e.g., a length-dependent pattern or "stocking loss," and proceed accordingly to prove or disprove its existence. As examiners can apply stimuli with different intensities inadvertently and as patients have different thresholds for what they consider reduced (or increased), it is important to perform sensory testing in a reproducible and as unbiased manner as is possible. For this reason, there is a benefit from testing with the patient's eyes closed and with the addition of random null stimuli. This is particularly true with vibration where patients commonly confuse the touch of the tuning fork with vibration as the sensation in question. Using the tip of the examiner's finger as a random substitute for the tuning fork is a means to insure that the patient is responding positively to vibration and not simply to pressure.

There are a few important points to recognize in performing the sensory examination. As already emphasized, it is not uncommon to find an absence of convincing sensory loss to multiple modalities in a symptomatic region in a person with a bonafide neurologic injury. Conversely and somewhat paradoxically, it is not uncommon to find patients who claim to react to a stimulus in a hypersensitive manner in an area that they claim to be numb in the setting of a partial nerve injury. Lastly, it is important to realize that the topographical area where sensory symptoms are perceived and sensory loss is found is often far smaller than published anatomical charts would suggest for any nerve or dermatomal distribution. Presumably, this is the result of the considerable overlap between contiguous nerve territories.

There are a limited number of functional sensory tests to corroborate the findings on the direct sensory examination. The best known of these is the Romberg test, which assesses proprioceptive loss in the lower extremities arising from either the peripheral or the central nervous system. The finger–nose test, also done with the eyes closed, is less sensitive analog to test for proprioceptive loss in the upper extremities. Stereognosis testing can be helpful at times. Even with severe nerve injuries, absolute anesthesia is rare. Patients who claim to feel absolutely nothing in the hands yet can readily manipulate an object in that hand with their eyes closed are unlikely to have the degree of sensory loss that is claimed.

Common bedside screening tests of autonomic function include observation of pupillary responses both to light and to nuchal stimulation, observation of the feet for the presence of dry, cracked skin suggesting the possibility of anhydrosis, assessment of pulse variation in response to deep breathing, and, most commonly, orthostatic blood pressure and pulse measurements. The latter should be done after a few minutes in the supine position. Both blood pressure and pulse should be measured

immediately on standing (or sitting) and at 1-minute intervals for at least 3 minutes, depending on the index of suspicion.

Examination of young children, particularly infants, can be a challenge. Infants can be placed in a prone position to observe if they are capable of extending their head. An inability to do so suggests weakness of the neck extensor muscles. Most infants have considerable subcutaneous fat that makes muscle palpation quite difficult. Palpating neck extensor muscles is a good place to attempt this evaluation as little subcutaneous fat overlies this muscle group. Neck flexion strength can be assessed as the child is pulled by the arms from a supine to a sitting position. Crying during the examination allows the opportunity to assess the child's vocalization (e.g., presence of a weak cry) and fatigability to the physical examination. Muscle weakness in infants is usually characterized by an overall decrease in muscle tone and many children with profound weakness are characterized as a "floppy." This terminology does not necessarily imply a neuromuscular disorder. In fact, most floppy infants exhibit decreased tone secondary to a central nervous system problem. In view of prominent subcutaneous tissue, fasciculations may be visible only in the tongue. Observation of tremor is important as it may be a feature of spinal muscular atrophy and some hereditary neuropathies. It is important to examine the parents of floppy infants for the possibility of a neuromuscular disorder. This is particularly important in children suspected of having myotonic dystrophy. We have diagnosed a number of infants with congenital myotonic dystrophy by examining the mother who was asymptomatic. In addition, weakness can transiently develop in infants born to mothers with myasthenia gravis.

▶ WHAT IS THE NEUROMUSCULAR PROBLEM?

The following section will attempt to summarize the patterns of motor and sensory involvement that typify the diseases described in this text and that facilitate the localization process (Table 1–5). Further formulation of the differential diagnosis will require knowledge of the behaviors and natural histories of the disorders that are addressed in Tables 1–6 and 1–7 and described in detail in subsequent chapters of this book.

MOTOR NEURON DISEASES

The hallmark of the motor neuron diseases, also known as anterior horn cell diseases or motor neuronopathies, is painless weakness and atrophy. Although cramps and fasciculations can be theoretically seen with motor nerve disease at any location, they are far more prevalent in

▶ TABLE 1–5. PATTERNS OF MUSCLE WEAKNESS AND CORRELATIONS WITH NEUROMUSCULAR LOCALIZATION

Pattern of Weakness	Localization
• Weakness of extensor muscles in the upper extremities, flexors in the lower extremities	UMN
• Hemiparesis	UMN
• Multifocal, asymmetric weakness without sensory involvement	MND Multifocal motor neuropathy MG (uncommon)
• Multifocal, asymmetric weakness with sensory involvement	Polyradiculopathy Multifocal neuropathy
• Multifocal sensory loss	Dorsal root ganglionopathy
• Symmetric weakness, proximal or generalized without sensory involvement	Myopathy MND DNMT
• Generalized motor > sensory	Polyradiculoneuropathy
• Asymmetric cranial nerve ± limbs	MG
• Distal symmetric—motor only	Distal myopathies Distal spinal muscular atrophy
• Distal symmetric—sensory > motor	LDPN
• Multiple nerve—asymmetric	Multifocal PN
• Multiple root—asymmetric	Polyradiculopathy
• Multiple nerves and roots, single extremity	Plexopathy
• Single root	Monoradiculopathy
• Single nerve	Mononeuropathy

UMN, upper motor neuron; MND, motor neuron disease; MG, myasthenia gravis; LDPN, length-dependent polyneuropathy; PN = polyneuropathy; DNMT = disorders of neuromuscular transmission.

▶ TABLE 1–6. NEUROMUSCULAR DISORDERS PRESENTING WITH ACUTE OR SUBACUTE PROXIMAL WEAKNESS

Anterior horn cell
- Poliomyelitis

Peripheral neuropathy
- Guillain–Barré syndrome
- Porphyria
- Diphtheria
- Tick paralysis
- Toxic neuropathies
- Diabetic amyotrophy
- Vasculitis
- Carcinomatous infiltration (e.g., leukemia and lymphoma)
- Paraneoplastic neuropathy

Neuromuscular junction
- Botulism
- Lambert–Eaton syndrome
- Myasthenia gravis

Myopathy
- Periodic paralysis
- Electrolyte imbalance
- Endocrinopathies
- Inflammatory myopathies
  - Dermatomyositis
  - Polymyositis
  - Infectious myositis
- Toxic myopathies
- Metabolic myopathies
  - Glycogen and lipid disorders

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▶ TABLE 1–7. DIFFERENTIAL DIAGNOSIS OF CHRONIC PROGRESSIVE PROXIMAL WEAKNESS

Anterior horn cell
- Amyotrophic lateral sclerosis
- Spinal muscular atrophy type 3
- Kennedy's disease

Peripheral neuropathy
- Chronic inflammatory demyelinating polyneuropathy
- Multifocal motor neuropathy
- Toxic neuropathies
- Neuropathy associated with systemic disorders
  - Connective tissue disease (e.g., vasculitis)
  - Diabetes mellitus
  - Amyloidosis
- Paraneoplastic
- Carcinomatous infiltration (e.g., leukemia and lymphoma)

Neuromuscular junction
- Lambert–Eaton syndrome
- Myasthenia gravis

Myopathy
- Muscular dystrophy
- Periodic paralysis
- Electrolyte imbalance
- Endocrinopathies
- Inflammatory myopathies
  - Dermatomyositis
  - Polymyositis
  - Infectious myositis
- Toxic myopathies
- Metabolic myopathies
  - Glycogen and lipid disorders

With permission from Dumitru D, Amato AA. Introduction to myopathies and muscle tissue's reaction to injury. In Dumitru D, Amato AA, Swartz MJ (eds). Electrodiagnostic Medicine, 2nd edn. Philadelphia: Hanley & Belfus, 2002, pp. 1232, Fig. 26–5.

disorders of the anterior horn. The absence of fasciculations does not preclude a motor neuron localization, particularly where there is considerable subcutaneous tissue that may obscure their observation. Sensory symptoms and sensory loss do not typically occur except in Kennedy's disease. Nonetheless, it may occasionally occur in amyotrophic lateral sclerosis (ALS) due to other unrelated problems or perhaps as a consequence of the potential multisystem nature of this disorder.[6]

As most motor neuron disorders are hereditary/degenerative in nature, they tend to have a progressive course. The pattern of weakness varies with the disorder. With amyotrophic lateral sclerosis (ALS), onset is typically focal, e.g. foot drop, with subsequent regional progression. Even early in the course, however, weakness can be recognized as being multisegmental and outside of a single nerve or nerve root distribution. Poliomyelitis and other neurotropic viruses may present focally or with marked asymmetries as well. With the infantile spinal muscular atrophies, the weakness tends to be symmetric and generalized with perhaps a proximal predominance. The distal spinal muscular atrophies have a distal, symmetric pattern of weakness that may mimic a neuropathy. Hirayama's disease presents focally in the distal aspect of one, and perhaps eventually both upper extremities. Kennedy's disease typically produces a pattern of proximal symmetric limb as well as bulbar weakness.

The recognition of motor neuron diseases is also aided by what they tend to spare. Most notably, patients with motor neuron diseases virtually never experience ptosis or ophthalmoparesis except in the rare cases of ALS, which behave more like a multisystem disorder. Impaired bulbar function (i.e., speech and swallowing) is common in many motor neuron diseases. Facial and jaw weaknesses may occur but are typically less prominent. Deep tendon reflexes tend to be lost unless there is concomitant UMN disease as in ALS.

DORSAL ROOT GANGLIONOPATHIES

These are disorders, also known as sensory neuronopathies, that tend to affect the sensory system only. They may be autoimmune, toxic, infectious, or at times degenerative in etiology. As a result, the chronological course is variable. They may or may not be painful, dependent on etiology. Like virtually all nerve diseases, distal aspects of limbs tend to be more afflicted than proximal. Sensory ataxia is common. A careful history and examination will often uncover affected areas that are affected proximally or in an asymmetric pattern in keeping with the proximal and sometimes random location of the pathological process.

Dorsal root ganglionopathies are clinically suspected when purely sensory complaints occur in a nonlength-dependent and multifocal pattern. As many polyneuropathies appear to be purely or predominantly sensory on a clinical basis, electrodiagnosis may be required to demonstrate that sensory fibers alone are affected. In polyneuropathies, there is almost always some indication of motor involvement, even when it may not be apparent clinically.

MONORADICULOPATHIES

Monoradiculopathies are among the most common neurological problems, almost always due to degenerative disk or spine disease. The prototypical symptom of an acute monoradiculopathy related to disk herniation is pain, limited to one extremity traveling along the course of the involved dermatome. The pain may not affect the entire dermatome simultaneously, e.g., buttock and anterolateral leg pain sparing the thigh in an L5 radiculopathy. Contrary to common belief, the pain usually begins in the scapular and the buttock area rather than the neck or back. Sensory and motor deficits should be confined to a single segment but are distributed in multiple nerve distributions that share that particular myotomal distribution. The degree of deficit may vary and is often not as extensive as would be predicted from a dermatomal map or from a list of muscles innervated by that nerve root. One helpful clinical caveat is the recognition that a muscle is essentially never completely paralyzed from a lesion affecting only a single nerve root, as all muscles have multiple segmental innervation. A deep tendon reflex(s) may be diminished if appropriate to the involved root. The pain of a monoradiculopathy in the lower extremity may be reproduced by the straight-leg- or reverse straight-leg raising signs. In the cervical region, it may be reproduced by extending and laterally bending the head and neck toward the symptomatic side.

Pain may not be as prominent in chronic radiculopathies from spondylotic spine disease. In addition, multiple rather than single nerve roots are more commonly affected by this process.

POLYRADICULOPATHY

Lumbosacral spinal stenosis is the most common cause of polyradiculopathy. It typically presents with the syndrome of neurogenic claudication without objective neurologic signs at least early in the course and is described in detail in Chapter 22.

With the exception of lumbar spinal stenosis and the polyradiculoplexothy of diabetes, polyradiculopathy is relatively uncommon and is typically related to disorders that may produce a chronic meningitis. Neoplastic meningitis and certain inflammatory (e.g., sarcoid) and infectious (e.g., Lyme) disease disorders are notable examples. Limb or, in the case of thoracic involvement, trunk pain with radicular characteristics is the rule. Typically, these disorders begin in a single segment and spread in either a regional or a multifocal fashion. As both motor and sensory fibers are involved, it can closely mimic a multifocal polyneuropathy. If recognized early before confluence of deficit occurs, the motor, sensory, and reflex abnormalities may be recognized as segmental. Cranial nerves, both motor and sensory, are commonly affected in these disorders

PLEXOPATHY

A plexopathy is suspected when a typically painful disorder is restricted to a single limb, with the sensory, motor, and reflex deficits being more widespread than can be explained on the basis of a single nerve or nerve root involvement. Pain is the rule rather than the exception, as the causes of plexopathy are most commonly traumatic, inflammatory, or related to tumor or other diseases that may either compress or infiltrate. Occasionally, most notably with acute brachial plexus neuritis, sensory signs and symptoms may be modest or nonexistent. The reasons for this may be multifactorial. This disorder has a predilection affecting purely motor nerves (e.g., the long thoracic or anterior interosseous). In fact, it is this multifocal nerve pattern that often serves as a major diagnostic clue. The motor predominant nature of acute brachial plexopathy may be related to a demyelinating pathophysiology that may preferentially affect motor function in a manner similar to the Guillain–Barré syndrome.

MONONEUROPATHY

Mononeuropathy syndromes are usually readily recognizable due to the anatomic vulnerability of specific nerves in specific locations to compression or entrapment. The mode of presentation is variable, in part due

to the constituency of the nerve (e.g., pure sensory nerves such as the lateral femoral cutaneous nerve) but more commonly due to the pathophysiology of the disorder. Mononeuropathies may present with symptoms due to axon loss or any of the mechanisms of acquired demyelination. In the case of carpal tunnel syndrome and ulnar neuropathies at the elbow, sensory symptoms predominate at least initially. With common peroneal or radial neuropathies at the spiral groove, motor effects are more noticeable. Pain may or may not be an issue. Pain without motor, sensory, or reflex signs or symptoms is rarely due to a definable mononeuropathy.

In any event, signs and symptoms should be restricted to the distribution of a single peripheral nerve, distal to the site of nerve injury. The converse is not always true. For example, it may be very difficult to demonstrate weakness of ulnar forearm muscles, which are at risk from ulnar neuropathies at the elbow. This phenomenon has been attributed to selective fascicular involvement. As nerve fibers destined for the same muscle tend to sequester themselves in the same fascicle even in proximal locations, these fascicles may be relatively spared from a compression or entrapment process that may affect certain fascicles more than others.

LENGTH-DEPENDENT POLYNEUROPATHY

This is one of the most common neurological disorders with hundreds of potential etiologies. As a result, there is a fair heterogeneity in clinical expression. Conceptually, the majority of these disorders result from toxic, metabolic, or hereditary disturbances of cell body metabolism or myelin growth resulting in impaired axon or nerve impulse transport or conduction. This provides a cogent explanation for preferential involvement of most distal aspects of the longest nerves in the body affected in a symmetric, "length-dependent" fashion. Usually, sensory, motor, and reflex functions are impaired in this length-dependent pattern, but all are not equally noticeable.

Sensory symptoms may predominate, as the nerve endings of the feet have no backup system once affected. Denervation of intrinsic foot muscles is clinically masked by leg muscles, which provide identical toe flexor and extensor function. This is particularly true in the axonal neuropathies.

POLYRADICULONEUROPATHY

Polyradiculopathy refers to a disorder that affects multiple nerves both at the nerve and at the nerve root level. The most commonly encountered polyradiculoneuropathies are acquired, inflammatory, and demyelinating, e.g., the Guillain–Barré syndrome and chronic inflammatory demyelinating polyneuropathy. Uncommonly, this pattern may occur as an axon loss process secondary to a disorder like acute intermittent porphyria.

Polyradiculoneuropathies are usually readily distinguished from length-dependent polyneuropathy. They tend to be motor rather than sensory predominant. The pattern of involvement is typically symmetric but is usually more generalized and not length dependent. There may be cranial nerve involvement, which would be an extremely rare occurrence in most causes of length-dependent polyneuropathy. Reflex loss is typically generalized rather than length dependent. This is a consequence of the demyelinating pathophysiology rather than the location of the nerve injury.

MULTIFOCAL NEUROPATHY

Multifocal neuropathy is frequently referred to as mononeuritis multiplex or multiple mononeuropathies. It is not a universally accepted term but will be the preferred term in this chapter. Multiple mononeuropathies is an equally accurate descriptor although may imply a more benign multifocal compressive syndrome to some. Mononeuritis multiplex is a frequently used designation that implies an inflammatory pathology that may not exist or may go unproven. For this reason, it would best be avoided.

The deficits of multifocal neuropathy are often abrupt and painful, occurring haphazardly (although usually distally) and asymmetrically, with weakness and sensory loss being mapped to individual peripheral nerve distributions in multiple extremities. Clinical recognition may depend on examination of the patient early in the disease, or obtaining an accurate history of early disease evolution, prior to the inevitable confluence of deficits.

NEUROMUSCULAR TRANSMISSION DISORDERS

These disorders are difficult to lump together from a clinical perspective, as each of their clinical behaviors is different. Like motor neuron disease and myopathy, the signs and symptoms are attributable exclusively to the motor domain. As the neuromuscular junction is a more physiologically dynamic structure than nerve or muscle, fluctuations in strength and stamina are hallmarks of these disorders. In disorders of neuromuscular transmission, muscle atrophy is notable for its absence.

In postsynaptic disorders of neuromuscular transmission like myasthenia, for reasons not clearly

understood, there is a predilection for cranial innervated musculature. Ptosis, diplopia, dysarthria, dysphagia, and chewing difficulties are common complaints. The deficits can be quite asymmetric and at times remarkably focal. Rarely, myasthenia may present with limb weakness with little, if any, oculobulbar involvement. Finger and foot drop are perhaps the two most common presentations of this phenomena. Postsynaptic disorders of neuromuscular transmission do not affect muscarinic, cholinergic receptors or the autonomic nervous system. Pupils should be spared even with complete ophthalmoparesis. Deep tendon reflexes are commonly spared in myasthenia gravis unless involved muscles are significantly weak.

Signs and symptoms of cholinergic dysautonomia are commonplace in presynaptic disorders of neuromuscular transmission such as botulism and the Lambert–Eaton myasthenic syndrome. Weakness in these two disorders tends to be symmetric and is often proximally predominant and generalized. Cranial nerve involvement is very common in botulism. It does occur in the Lambert–Eaton myasthenic syndrome, although less commonly than in either botulism or myasthenia gravis. Deep tendon reflexes are commonly lost in a generalized pattern in any presynaptic disorder of neuromuscular transmission.

MYOPATHIES

Myopathy is often suspected in the setting of symmetric, usually painless weakness. Symmetry is a relative term, however, and minor asymmetries are common in myopathy and notable asymmetries may occur in disorders such as facioscapulohumeral muscular dystrophy and in inclusion body myositis. The distribution of weakness is often thought to be primarily proximal, but there are many notable exceptions. Myopathies may also be recognized and at times defined by regional patterns of weakness, e.g., facioscapulohumeral or oculopharyngeal dystrophy. Many myopathies along with many motor neuron diseases and disorders of neuromuscular transmission produce neck extension and particularly neck flexion weakness. Cranial muscle involvement is variable. Dysphagia, ptosis, ophthalmoparesis, facial, jaw, and tongue weakness may occur and may again aid in the differential diagnosis of myopathic disorders. Reflexes may be lost or preserved, depending on the pattern and severity of muscle involvement.

Attention to other elements of the examination may aid in the identification of the existence, type, and potential complications of muscle disease. Percussion, grip, or electrical myotonia will serve to identify a select group of myopathies (Table 2–Chapter 2). A number of myopathies may associate with joint contractures or skeletal abnormalities. Muscle hypertrophy is constant feature of the dystrophinopathies and may occur with certain limb girdle dystrophy phenotypes as well as infiltrative disorders of muscle such as amyloid myopathy. Involvement of ventilatory and cardiac muscle as well as other organ systems may aid in diagnosis and allow anticipation of future morbidity (Table 1–8).

▶ TABLE 1–8. NEUROMUSCULAR DISORDERS ASSOCIATED WITH VENTILATORY MUSCLE WEAKNESS

Anterior horn cell
Poliomyelitis
Amyotrophic lateral sclerosis
Plexopathy
Brachial plexus neuropathy with phrenic nerve involvement
Peripheral neuropathy
Guillain–Barré syndrome
CIDP (rare—consider POEMS syndrome)
Critical illness neuropathy
CMT 2C
Multifocal motor neuropathy with phrenic nerve involvement (rare)
Neuromuscular junction
Botulism
Myasthenia gravis
Myopathy
Muscular dystrophies
Dystrophinopathy
Myotonic muscular dystrophy
Limb-girdle muscular dystrophy (certain genotypes)
Congenital
Emery–Dreifuss
Metabolic myopathies
Acid maltase deficiency
Carnitine deficiency
Toxic myopathies
Critical illness myopathy
Congenital myopathies
Myotubular myopathy
Nemaline myopathy
Inflammatory myopathies
Polymyositis and dermatomyositis (rare) (consider associated interstitial lung disease)
Mitochondrial myopathies (rare)

▶ SUMMARY

Diagnostic accuracy is in large part dependent on a clinician's ability to elicit pertinent information from both the patient's history and the examination, discard information that is not germane to the patient's current problem, and formulate a differential diagnosis by accurately matching the features and behavior of the patient's

illness with those of different diseases. This chapter has addressed the first part of this problem-solving approach. Subsequent chapters will discuss the features of the neuromuscular diseases whose diagnoses this textbook will hopefully aid in.

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CHAPTER 2

Testing in Neuromuscular Disease—Electrodiagnosis and Other Modalities

▶ INTRODUCTION

The role of laboratory testing in the diagnosis of neuromuscular disease does not differ from the general practice of neurology or from the philosophies or principles emphasized in the previous chapter. Tests are ideally used to support a clinically established working diagnosis, not in a random search process.

This chapter will focus on nonhistological tests that are both available and potentially useful to the neuromuscular clinicians in their assessment of patients. In keeping with the philosophy of this text, emphasis will be placed on tests that have pragmatic application. The science behind the testing will be provided only to the extent necessary to understand the utility, performance, interpretation, and limitations of a test within a given clinical context.The following topics will be addressed:

- Electromyography (EMG) and nerve conduction studies (NCS), collectively known as electrodiagnosis (EDX)
- Quantitative sensory testing (QST)
- Autonomic nervous system testing (ANST)
- Routine laboratory (blood) testing
- DNA mutational analysis
- Biochemical testing for inborn errors of metabolism
- Serological testing
- Cerebrospinal fluid (CSF) analysis
- Nerve and muscle imaging

For purposes of understanding, it is important to define terms. In this chapter and in this book, neuromuscular disease will refer to a pathological process that affects the integrity and/or function of somatic peripheral motor and sensory neurons, neuromuscular junctions, and skeletal muscle. Disorders at or distal to the anterior horn cells including the neuromuscular junction and muscle will be discussed in the motor system. Within the sensory system, disorders affecting the dorsal root ganglia and their respective peripheral nerve components will be addressed. Disorders of the autonomic system and cranial nerves will discussed only as required to fully understand the disorders that primarily affect the somatic peripheral nervous system.

▶ EMG AND NCS (EDX)

BASIC PRINCIPLES

Physician Skill and Knowledge

EDX, like all tests, have limitations, as do the people who order and perform them. The most satisfactory results occur when the physician ordering the test understands its value and limitations and then poses specific questions to the electromyographer that the test is capable of answering. A satisfactory result is also dependent on an electromyographer who examines the patient, understands the differential diagnosis of the clinical problem, and tailors the electrodiagnostic examination to adequately explore those possibilities. In keeping with these philosophies, it is readily understandable that the nerves tested during NCS and the muscles selected for EMG are determined on a case-by-case basis and may be modified as the examination proceeds.

Temperature Considerations

Attention to detail is as important in EDX. This is particularly true as it pertains to limb temperature. As a general rule, hand temperatures of >33°C and foot temperatures of >31°C are desirable. Although warm water baths and heating lamps may be used, reusable microwaveable heating pads applied to the limbs are the most effective technique, in the authors experience, for obtaining and maintaining this thermal environment.

With cold limbs, amplitudes of both compound motor action potential (CMAP) and sensory nerve action potential (SNAP) are increased. Abnormally low CMAP and SNAP amplitudes could be potentially normalized. Conversely, conduction speeds are reduced, including slowing of conduction velocities and prolongation of distal, F wave, and H reflex latencies (Fig. 2–1).

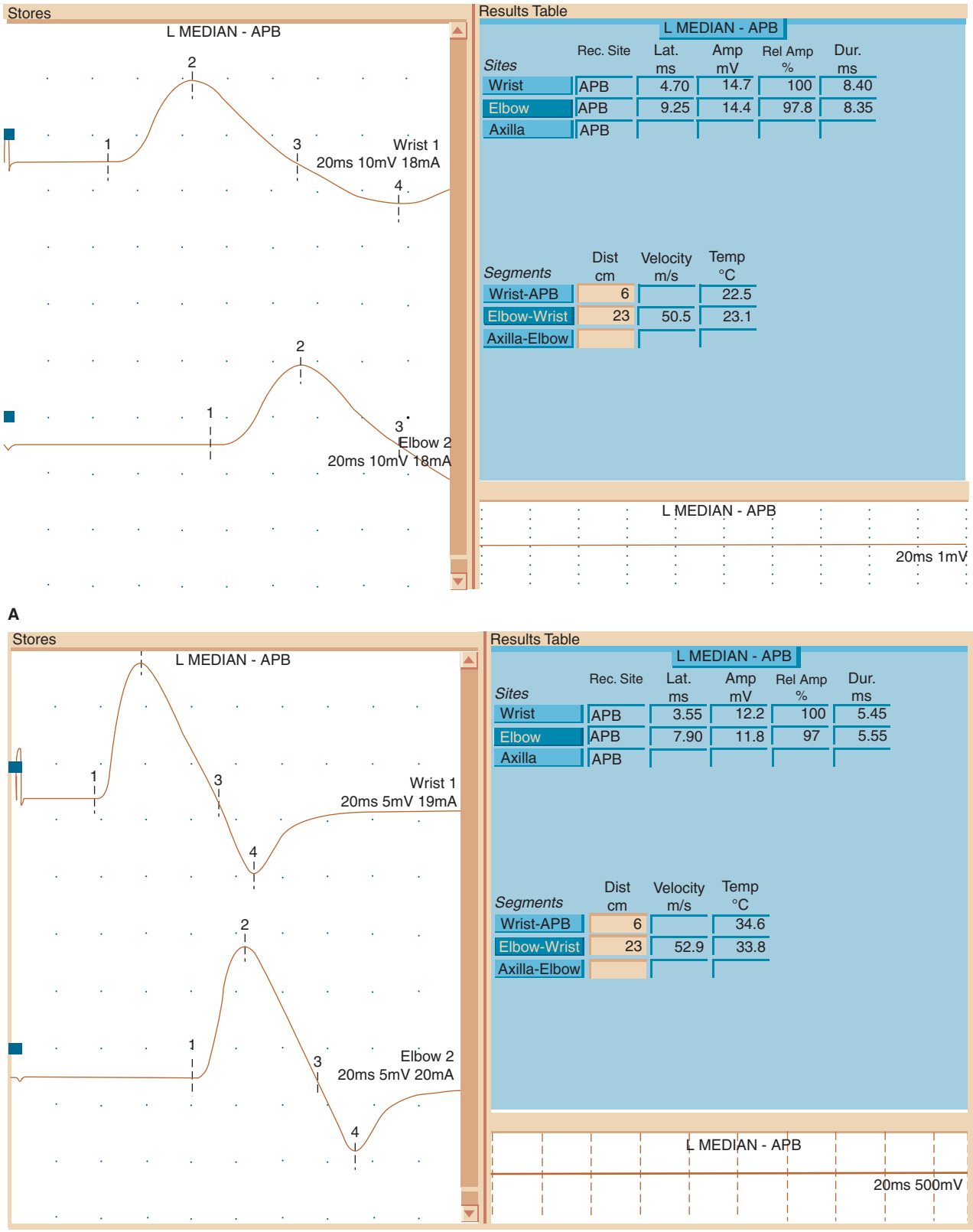


Figure 2–1. Effect of cool limb temperature on nerve conduction studies—median CMAPs (compound muscle action potentials) demonstrating factitiously significant increase in distal latency, slightly decreased conduction velocity, and increased amplitude (note different gain settings) following cooling (A) and corrected by limb warming (B).

Repetitive stimulation techniques are also adversely affected by cool limb temperatures potentially producing a false-negative result. Although it would be unusual for fibrillation potentials to disappear with limb cooling, their density and therefore their detection may be hampered under these conditions. In summary, with the exception of cold-induced myotonic discharges in paramyotonia congenita (PC), the accuracy of EDX is improved upon by establishing and maintaining adequate limb warmth.

Test Construction and Reporting

There are differing opinions regarding the role of clinical assessment in the construction and reporting of the EDX evaluation. It has been suggested that EDX conclusions should be based solely on the results of the study and should not be influenced by clinical bias. The potential risk is that meaningful EDX observations will be ignored if these do not conform to a preexisting clinical belief. This potential bias is a valid risk that should be considered and avoided when possible. Having said that, it can be argued that clinical perspective in an electrodiagnostician does more good than harm and is integral to the efficient construction and accurate interpretation of an EDX study. There are a number of lines of evidence to support this latter perspective.

For example, there are disorders that share identical electrodiagnostic signatures but have different etiologies, natural histories, and treatment potential. For example, early amyotrophic lateral sclerosis (ALS) affecting the lower extremities and the polyradiculopathy of severe lumbosacral spinal stenosis or a dural arteriovenous malformation may be electrodiagnostically indistinguishable.[1–3] The EDX conclusions in this case will be enhanced by the weighting provided by clinical insight. In adults in particular, patients may have more than one disorder affecting their neuromuscular system. If this is the case, accurate EDX conclusions will be confounded without the clinical insights necessary to distinguish which abnormal EDX parameters are and which are not germane to the problem at hand. A third argument in support of supplementing EDX impressions with clinical correlations is the realization that in some cases, pathology may be subclinical. It is not uncommon to find mild median nerve conduction slowing across the wrist in individual with a repetitive hand use vocation whose complaints bear no resemblance to the clinical phenotype of carpal tunnel syndrome. Reporting in this case, if made solely on the basis of EDX data, without consideration of the clinical aspects of the case, risks misdiagnosis and the potential of unnecessary surgery.

Normative Data

Historically, it was recommended that every laboratory establish their own normative data. Improvements and standardization of commercially manufactured equipment allow for the more confident use of published normative data. It is important to recognize, nonetheless, the potential pitfalls of population-based "normal" values. Normative data are influenced by age. EDX in infants has to be interpreted by a completely different set of norms than are used in adults. By the same token, conduction studies have to be more cautiously interpreted in the elderly, particularly lower extremity sensory conductions. Although sural and superficial peroneal SNAPs are elicitable in many patients 80 years of age and older, these may be absent in a seemingly normal septuagenarian. This may confound the distinction between two common problems in this age group, peripheral neuropathy and lumbosacral polyradiculopathy due to spinal stenosis, the distinction of which relies heavily on evaluation of SNAPs.

Another age-related misinterpretive risk stems from the recognition that larger motor unit potentials (MUPs) may be seen in seemingly normal elderly individuals. This has been attributed to reinnervation resulting from (1) the wear and tear of the aging process in intrinsic hand or foot muscles, (2) motor unit loss resulting as a normal component of aging, or (3) in response to asymptomatic spondylosis in the lumbar or cervical spine.

Normal values in EDX occupy a wide range both within and between different groups of individuals and even different segments of nerve. Any parameter measured may be within normal limits for a population but may be distinctly different from the patient's baseline. The latter is of course frequently unknown. In the case of focal or unilateral problems, the best normative values come from the patient's opposite limb. In most laboratories, a side-to-side amplitude difference of more than 50% is considered abnormal. Even this represents a potentially insensitive means to detect subtle nerve pathology.

Timing

There are some circumstances in which timing considerations are crucial. In general, it is estimated that complete Wallerian degeneration requires 3–5 days to produce a noticeable decline in CMAP amplitudes, with the nadir occurring between days 7 and 9. In sensory nerves, there is a slight lag with amplitude loss becoming apparent between the 5th and 7th days, with the SNAP amplitude reaching its lowest point by the 10th or 11th day.[4] For this reason, an interval of 10 days to 2 weeks between injury and the performance of NCS is ideal in most instances. There is a risk of false interpretation if NCS are preformed prematurely. Normally, identification of a normal CMAP amplitude distal to a lesion and reduced amplitude above the lesion would imply the existence of a demyelinating conduction block. If motor conductions are performed hyperacutely, an axon loss lesion may be falsely interpreted as demyelinating conduction block.

Fibrillation potentials and positive waves, the most sensitive indicator of recent axon loss on EMG, may develop within days in muscles that are in close anatomic proximity to the injured nerve. Three weeks may be required to develop a full density and distribution within all muscles at risk. As many patients may be reluctant to undergo multiple examinations, the EDX should be postponed for 3 weeks after disease onset in most circumstances.

There are at least two circumstances in which it may be preferable to perform EDX earlier than the normal 3-week recommendation. One of these occurs when there is the suspicion or knowledge of a preexisting nerve injury. It may be important for either legal or medical reasons to distinguish between new and old. Performing two examinations, one as early as possible and then a second examination a month or more later, would be best suited to address this issue. A second scenario would be a suspected Guillain–Barré syndrome (GBS) where rapid EDX support for the diagnosis is desired. As in other neuromuscular disorders, it may require days or weeks for the EDX abnormalities characteristic of GBS to fully develop. Nonetheless, the rapid evolution of NCS abnormalities, even if not diagnostic, in the absence of findings characteristic of other potential causes of acute generalized weakness, can be reassuring to the clinician and guide management decisions in the critical first week of the illness.

PERFORMANCE OF THE ELECTRODIAGNOSTIC EXAMINATION

The routine EMG/NCS examination traditionally consists of motor NCS, sensory NCS, and the needle electromyographic examination. F waves and H reflexes are also commonly tested although in most cases provide complementary rather than novel information. As mentioned previously, the nerves and muscles tested are selected on a case-by-case basis. Initial selection is based on the diagnostic question posed and the clinical information available and is further modified as the test unfolds. It is appropriate to emphasize that techniques used to detect disorders of neuromuscular transmission (DNMT) such as repetitive motor nerve stimulation (RNS) testing and single fiber EMG (SFEMG) are not part of the routine evaluation in most laboratories. Once again, the importance of clinical surveillance in test construction is emphasized.

NERVE CONDUCTION STUDIES

Motor Nerve Conductions

Motor nerve conductions are performed by applying an active surface recording electrode overlying the midportion of a muscle belly. This position is chosen to be in proximity to the motor point, i.e., the confluence of neuromuscular junctions. In addition, a reference electrode is used in proximity to but not on the muscle belly. The response sought for, referred to as a compound muscle action potential (CMAP), is obtained by stimulating the nerve in question while recording from a muscle that it innervates. To elicit the desired response, the intensity of the electrical stimuli applied to the nerve is increased until all involved axons and muscle fibers are activated and the maximal CMAP response is obtained. This is commonly referred to as the supramaximal stimulus and is the desired effect in all routine NCS. Each nerve tested may be stimulated at one or more locations, limited primarily by anatomical considerations and patient tolerance.

Readily testable motor nerves are the median, ulnar, radial, accessory, facial, tibial, and common peroneal. The phrenic, femoral, axillary, and musculocutaneous can be tested, although in each case technical issues may make reliable and reproducible information more difficult to obtain. The CMAP waveform that is obtained represents all of the individual single muscle fiber action potentials (SFMAPs) within that muscle activated by the nerve stimulus. Because different nerve fibers within a nerve have different conduction velocities, the waveform is dome-like rather than spiked in its configuration. The proximal or left-hand side of the waveform represents the action potentials of the fibers innervated by the fastest conducting axons. The trailing aspect of the dome represents the action potentials of the muscle fibers innervated by the slowest conducting motor axons (Fig. 2–1). As stimuli are delivered at increasing distances from the target muscle, the distance between the initial and terminal aspects of the CMAP waveform widens. This results in an increasing duration of the CMAP waveform without a reduction in the area under the curve, as the number of activated nerve and muscle fibers remain the same. This is the basis of the normal physiological waveform dispersion described below.

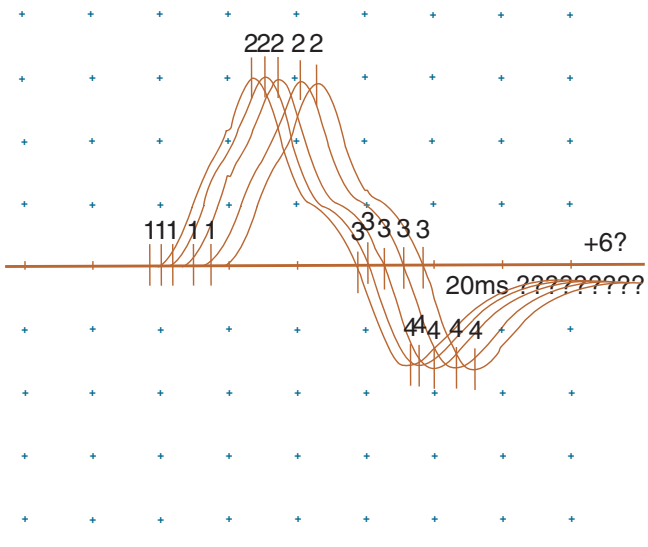
Typically, three parameters are measured and one is more subjectively assessed. The baseline to peak amplitude and the area under the curve of the CMAP waveform not only are reflections of the number of viable muscle fibers but are indirectly a measure of the number of viable and excitable axons that innervate them. Therefore, the CMAP amplitude provides an estimate of the number of functioning axons, neuromuscular junctions, and ultimately muscle fibers. In some instances, as will be subsequently described, the CMAP amplitude may be adversely affected by diseases that only affect the integrity of the myelin sheath.

The other two parameters measured are distal latency (time between stimulus delivery and initial activation of muscle) and conduction velocity. These are

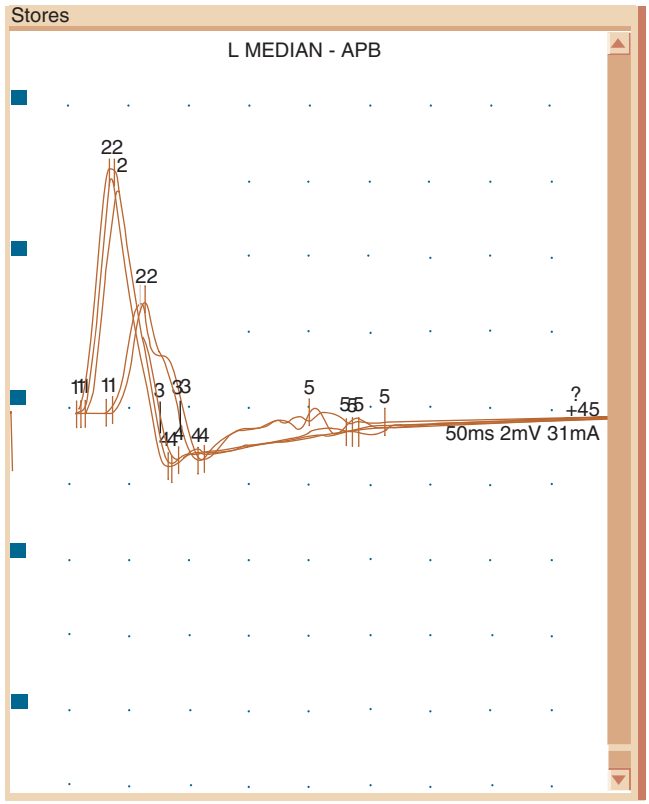
primarily measures of conduction speed and therefore of myelin function. Although both conduction velocity and distal latency measure conduction speed, these are reported separately in motor conduction studies for a number of reasons. The distal latency reflects conduction along different segments of nerve (wrist to hand or ankle to foot) than the conduction velocity (elbow to wrist or knee to ankle). In certain pathological conditions, one parameter may be abnormal whereas the other remains unaffected. Distal latency and conduction velocity are reported differently for purposes of technical accuracy. Distal latency measures not only nerve conduction but neuromuscular transmission time as well. Additionally, terminal nerve twigs attenuate in diameter and have a conduction velocity that does not accurately reflect conduction speed in the more proximal nerve.

The last parameter to be assessed on a more subjective basis is CMAP morphology. Although morphological changes can be measured by comparing ratios of CMAP duration to amplitude, these are usually observational and descriptive in nature. Subtle changes may occur in normal individuals when CMAPs are obtained from stimulation at different points along the course of a nerve. These changes consist of amplitude reduction and increased waveform duration, with relative preservation of area under the curve. With this physiological dispersion, the CMAP amplitude with proximal stimulation should never drop below 80% of that obtained from the most distal stimulus site. Nerve root stimulation sites provide the notable exception to this rule.[5] More dramatic reductions of CMAP amplitude, particularly over short segments of nerve, should be interpreted as either demyelinating pathology or technical error (Fig. 2–2a and b).

CMAP afterdischarges represent one other potential alteration of CMAP morphology. When present, these repetitive CMAPs follow a single supramaximal nerve stimulus. These appear as multiple negative peaks in the immediate aftermath of the initial CMAP detectable either with routine motor conductions or with F wave assessment. Afterdischarges are not uniform with consecutive stimuli and have much smaller amplitudes than the initial supramaximal response (Fig. 2–3). These occur rarely, typically in disorders in which nerve or muscle depolarization persists or repolarization is delayed. Their value is their specificity and the limited number of disorders with which they are known to associate with. This differential diagnosis includes disorders of nerve potassium channels such as Issacs' syndrome,[6] muscle channelopathies (e.g., paramyotonia congenita (PMC), myotonia congenita, and potassium-aggravated myotonia), or disorders in which there is prolonged cholinergic activity at neuromuscular junctions.[7,8] Toxic exposures to organophosphates or congenital acetylcholinesterase deficiency are the most notable examples of the latter.[9]



A



B

Figure 2–2. (A) Short segmental incremental stimulation in normal individual demonstrating identical CMAP (compound muscle action potential) waveforms with equivalent spacing between consecutive waveforms and (B) ulnar neuropathy at the elbow with focal demyelination with conduction block (amplitude reduction between responses 3 and 4), focal slowing (widening baseline interval between responses 3 and 4), and mild temporal dispersion (increased CMAP duration between responses 3 and 4).

Sensory Nerve Conductions

Sensory conduction studies may be performed percutaneously. They are more commonly performed by attaching the same or similar recording electrodes on the surface of the skin over a sensory or mixed nerve. The tested nerve is then stimulated at either a more proximal or a distal location than the recording site. The former technique is described as antidromic, as the stimulus travels in the direction opposite to that of normal centripetal physiologic conduction in sensory nerve fibers. With stimuli delivered distal to the recording site, conduction is considered orthodromic. Nerves routinely studied include the median, ulnar, dorsal cutaneous ulnar, radial, medial antebrachial cutaneous, lateral antebrachial cutaneous, sural, and superficial peroneal. The lateral femoral cutaneous, saphenous, and medial and lateral plantar nerves are less frequently tested. These latter studies are fairly easy to obtain in the young, healthy, slender, and nonedematous but can be technically difficult in those with the opposite characteristics. Unlike motor conductions, SNAPs are measured in microvolts rather than millivolts, making them technically more difficult for an inexperienced technician or physician to obtain.

In many laboratories, only two parameters are measured: SNAP amplitude and distal latency or conduction velocity (Fig. 2–4). As there are no neuromuscular junctions to contend with in sensory nerves, both the distal latency and the conduction velocity are measures of nerve conduction speed, differing only in the segment of nerve tested. Either or both parameters may be reported. With motor conductions, there are some disorders in which distal latencies are prolonged disproportionate to forearm or leg conduction velocities. As there are few, if any, recognized conditions in which conduction speed is consistently more affected in one segment of sensory nerves than another, it can be argued that the reporting of distal latency as the sole measurement of sensory conduction speed is adequate. With motor

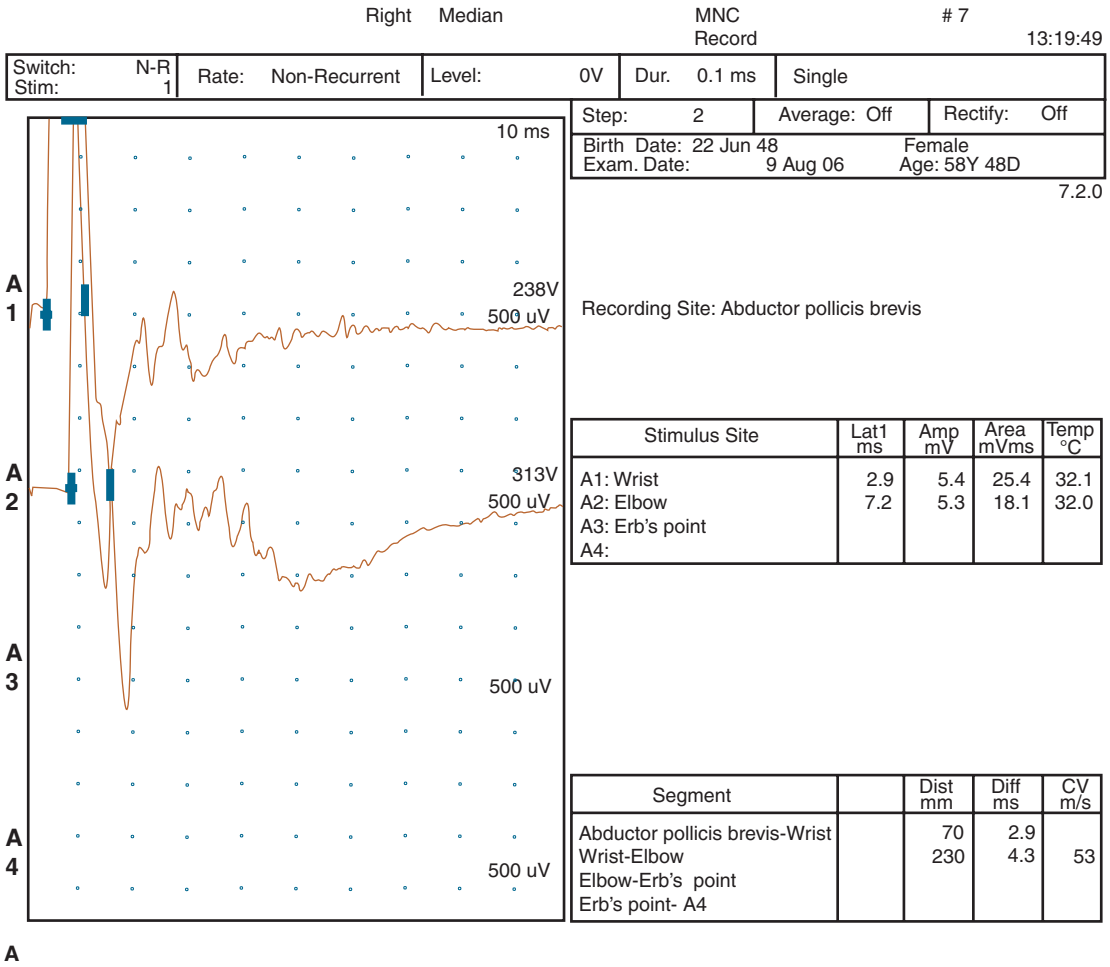
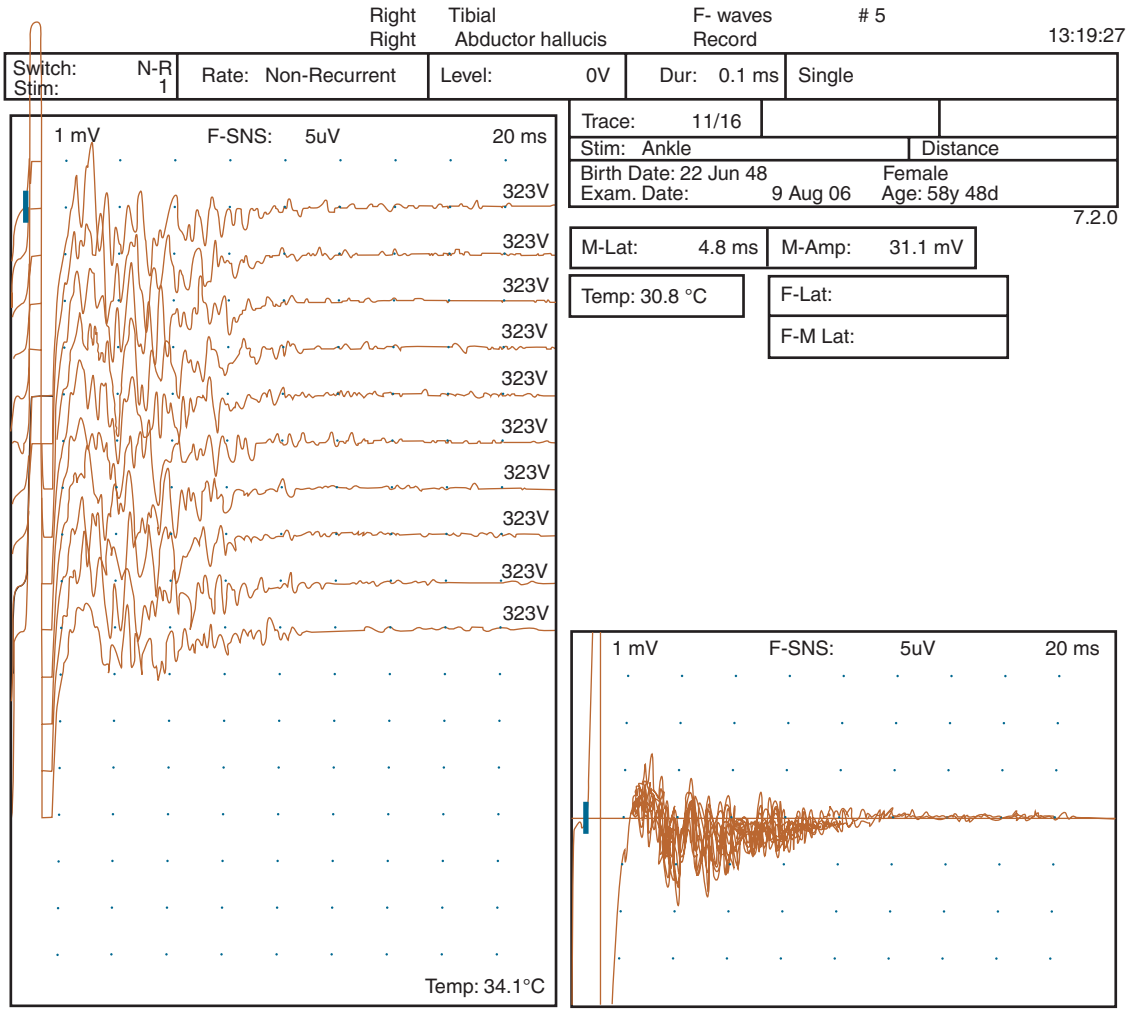


Figure 2–3. After discharges in neuromyotonia with routine motor conduction studies (top) and with F wave determinations (bottom). (Reproduced with courtesy permission of Drs. Alpa Shah and Steven Vernino, University of Texas Southwestern.)



B

Figure 2–3. (Continued)

distal latencies, the onset of the waveform is used for measurement, thereby identifying the fastest conducting axons. With SNAPs, the distal latency is typically measured from the waveform peak rather than the onset. This is done for technical reasons, as the onset of the SNAP waveform may be difficult to reproducibly identify. If sensory conduction velocities are to be measured, then identification of negative peak onset latency is required as well.

The second and more important SNAP parameter is amplitude. As sensory conductions involve nerve rather than muscle action potentials, amplitude reduction does not occur on the basis of impaired neuromuscular transmission or myofiber atrophy/loss. With the exception of certain types of demyelinating pathology described below, reduced SNAP amplitude indicates either advanced age, excessive subcutaneous tissue or fluid, poor technique, or, most commonly, loss of peripheral sensory axons.

Changes in waveform morphology are not of particular value in sensory conductions. Waveforms recorded over long distances are typically significantly reduced in amplitude and prolonged in duration in comparison to their CMAP counterparts (Fig. 2–4). This is due to the same principle of physiological dispersion described above. This phenomenon is more pronounced than its motor counterpart due to the far wider range of conduction velocities in sensory nerves. As a result, attempts to identify demyelinating conduction block or significant morphological differences in SNAP waveforms are not routinely attempted, particularly over long conduction distances.

F Waves and H Reflexes

Motor and sensory conduction studies are typically performed in the below elbow and knee segments where nerves are more anatomically accessible. F waves and H

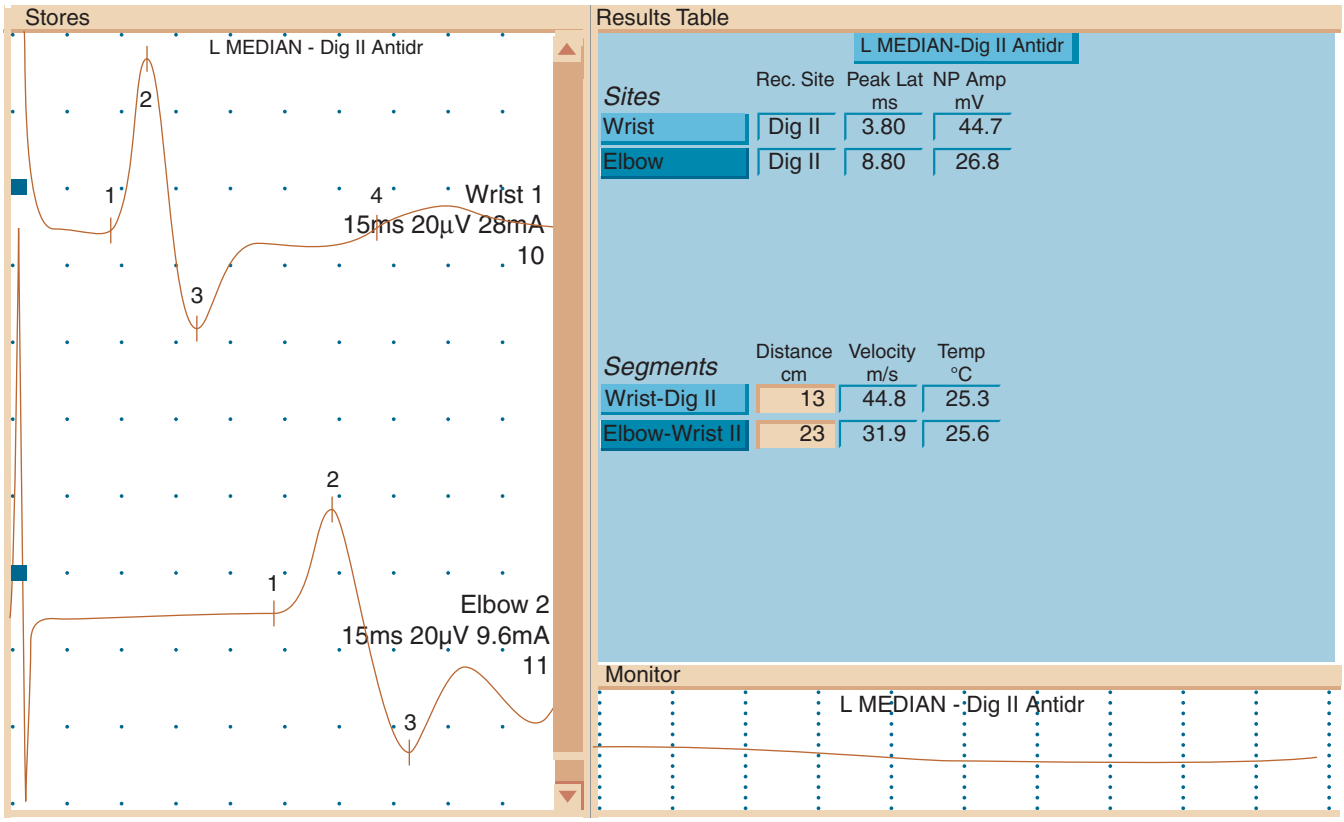


Figure 2–4. Sensory nerve action potentials in a normal individual demonstrating normal physiological dispersion over distance with decreased amplitude and prolonged duration of median SNAP (sensory nerve action potential) waveform stimulating at elbow (bottom) as compared to stimulating at the wrist (top).

reflexes have potential value as a result of their ability to assess conduction in more proximally located nerve segments. F waves can be obtained following supramaximal stimulation from any motor or mixed nerve in a normal individual, most of the time. These can be difficult to obtain in certain nerves, e.g., common peroneal, even in the apparent absence of pathology. For that reason, it can be perilous to suggest the existence of nerve injury based solely on the absence of an F response from a single nerve. In normal adults, H reflexes can be elicited from the soleus muscle while stimulating the tibial nerve and, on occasion, from the flexor carpi radialis. Identification of H reflexes in other nerve/muscle pairs implies the existence of upper motor neuron disease.

The relevant anatomy and physiology of an F response can be described in the following manner. When a supramaximal stimulus is delivered to a nerve, the primary response is the CMAP (M wave) as previously described. This results from the orthodomic conduction of a nerve action potential along the supramaximally stimulated motor nerve fibers. In addition, the initial nerve depolarization also produces an antidromic action potential traveling centripetally toward the spinal cord. At the level of the corresponding anterior cell(s), this antidromic action potential establishes a persistent or second action potential at the level of either the perikaryon or its axon hillock. The action potential produced at this location is carried in a centrifugal or orthodromic direction along the entire length of one or more of the same motor axon(s) back to the original target muscle. As a result, the muscle is depolarized twice in response to a single stimulus, the second muscle action potential having understandably a much longer latency and smaller amplitude (F wave). Unlike the initial CMAP, which represents the action potentials all of the responsive muscle fibers, each delayed (F) response represents the action potentials of muscle fibers belonging to a single motor unit. With each sequential stimulus, different motor units are typically activated. As a result, sequential F wave responses typically have slightly different latencies and morphologies in comparison to those occurring with the previous or subsequent stimuli.

F waves have limitations. Even in a normal nerve/muscle pair, F waves do not result from each stimulus. Amplitude measurements are of no particular value, as these represent the action potentials of only a small and varying proportion of single muscle fibers in response to each individual stimulus. There is heterogeneity of

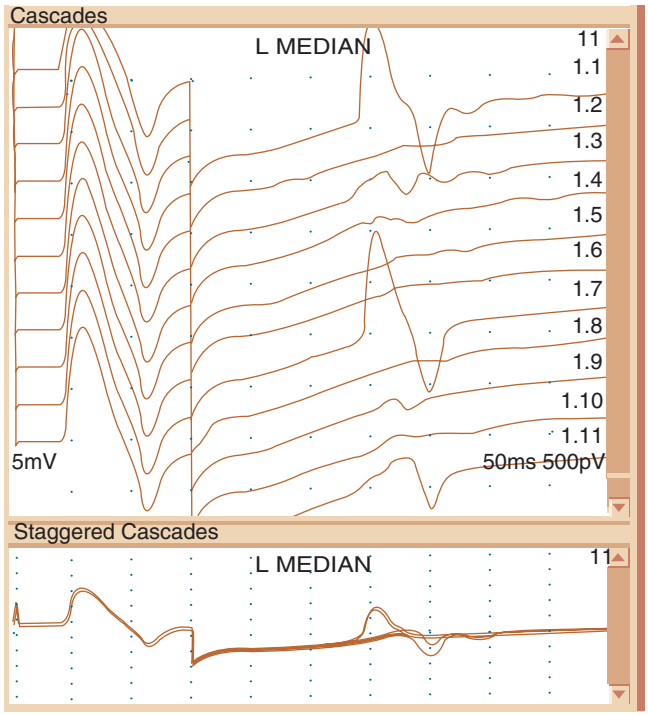


Figure 2–5. F waves—11 consecutive supramaximal stimuli delivered to the median nerve at the wrist in a normal individual while recording from the abductor pollicus brevis muscle demonstrating uniform CMAPs (compound muscle action potentials) but typical F wave behavior, i.e., waveforms that are variable in occurrence, latency, and morphology.

F wave latencies as sequential responses rarely arise from motor axons with identical conduction velocity (Fig. 2–5). A number of latency measurements can be made, the response with the shortest latency typically being the parameter reported. The potential value of F waves is their ability to detect conduction slowing over the segments of nerve not tested by routine conduction velocity measurements, i.e., the proximal to elbow and proximal to knee segments. This value is most apparent early in the course of acquired demyelinating neuropathies, where prolonged F wave latencies may occur prior to slowing of conduction velocity or prolongation of distal latency. This pattern would suggest a demyelinating pathophysiology in a proximal location. In most cases however, F waves are either absent, or prolonged in the setting of slowed conduction velocities. Simultaneous slowing of conduction velocities and F waves has no localizing value, as the slowing of the F latency may represent pathology in the proximal nerve segment, distal or both.

The H reflex represents the electrophysiological analog of the Achilles deep tendon reflex. As in the F response, the stimulus applied to the tibial nerve in the popliteal fossa will travel in two directions. Unlike F waves, the H reflex is obtained with a submaximal stimulus intensity. With delivery of stimuli of low intensity and long duration, the lower-threshold sensory fibers within the tibial nerve are activated preferentially. As a result, this action potential is propagated centripetally or orthodromically along tibial and eventually sciatic sensory fibers. Entry through the dorsal root of the S1 segment allows completion of a monosynaptic reflex to S1 anterior horn cells. The H reflex produced technically represents a CMAP arising from the soleus muscle although it is rarely referred to as such. Typically, the H reflex has a latency in the high 20 to mid-30 microsecond range, depending on patient height.

As the intensity of the stimulus delivered to the tibial nerve increases, two things happen to explain H reflex behavior. Both of these phenomena aid in H reflex identification. With increasing stimulus intensity, action potentials will develop within tibial motor fibers. These travel in both an antidromic and an orthodromic direction. The orthodromic impulses will activate the soleus muscle producing a typical CMAP. This has a far shorter latency than the H reflex and does not typically make its appearance until the H reflex is well established. The antidromic action potentials created in tibial motor fibers have a different effect. These will collide with the orthodomic action potentials within motor fibers that create the H reflex somewhere between stimulus site and spinal cord. As the stimulus intensity increases, more antidromic tibial motor action potentials occur resulting in increasing collision. This results in a progressive decline and eventual disappearance in H reflex.

In summary, in response to sequential stimuli of 0.5–1 millisecond duration delivered to the tibial nerve in the popliteal fossa with increasing intensities, the H reflex appears first. Subsequently, the CMAP appears and enlarges to its supramaximal amplitude while the H reflex declines in amplitude and disappears. The tibial motor fibers distal to the stimulus site are depolarized twice, whereas both the tibial sensory fibers and the tibial motor fibers proximal to the stimulation site are depolarized once in response to a single stimulus (Fig. 2–6).

Both the maximal amplitude and the shortest latency of the H reflex can be measured. The former estimates the number of viable motor units and muscle fibers within the S1 segment/soleus muscle complex. The latter provides at least an estimate of conduction speed within the motor and sensory fibers of the S1 segment. As in case of F waves, H reflexes have greatest utility and localization value when these are abnormal in the setting of normal routine conduction parameters. This applies most frequently early in the course of acquired demyelinating polyneuropathies. In addition, these have value in the assessment of S1 radiculopathies. If an H reflex is absent more than a week after symptom onset in the setting of normal routine conduction parameters and reduced recruitment in S1 innervated muscles, proximal

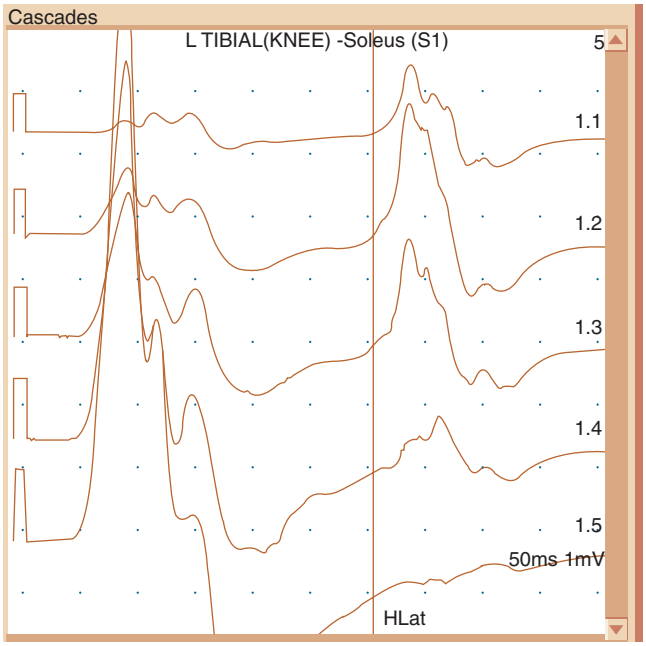


Figure 2–6. H reflex—five consecutive and increasing stimuli to the tibial nerve in the popliteal fossa in a normal individual, recording from the soleus demonstrating a typical H reflex pattern, i.e., H reflex amplitude initially > M response amplitude, subsequent peaking than decline, and eventual absence of H reflex, associated with gradual increase to supramaximal M response. Note uniform H reflex latency.

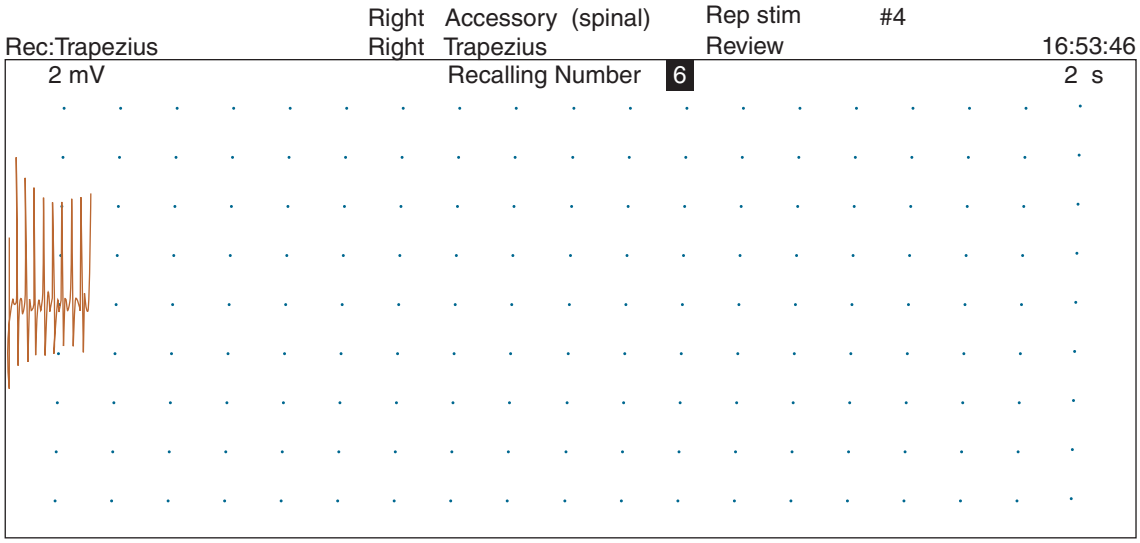
conduction block in the tibial nerve, sciatic nerve, sacral plexus, or S1 nerve root can be inferred. Focal slowing of nerve conduction in a proximal location is theoretically detectable by H reflex assessment. In reality, this slowing is usually obscured by normal conduction speed in the other normal and more extensive parts of the S1 reflex arc. Attempts to provide an anatomic diagnosis of a focal neuropathy or radiculopathy on the basis of by F and H responses alone should be discouraged.

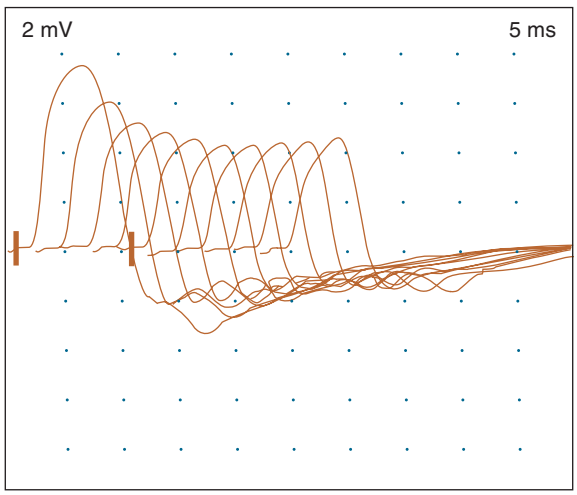
Repetitive Nerve Stimulation

RNS evolves from the understanding of the normal physiology of neuromuscular transmission. Muscle end-plate potentials (EPPs) are the precursors of muscle fiber action potentials. Unlike nerve or muscle action potentials that are all or none events that precede and follow EPPs respectively, EPPs are graded. Their amplitudes are proportionate to the number of successful interactions between cholinergic quanta and muscle end-plate receptor sites. Quantal release of acetylcholine (ACH) decreases with successive stimuli delivered in intervals of greater than 200 microseconds (<5 Hz). Under normal circumstances, this quantal and resultant EPP decline is of no practical importance, as there is an excess of presynaptic quantal release resulting in a considerable physiologic reserve. With disease states that alter either the presynaptic release of ACH or postsynaptic receptor responsiveness, this reserve may decline to the point of neuromuscular transmission failure at multiple neuromuscular junctions. As a result, slow (2–5 Hz) repetitive stimulation produces a successive decline in EPP, resulting in turn in a progressive decline or decrement in CMAP amplitude from its typically normal baseline (Fig. 2–7). This phenomenon may occur in either presynaptic or postsynaptic DNMT. To avoid false-positive results based on technical factors, a decrement of at least 10% is required to be considered abnormal. This decremental response is the electrophysiologic analog of the clinical manifestations of muscle fatigue and weakness.

It is important to be aware of the existence and the physiological basis of decremental morphology. Pathological decrements are not linear. Typically, the CMAP decline between two consecutive responses is greatest between the first and second stimuli and reaches its nadir by the fourth response. The reason for this phenomenon is the mobilization of ACH stores in the presynaptic neuron that allows delayed restoration of the immediate release pool. This allows for partial augmentation of the EPP after the fourth or fifth consecutive stimulus. With subsequent stimuli, the CMAP amplitude then begins to increase slightly although never reaches the size of the initial response. If a train of 8–10 stimuli are delivered, the resulting configuration will have an asymmetric saucer-like appearance, with the left edge being higher. This configuration is of particular importance in distinguishing variation in CMAP amplitude due to disease from that due to technical considerations.

The electrophysiologic basis of the incremental response is closely related to the role of calcium in the presynaptic release of ACH. When presynaptic ACH release is impaired by disease, it can be enhanced by augmenting the concentration of calcium in the presynaptic terminal. In a seemingly paradoxical manner, this can be accomplished by the delivery of sequential stimuli at high frequency or at intervals shorter than 200 microseconds, i.e., by stimuli delivered at rates in excess of 5 Hz. In presynaptic DNMTs, the baseline CMAP is typically reduced, at times dramatically. It can be increased by a factor of 2 or more by either "fast" repetitive stimulation (5–50 Hz) or, more humanely, 10 seconds of isometric exercise of the muscle in question followed by a second, rapidly delivered supramaximal stimulus (Fig. 2–8). The former technique is usually reserved for those individuals who cannot perform or cooperate with the postexercise technique. An incremental response is defined by a >100% increase in CMAP amplitude comparing the postexercise response to the baseline. The degree of increment is proportionate to the degree the baseline CMAP is reduced. In other words, the amplitude of the





Stim.Mode: Train / Single

Stim Freq:	3 Hz	No. in Train:	10
Stim Dur:	0.2 ms	Stim Rjct:	0.5 ms
Stim Site:			
Time:	16:51:22		
Comment:			

Pot no.	Peak Amp mV	Amp. Decr %	Area mVms	Area Decr %	Stim. level
1	7.61	0	45.20	0	36.1mA
2	6.18	19	33.30	26	36.1mA
3	5.13	33	28.10	38	36.1mA
4	4.84	36	25.80	43	36.1mA
5	4.47	41	24.20	46	36.1mA
6	4.51	41	22.40	50	36.1mA
7	4.33	43	22.20	51	36.1mA
8	4.50	41	22.30	51	36.1mA
9	4.42	42	22.30	51	36.1mA
10	4.66	39	22.80	50	36.1mA

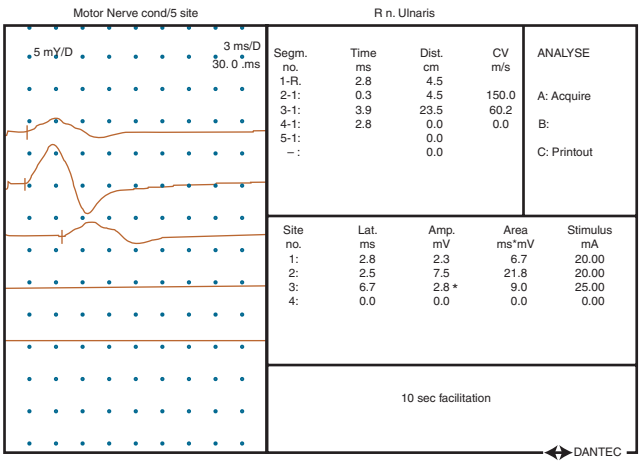
Figure 2–7. Decremental response to slow (3 Hz) repetitive stimulation with typical pattern in myasthenia gravis (note normal initial CMAP amplitude of 7.61 mV).

incremented CMAP cannot exceed the premorbid maximal CMAP amplitude of that muscle.

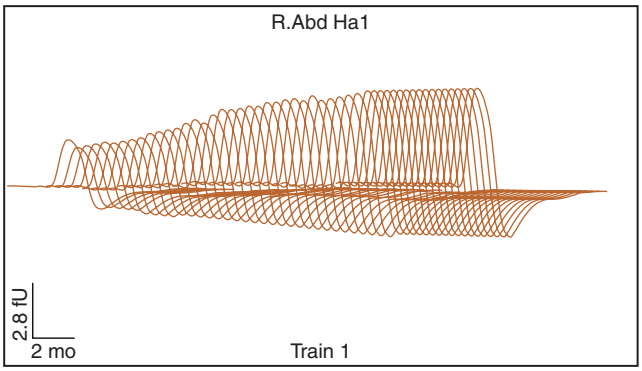
A so-called physiologic increment may occur in normal patients but typically does not exceed 40% of the baseline. Typically, the increased amplitude of a physiologic increment is associated with reduced CMAP duration, implying a more synchronous discharge of the component SFMAPs that constitute that CMAP waveform.

RNS is performed on motor nerves in a manner identical to routine motor conduction studies, with the exception of the manner of stimulus delivery. As mentioned above, the diagnostic yield of RNS will improve by ensuring that the tested muscle is warm and by removing drugs that augment neuromuscular transmission prior to testing. RNS often produces unwanted movement artifact, which may require limb immobilization in order to secure a technically reliable study. The electrodiagnostic approach to a suspected DNMT is dependent on the clinical context and on the initial, supramaximal CMAP amplitude. Presynapatic DNMT have electrophysiological properties that are both shared and distinct in comparison to their postsynaptic counterparts.

In suspected myasthenia gravis (MG) or when the initial CMAP amplitude is normal, a decremental response to slow repetitive stimulation is initially sought for. Ideally, it would be performed on a clinically weak muscle. The absence of decremental response to slow repetitive stimulation in such a muscle would preclude the diagnosis of autoimmune MG as the cause of that weakness. In general, distal nerves are technically easier but have a lower diagnostic yield, particularly in ocular and other limited forms of MG. If a decrement is demonstrated, the train of stimulation can be repeated



A



B

Figure 2–8. Incremental response to brief (10 seconds) exercise in patient with LEMS (A) (trace 1 ulnar CMAP at baseline stimulating at wrist, trace 2 ulnar CMAP immediately after 10 seconds of isometrically resisted finger abduction stimulating at wrist, trace 3 ulnar CMAP 1 minute later stimulating at elbow). Incremental response to 20 Hz fast repetitive stimulation (B). CMAP, compound muscle action potential; LEMS, Lambert–Eaton myasthenic syndrome.

following 10–15 seconds of exercise to look for postexercise facilitation or decrement repair. If a decrement is not demonstrable at baseline, repeating the train once a minute for 5 minutes following 1 minute of exercise applied to that muscle may improve diagnostic yield. This phenomenon is referred to as postexercise exhaustion. Presynaptic DNMTs also have a decrement with low rates of repetitive stimulation but are distinguished from MG on the basis of low baseline CMAP amplitudes. Although it does not define a presynaptic DNMT, a decremental response to slow repetitive stimulation may be easier to demonstrate early in the course of these disorders than its incremental counterpart, as the baseline CMAP amplitude may not have declined to the point where a significant increment is possible.

In a suspected presynaptic disorder or when the initial CMAP is reduced, an incremental response is initially sought by restimulating the nerve following 10–15 seconds of exercise.

Short- and Long-Exercise Tests

DNA mutational analyses for the nondystrophic ion channel disorders are not readily available. Short- and long-exercise tests have been developed in an attempt to identify the existence of and to differentiate between these sodium, chloride, and calcium channel disorders.[7,8] The short- and long-exercise tests are variations of standard motor NCS, typically using the ulnar nerve or common peroneal nerve recording from the abductor digiti minimi or extensor digitorum brevis muscles, respectively. Both exercise tests require careful attention to uniform patient positioning, limb temperature, muscle relaxation, and stimulus intensity.

The short-exercise test is performed by having a patient isometrically exercise the abductor digiti minimi or extensor digitorum brevis for 10 seconds, followed by sequential CMAP amplitude measurements obtained by single supramaximal (and nonvarying) stimuli delivered immediately after exercise and at 10-second intervals for a total of 50 seconds. Typically, repeated stimuli at 10-second intervals are delivered on a preliminary, pre-exercise basis to insure a stable baseline. After a 10-second rest between trials, two subsequent trials are recommended, which provide further discriminating value between different mutations and resultant phenotypes as subsequently described. This test has been further modified by using the same algorithm following limb cooling.[8]

In normal individuals, a transient increase in CMAP amplitude approximating 5% is noted immediately post exercise, without change in waveform morphology. The CMAP reverts to its baseline amplitude within 10 seconds post exercise. In studied normal patients, variations of the initial postexercise CMAP response were considered normal if within the −10% to +20% range of baseline CMAP amplitude, although no patient studied had a response greater than +14% or less than −6%.[7] Afterdischarges, as described previously in this chapter and subsequently in this section, are not expected in normal individuals.

In chloride channel disorders associated with myotonia congenita phenotype (MC), and to a lesser extent in sodium channel disorders producing PC, two distinct abnormalities can be observed.[7] One is a decline in postexercise CMAP amplitude, which is commonly in the 50% range and persists on average for 20–40 seconds in MC and in excess of 1 minute in PC. This phenomenon

has been demonstrated in 83% of patients with MC and 55% of patients with PMC with known mutations.[7] The other abnormal response is the presence of afterdischarges, also referred to in this case as postexercise myotonic potentials. There are typically two or three of these, which are much smaller than the original CMAP, decline sequentially in amplitude, and disappear after 10–30 seconds post exercise. These do not typically decrease with a train of 3 Hz stimuli delivered immediately post exercise. These have only been shown to occur in channel disorders associated with myotonia and do not typically occur in channelopathies manifesting only with the periodic paralysis phenotype.[7]

Conversely, the CMAP amplitudes typically increase post exercise in the short-exercise test in patients with sodium channel mutations producing the hyperkalemic periodic paralysis phenotype (hyperPP) and do not change in either the calcium (hypoPP-1) or the sodium (hypoPP-2) channelopathies producing the hypokalemic periodic paralysis phenotypes. In the case of hyperPP, 83% of affected individuals will have a significant (>20%) increase in their immediate postexercise CMAP that typically persists for more than a minute.[7]

Sequentially performed, repeated postexercise trials appear to have additional discriminating value. In hyperPP, CMAP amplitudes continue to increase with the second and third trials. With at least one PMC genotype, CMAP amplitudes decline further with subsequent trials, whereas in MC, the initial postexercise decline is repaired with CMAP normalization with subsequent trials. Conversely, the CMAP reduction gradually normalizes in chloride channel disorders. Repeated trials result in disappearance of afterdischarges in those disorders in which these occur.

Progressive muscle cooling may add further discriminating value.[8] Cooling results in a progressive decline in CMAP amplitude associated with a progressive increase in CMAP duration in response to single stimuli delivered without exercise in a progressively cooled limb. This phenomenon occurs in normals as well as in individuals with chloride channel mutations causing myotonia congenita (MC) and sodium channel mutations resulting in PMC. With the application of cold and repeated short exercise to patients with PMC, the decline in CMAP amplitude is exaggerated so that the degree of CMAP reduction following the first postexercise trial with cold is of similar magnitude to the response after the third trial with normal limb temperatures. In some patients with PMC, the response to repeated short exercise may mimic the response seen in patients with MC whose limbs are warm but revert to a more typical PC pattern when the limbs are cooled, that latter pattern being worsening CMAP decline with subsequent postexercise trials.[8]

In patients with chloride channel disorders, the response to three consecutive trials of short exercise was similar in pattern in cold limbs as opposed to those that were warm. The magnitude of the CMAP reduction was amplified in cold limbs, however, in individuals with dominant as opposed to recessively inherited forms of MC. In patients with some sodium channel genotypes that produce neither a PMC hyperPP, nor a hypoPP(2) phenotype, repeated postexercise testing will produce a pattern reminiscent of PC rather than the characteristic lack of response with warm limb temperatures.

The long-exercise test involves isometric contraction of the tested muscle for 5 minutes with 3–4-second periods of rest at 30–45 seconds intervals. CMAP amplitudes in response to single, supramaximal stimuli that do not change in intensity are recorded every minute during exercise, immediately post exercise, every minute for the initial 5 minute postexercise period, and finally every 5 minutes for 40–45 minutes. The normal pattern is a mild decrease of CMAP amplitude of approximately 5% with a greater increase in duration and area that occurs immediately post exercise and then normalizes within the following minute and remains unchanged for the remainder of the test.[7] Amplitude responses that do not fall outside the −20% and +10% range are considered normal.

Abnormal responses to long-exercise testing occur in both the nondystrophic myotonic and the periodic paralysis phenotypes. Their patterns are fairly distinctive and homogeneous. With the chloride channel disorders, an immediate but small decline in CMAP amplitude occurs in some patients, which tends to rapidly normalize. Patients with PMC tend to have a significant immediate postexercise CMAP amplitude decline. It averages about 66% and persists for at least half an hour although tends to gradually improve throughout that time period. Patients with other sodium channel nondystrophic myotonia phenotypes such as potassium-associated myotonia have normal responses mimicking controls. Patients with periodic paralysis phenotypes tend to have significant CMAP amplitude reductions. The pattern of this decline appears to be distinctive for different genotypes. With sodium channel hyperPP genotypes, the decline begins immediately or soon after exercise is completed. With hypoPP-1, the CMAP amplitude decline tends to be delayed in onset but just as severe and persistent. The CMAP amplitude decline in hypoPP-2 tends to be delayed and less severe than either its hyperPP or its hypoPP-1 counterparts. The CMAP amplitude loss in hyperPP can be partially repaired by an imposed period of short exercise.[7] Table 2–1 summarizes the correlations between phenotype, ion channel mutation, and electrophysiological profile.

▶ **TABLE 2–1. SHORT- AND LONG-EXERCISE TESTS IN THE NONDYSTROPHIC MYOTONIAS AND PERIODIC PARALYSES**[7]

Phenotype	Channel	Short-Exercise Test	Afterdischarges	Response to Repeat Short Exercise	Response to Cooling and Repeat Short Exercise	Long Exercise	Myotonic Discharges on EMG
Myotonia congenita	Chloride	↓ CMAP amplitude	Yes	Repair of CMAP amplitude	Exaggerated ↓ CMAP amplitude in AD genotypes	No significant change	Yes
Paramyotonia congenita	Sodium	↓ CMAP amplitude	Yes	Further CMAP amplitude ↓	Exaggerated ↓ CMAP amplitude	↓ CMAP amplitude	Yes
Other sodium channel myotonias	Sodium	No change	No	No change	↓ CMAP amplitude similar to PC	No change	Yes
Hyperkalemic periodic paralysis	Sodium	↑ CMAP amplitude	No	Further CMAP amplitude ↑	?	↓ CMAP amplitude immediately	Yes
Hypokalemic periodic paralysis hypoPP-1	Calcium	No change	No	NA	?	↓ CMAP amplitude—delayed	No
Hypokalemic periodic paralysis hypoPP-2	Sodium	No change	No	NA	?	↓ CMAP amplitude—delayed	No

EMG, electromyography; CMAP, compound muscle action potential.

Motor Unit Number Estimates

Considerable motor unit loss can occur without clinically evident weakness. This is particularly true in slowly progressive disorders where collateral sprouting and reinnervation are at least partially compensatory. In patients with ALS, it has been shown that the CMAP amplitude may not reliably decline until the estimated number of motor units drops below 10% of normal.[10]

Numerous motor unit number estimation (MUNE) techniques have been developed in an attempt to count the number of viable motor units in a given muscle.[11] This has been done with the belief that MUNE would represent a more accurate means to monitor disease course or to detect a response to treatment than measurements of strength. MUNE is, in large part, a research technique, with limited application in the daily practice of neuromuscular disease. It tends to be time consuming and, to some extent, technically limited. Unlike standard EDX techniques, which can offer a panoramic perspective on multiple nerves and multiple muscles, MUNE is typically done on one or a limited number of nerves in a single setting. In addition, individual techniques have their limitations including the nerve/muscle pairs that are accessible to them.[11]

MUNE has probably been most frequently used in the ALS population and has been successfully used in at least two clinical trials.[12–14] Multiple authors have demonstrated that MUNE drops and the size of individual MUPs increases sequentially in patients with ALS, consistent with the progressive denervation and reinnervation that typically occur in this disorder.[10,13–18]

NEEDLE EMG

Spontaneous Activity

Needle EMG is performed by inserting a recording electrode into muscle, typically one at a time, and assessing that muscle's electrical activity. EMG is interpreted by determining the type of abnormality within a specific muscle, identifying the pattern of muscles in which those abnormalities occur, and then correlating these results with those of NCS. Muscles are typically evaluated under three conditions: at rest, with minimal voluntary activation, and with maximal or near-maximal muscle activation. At rest, the electromyographer searches for abnormal spontaneous activity. With the exception of end-plate spike and noise created by miniature end-plate potentials, the normal muscle is electrically silent in the absence of needle movement. There are a number of abnormal waveforms that may occur, including fibrillation potentials, positive sharp waves (both of which together have been referred to as denervation potentials), myokymic discharges, myotonic discharges, complex repetitive discharges, and neuromyotonic discharges (Figs. 2–9 to 2–13). Of these, fibrillation potentials and positive sharp waves are the most prevalent. Fig. 2–9 When present, these suggest that anatomic continuity has been lost between a muscle fiber and its innervating axon. As described below, this is unlikely to be the sole explanation for their occurrence. Fibrillation potentials and positive waves occur most commonly in association with axon loss. This axon loss may result from disease anywhere between anterior horn cell and terminal nerve

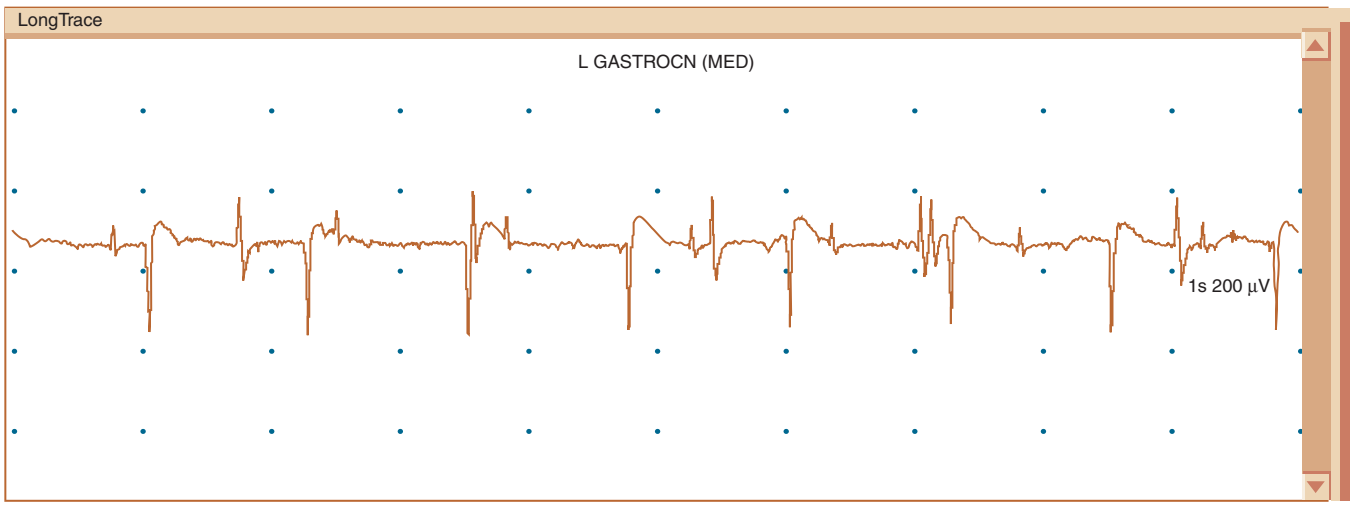


Figure 2–9. Fibrillation potentials and positive waves—single action potentials that usually fire with metronomic frequency; fibrillation potentials have short duration, positive waves with characteristic configuration and longer duration. The sound produced by fibrillations can be described as a "ticking." Positive waves have a more nonspecific, duller sound than fibrillation potentials, with recognition based more on their firing pattern and characteristic shape. These waveforms may occur in isolation or concurrently as in this figure.

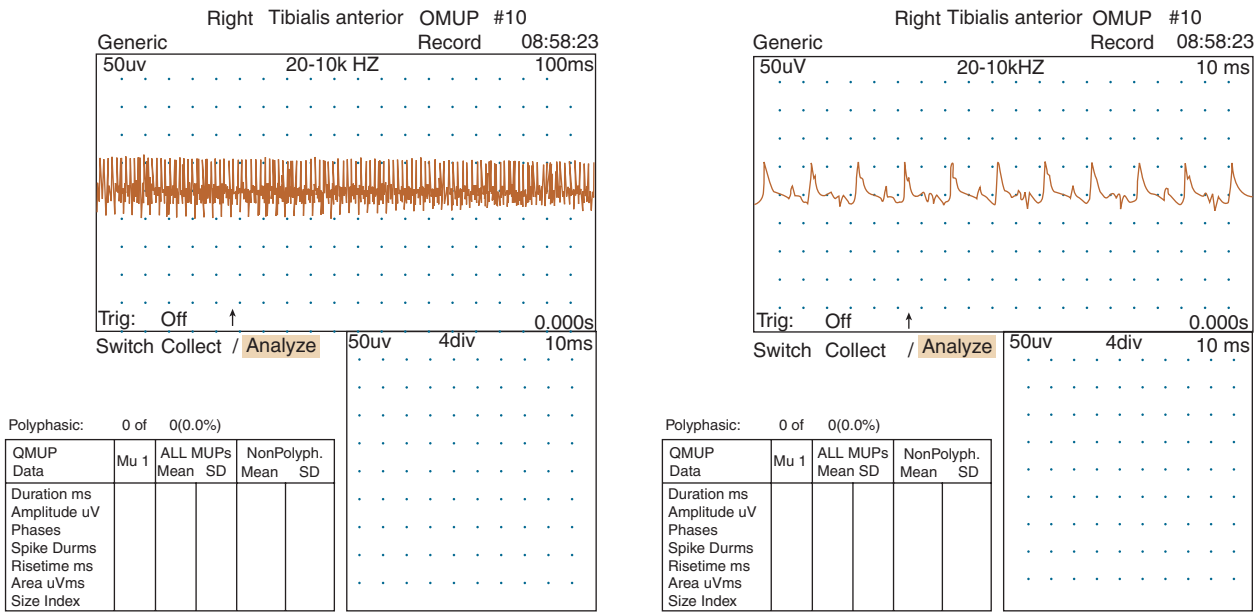


Figure 2–10. Complex repetitive discharges—a discharge with abrupt onset and cessation, the sound produced frequently described as "machinery like."

twig. These denervation potentials are not specific for axon loss. They may be observed in both DNMT and certain muscle diseases. In both cases, effective denervation occurs even in the presence of normal nerves. In the former, the axon may be effectively separated from its target muscle by ablation of the neuromuscular junction. In myopathy, particularly those associated with segmental necrosis of muscle, viable segments of muscle may be separated from segment of muscle containing the neuromuscular junction, effectively denervating segments of viable muscle. It is in muscle disease, however, where the denervation paradigm becomes flawed in its attempt to explain the presence of fibrillation potentials and positive waves. There are a number of myopathies, notably the channelopathies, and some of the congenital and mitochondrial myopathies, where these forms of abnormal spontaneous activity occur in the apparent absence of denervating mechanisms. Presumably, muscle membrane instability provides an alternative explanation for this form of waveform generation.

Other forms of abnormal spontaneous activity are less common. Complex repetitive discharges are

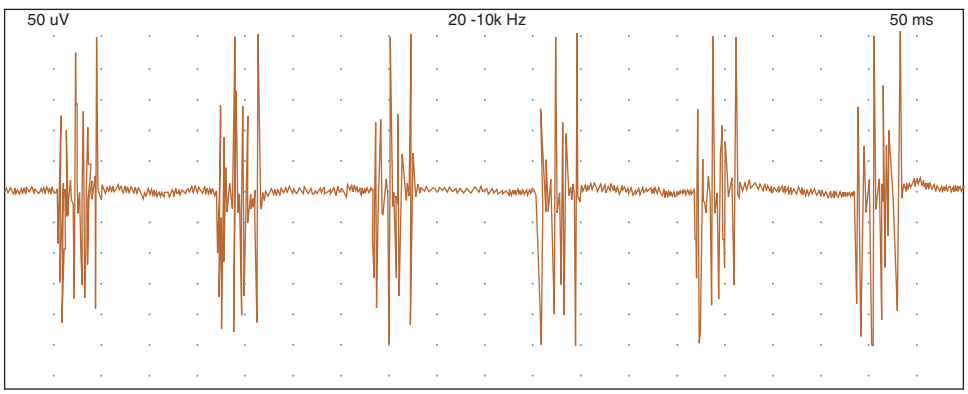


Figure 2–11. Myokymic discharges—semirhythmic grouped discharges, the sound produced frequently likened to the troops marching. (Reproduced with courtesy permission of Dr. Devon Rubin, Mayo Clinic, Jacksonville.)

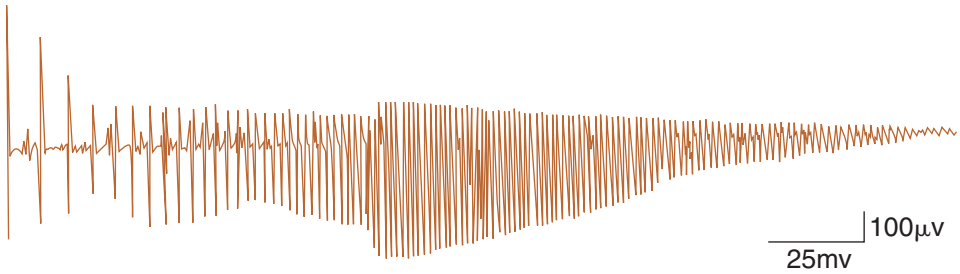


Figure 2–12. Myotonic discharges—with variable waveform amplitude and frequency, producing a waxing and waning discharge likened to an accelerating and decelerating chain saw or motorbike motor.

nonspecific and occur in both chronic nerve and muscle disorders (Fig. 2–10). Complex repetitive discharges have a machinery-like sound that typically starts and stops abruptly. These are thought to originate from a reverberating circuit that develops within contiguous myofibers. Myokymic discharges are grouped discharges of two or more MUPs that fire repeatedly in a semirhythmic manner with interval gaps of electrical silence. The sound produced has been likened to troops marching. These originate from peripheral nerve and probably result from ephaptic transmission between injured, contiguous axons. Myokymic discharges can be seen in a number of different etiologies of nerve disease (Fig. 2–11). These may be associated with disorders as mundane as carpal tunnel syndrome or as unusual as rattlesnake envenomation. In the cranial musculature, these are most commonly associated with multiple sclerosis, GBS, and brainstem neoplasms. These are common in disorders of neural overactivity such as the cramp fasciculation and Issacs' syndrome. These are most notorious as a marker of radiation-induced nerve injury.

Myotonic discharges originate from muscle and are primarily associated with heritable but occasionally acquired muscle disease (Fig. 2–12). These produce a waxing and waning sound historically likened to a dive bomber. From a more contemporary perspective, a revving chain saw or motor bike may represent a more apt simile. Myotonic discharges do not sustain themselves and typically dissipate until such time that they are provoked by the next needle movement or muscle contraction. Their presence often obscures the ability to adequately study MUPs or other forms of abnormal spontaneous activity. Myotonic discharges are the major EDX signature of myotonic muscular dystrophies: PMC and MC. These are also seen in certain glycogen storage disorders, most notably acid maltase, branching and debranching enzyme deficiencies, myofibrillar myopathy, and hyperkalemic periodic paralysis, and occasionally in toxic and inflammatory myopathies (Table 2–2).

Neuromyotonic discharges are infrequently seen (Fig. 2–13). Their duration is brief as their high frequency (150–300 Hz) precludes them from sustaining themselves for protracted periods. The sound these create has been likened to the scream of a formula-one race car engine. These are most closely linked to the disorder known by the names neuromyotonia, Issacs' syndrome, or the syndrome of continuous muscle fiber activity. These can be occasionally seen in other nerve disorders. An analogous discharge, the neurotonic

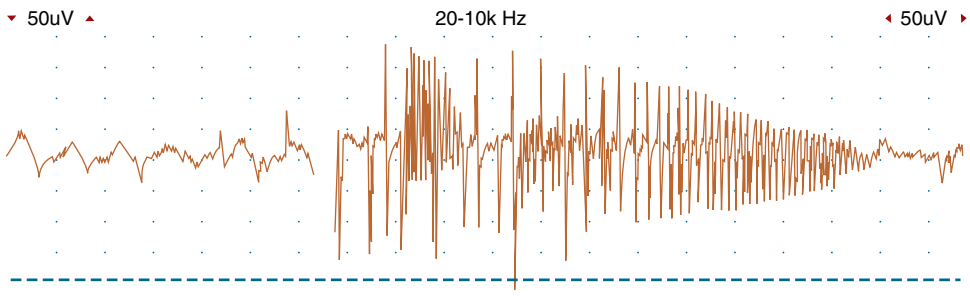


Figure 2–13. Neuromyotonic discharges—very high-pitched discharges with sound likened to "screaming formula one race car" engine. (Reproduced with courtesy permission of Dr. Devon Rubin, Mayo Clinic, Jacksonville.)

TABLE 2–2. DISORDERS ASSOCIATED WITH MYOTONIC DISCHARGES

Myotonic muscular dystrophy types 1 and 2
Myotonia congenita
Paramyotonia congenita
Hyperkalemic periodic paralysis
Azacholesterol
Monocarboxylic acids
Colchicine myopathy
Cholesterol lowering agent myopathy
Hypothyroidism
Inflammatory myopathies (rare)
Acid maltase deficiency
Branching enzyme deficiency myopathy
Debranching enzyme deficiency myopathy
Hereditary vacuolar myopathies (Danon disease and x-linked myopathy with excessive autophagy)
Myofibrillar myopathy and other distal myopathies with rimmed vacuoles
Welander myopathy

discharge, may be recorded from muscles during intraoperative monitoring procedures as an indicator that the innervating nerve has been irritated.

Motor Unit Analysis

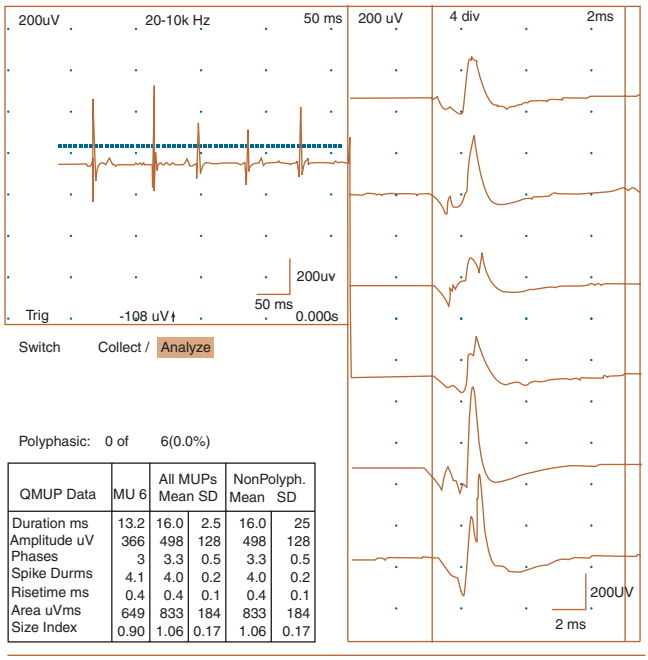
The purpose of examining the muscle under conditions of minimal voluntary activation is to assess the morphology of individual MUPs. The motor unit consists of an anterior horn cell, its axon, and all of the muscle fibers it innervates. The MUP refers to the single fiber action potentials, arising from the muscle fibers of that MUP, that are within the recording radius of the needle. MUPs become smaller when there is a loss, or effective loss, of muscle fibers within the motor unit. This typically occurs in disorders of muscle and neuromuscular transmission. In the former, the number of fibers within the motor unit decreases as a result of myofiber degeneration. Alternatively, the size of the action potential that each fiber generates decreases as a result of myofiber atrophy. In DNMT, the amplitude and/or duration of the MUPs may decrease from blockade of neuromuscular transmission, effectively reducing the number of single fiber muscle action potentials (SFMAPs) contributing to that MUP.

Conversely, MUPs typically become larger following chronic denervation and reinnervation. An orphaned muscle fiber deprived of its axon supply may be reinnervated and effectively adopted by a collateral nerve twig belonging to a neighboring viable motor axon. As a result, surviving motor units in the aftermath of axon loss will typically grow both in amplitude and in duration, typically within months after an insult occurs or begins. MUP morphology does not change in a substantive manner in a purely demyelinating nerve disorder, although both increased duration and polyphasia may result from variable conduction slowing in terminal nerve twigs.

MUPs typically have triphasic configurations, although MUPs with a few extra turns or phases are not rare. A polyphasic or serrated MUP morphology implies that, for whatever reason, the individual SFMAP components of that MUP have become desynchronized. Polyphasic MUPs have nonspecific significance. If pathologically based, these imply that the process is subacute, i.e., of weeks' to months' duration. Mildly polyphasic units infrequently occur in normal muscles. Polyphasic MUPs can be seen in myopathies, axon loss, and demyelinating nerve disease. Polyphasic motor units will eventually reconfigure themselves into a triphasic configuration, even in those MUPs that have been exceptionally enlarged as might occur, e.g., in remote polio.

The concepts outlined in the preceding three paragraphs are generally accurate but have exceptions. Large motor units reminiscent of denervation occur in chronic myopathies.[19] Conversely, in certain axon loss disorders, small motor units referred to nascent units may be seen. These occur because of a concomitant reduction in MUP size and MUP number. A severe monophasic nerve injury where early reinnervation allows for only a limited number of myofibers to be initially incorporated into the motor unit is probably the most common situation in which nascent units occur. These may also be seen in rapidly evolving denervating disorders in which effective reinnervation does not occur, and in which degeneration of terminal twigs occurs early in the disease course. The familial form of ALS associated with the A4V mutation of the SOD1 gene is perhaps the most notable example of this latter mechanism. In either case, small motor units from nerve and muscle disease may be distinguishable by their characteristic recruitment patterns as described below.

MUP variability or instability refers to the alteration of MUP morphology on consecutive discharges (Fig. 2–14). Under normal circumstances, all of the single fiber action potentials of a given motor unit discharge concordantly with each action potential of the parent axon. As a result, as long as the needle position is stable, the MUP will have an identical configuration each time it discharges. With disordered neuromuscular transmission, transmission at one or more individual neuromuscular junctions may be delayed or actually fail. As this is a dynamic process affecting different neuromuscular junctions with consecutive discharges, the configuration of the MUP may change quite dramatically. Variability of amplitude is best demonstrated by having the patient minimally activate the muscle being tested, in



QMUP Data	MU 6	All MUPs Mean	All MUPs SD	NonPolyph. Mean	NonPolyph. SD
Duration ms	13.2	16.0	2.5	16.0	25
Amplitude uV	366	498	128	498	128
Phases	3	3.3	0.5	3.3	0.5
Spike Durms	4.1	4.0	0.2	4.0	0.2
Risetime ms	0.4	0.4	0.1	0.4	0.1
Area uVms	649	833	184	833	184
Size Index	0.90	1.06	0.17	1.06	0.17

Figure 2–14. Motor unit potential (MUP) variability.

order to isolate an individual MUP while using slow sweep speeds (50–100 ms/division). This allows the examiner to visualize the same MUP multiple times on the same screen. Variability in configuration is best seen with fast sweep speeds (1–5 ms/division), which will enhance the detection of MUP morphological changes. MUP variability is best known as an EDX feature of DNMT. It can often be seen, if looked for, in early reinnervation where neuromuscular junctions are immature. Traumatic nerve injury and ALS are notable examples.

Motor Unit Recruitment

Finally, the examiner attempts to estimate the number of MUPs that the patient is capable (or willing) to activate. This is done by having the patient gradually increase the amount of isometric tension in the muscle being tested. Under normal circumstances, an increasing number of MUPs will be recruited, i.e., seen and heard on the EMG machine display. Each has its own distinctive sound and configuration as the makeup and geographical location of each MUP and its relationship to the recording electrode differs for each MUP with each distinct needle placement.

In axon loss, and in demyelinating neuropathies with conduction block, there are a reduced number of motor units or motor units that can be recruited. As a result, the remaining activatable MUPs that fire do so with a greater frequency than normal, in an attempt to compensate for MUP loss. Reduced recruitment, as this is called, is indicative of either motor unit loss or inactivation resulting from demyelinating conduction block. Reduced recruitment is one cause of a reduced interference pattern, but the two terms are not synonymous. A reduced interference pattern may also occur as a result of a patient's inability or unwillingness to fully activate all MUPs at their disposal due to disorders of the central nervous system, pain, or malingering.

There are many strategies that have attempted to quantitate MUP loss. More often than not, reduced recruitment is subjectively estimated. The ear is quite sensitive in detecting rapidly firing MUPs in response to MUP loss. With full recruitment resulting in a full interference pattern, there will be an amorphous blending of the sound created by all activated motor units. With reduced recruitment, rapidly firing individual MUPs can be detected by hearing the distinctive sound that each MUP firing at an accelerated pace produces. This effect has been likened to the sound produced by a baseball card placed in the spokes of a child's moving bicycle.

There are more objective methods to be applied when reduced recruitment is not overtly obvious by scanning. These include quantitation of recruitment onset and recruitment ratio. Recruitment onset requires that the electromyographer counts the number of individual units as well as the firing frequency of each activated unit. The rule of fives is applied to determine whether recruitment is decreased. With minimal effort the first MUP is recruited at a low rate, usually around 5–7 Hz. As the patients increase their efforts, the initial MUP fires faster until a second unit is recruited. The frequency at which the second unit is recruited is termed the recruitment-onset frequency and is normally around 10 Hz. If a single MUP is firing at greater than 15 Hz and no other MUP is recruited, this is an objective measure of decreased recruitment. The recruitment ratio can be calculated as an alternative objective recruitment measurement. This involves taking the average firing rate of the units seen and dividing it by the numbers of individual units activated. A normal recruitment ratio should be 5 or less, with >10 being definitely abnormal. For example, if one MUP is seen firing at 15 Hz, one at 10 Hz, and one at 5 Hz, then the recruitment ratio is 3.3, which is normal.

In myopathies or DNMT, the problem is not a reduced number of motor units but reduced MUP size. As the amount of force generated by individual MUPs is often reduced, more motor units need to be recruited earlier than normal to generate the same amount of force. The firing rates of these MUPs remain normal. This effect has been termed as early or increased recruitment. In general, increased recruitment, proportionate to effort rendered, is a subjective and fairly insensitive EDX

measure and is usually not recognized until other EDX features of muscle disease are evident.

SFEMG and Other Specialized Techniques of Motor Unit Analysis

SFEMG has a number of potential applications. Its primary clinical application is to enhance the sensitivity of DNMT testing. Unfortunately, what it offers in sensitivity, it lacks that in specificity. For this reason, its greatest utility lies in its ability to discriminate between subtle presentations of DNMT from non-neuromuscular diseases. Its value in distinguishing one neuromuscular disorder from another is somewhat limited. It can be argued, however, that large jitter values associated with frequent neuromuscular blocking would be less likely to occur from diseases of anterior horn cell, nerve, or muscle. The enhanced sensitivity of SFEMG pertains to its ability to detect early abnormalities in neuromuscular transmission, which reflects delay rather than failure in neuromuscular transmission. As a result, SFEMG abnormalities may be detected in muscles that are not clinically weak. Neuromuscular transmission failure or blocking, as it is commonly called, is the neurophysiological analog of the decremental response sought with slow repetitive stimulation and is the basis of clinical fatigue and weakness. Additionally, because SFEMG is a needle rather than nerve conduction technique, the anatomic limitations are less than those imposed by RNS.

The basic goal of SFEMG is to capture and analyze two or more SFMAPs belonging to the same MUP. In order to do so, it is necessary to limit MUP recruitment to see, hear, and cleanly record these SFMAPs. In cooperative patients, this can be accomplished on a voluntary basis. In patients who are unable to activate a limited number of MUPs and maintain a stable level of recruitment for any reason, stimulated SFEMG, as described below, may well represent a better option. Historically, there are two significant technical differences between SFEMG and standard EMG recordings. Both involve limiting the recording radius so as to facilitate SFMAP acquisition and analysis. The first involves increasing the low-frequency (high-pass) filter setting to 500 Hz. The second is the use of a special SFEMG needle whose recording radius is smaller than its concentric or monopolar counterparts. In part due to the cost and inconvenience involved in the use of SFEMG needles that need to be both repeatedly sterilized and sharpened, electromyographers have begun to use standard, disposable concentric EMG needles for this purpose. Normative jitter data for concentric needles are approximately 5 microseconds less at any given age for any given muscle, in comparison to published norms using SFEMG needles (Sanjeev Nandedkar, personal communication).

The primary parameter measured by SFEMG is jitter that refers to the variation in the interval between two or more SFMAPs belonging to the same MUP. Jitter is a normal property of neuromuscular transmission. Its physiological basis is derived from the same variation in EPP resulting from consecutive nerve action potentials as was described in the section on RNS. The key to understanding jitter is derived from the observation that the slope of a membrane potential as it moves between its resting position and the muscle fiber's action potential threshold is proportionate to the size of the EPP. In other words, the higher the EPP, the steeper the slope and the shorter the interval between nerve and muscle fiber action potentials. As a result, the interval between consecutive discharges of two SFMAPs belonging to the same motor unit will fluctuate with the normal variation in quantal ACH release and EPP amplitude.

In practice, these two (or more) SFMAPS are captured by using a triggered delay line that will allow the electrodiagnostician to carefully manipulate the EMG needle until it is within an acceptable recording distance from an SFMAP. This is determined by the listening for the crisp sound that this SFMAP generates and then confirming the proximity by assuring that the rise time is less than 300 microseconds and the amplitude is greater than 200 microvolts. Typically, this is done with a sweep speed of 1 ms/division and a gain of 100–200 μV/division.

Once this SFMAP is isolated, subtle movements of the electrode are made in an attempt to find a second SFMAP belonging to the same motor unit, identified by its "time-locked" characteristics. Ideally, a steady, low level of contraction will allow the recording of a hundred consecutive discharges of this pair. At least 50 of these 100 discharges must originate from the fiber pair being studied for statistical purposes, as these hundred consecutive discharges may be contaminated by other MUPs other than the one being studied. Using a delayed trigger line will allow the SFMAP to appear on the screen in the exact same superimposed position. Under normal circumstances, the second potential of the pair will fire at slightly variable times (normal jitter) for the reasons described above, with waveforms representing the second of the two SFMAP waveforms being close to one another but not perfectly superimposed (Fig. 2–15a). The interval between the two (or more) spikes should be far enough apart to be measurable but not farther than 4 milliseconds, for purposes of measurement accuracy.

This variation in interpotential interval is usually expressed as the mean consecutive difference (MCD), a calculation readily computed by most contemporary EMG machines. The mean sorted difference (MSD) is also calculated and is a more accurate measure of jitter if the MCD/MSD ratio exceeds 1.25.

Assuming constant positioning of the needle in relationship to the muscle fiber pair, there are five normal physiological and anatomical factors that contribute to

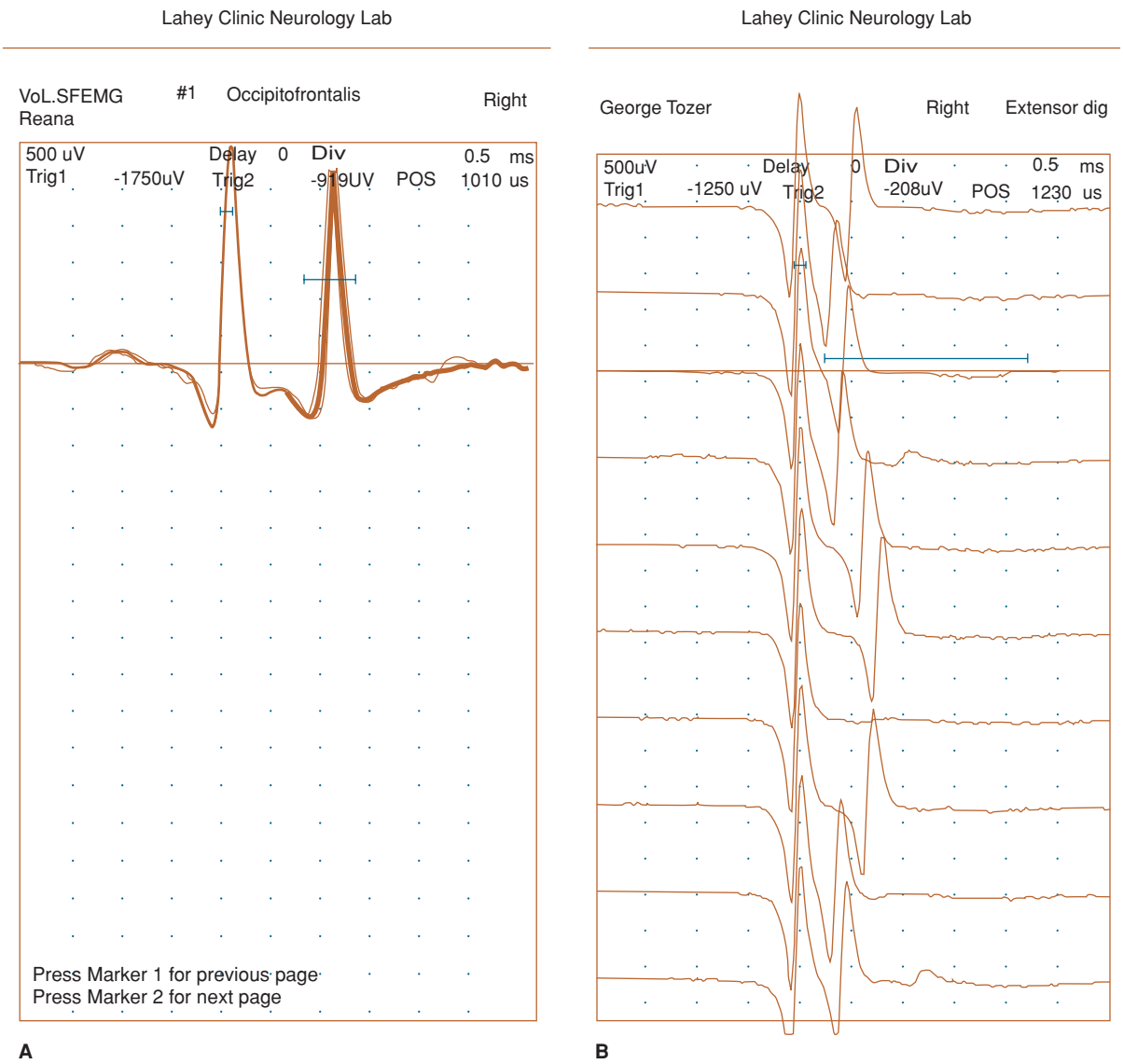


Figure 2–15. Single fiber electromyography demonstrating a normal recording (left) and increased jitter and blocking (right—seventh pair from top—arrow).

the interpotential interval: (1) the length of the terminal twigs, (2) the conduction velocity of the terminal twigs, (3) neuromuscular transmission time, (4) the distance between muscle fiber and recording needle, and (5) the velocity of muscle fiber action potential propagation. Of these, only three are physiological and therefore potentially capable of varying from discharge to discharge. As long as firing rate is kept relatively constant, and the interpotential interval does not exceed 4 milliseconds, jitter occurs almost exclusively on the basis of variable neuromuscular transmission time.

Normal values for jitter vary with patient age and muscle selected but are typically in the 15–45-microsecond range for 20 fiber pairs, the number that are usually acquired and analyzed to provide adequate statistical significance. As the need to acquire this amount of data of stems from the observation that MG can be as patchy electrophysiologically as it is clinically. Abnormally high jitter values can also be declared if 10% or two of 20 fiber pairs have jitter values that exceed a second higher set of normative values that are also age and muscle specific. The benefit of this second set of norms is that it allows this sometimes labor-intensive test to be terminated early if the test is strikingly abnormal.

Abnormally low jitter values are also potentially pathological. As an example, it has been described in disorders associated with myofiber splitting. Reduced jitter is uncommonly recognized as disorders with reduced

jitter values are uncommonly tested with this methodology.

The second parameter that is typically sought for is neuromuscular blocking. Blocking does not typically occur until jitter values are high, typically with MCD values in excess of 100 microseconds. Blocking is recognized when a triggering potential, identical in morphology to previous and successive triggering potentials, is unaccompanied by a second, time-locked SFMAP (Figure 2–15b). It is of course possible that the triggering potential itself is blocked, but it is likely that this occurrence would go unrecognized. Blocking rarely occurs in seemingly normal, older individuals.

Another parameter that can be measured by the SFEMG needle is fiber density, the electrophysiological analog of reinnervation and the type grouping seen on muscle biopsy. Fiber density is not as commonly used as a clinical tool as are assessments of jitter and blocking. Under normal circumstances, a random placement of the SFEMG needle will reveal only a single fiber action potential from a given motor unit 60% of the time. A couplet, as sought after for jitter measurements, will be identified in 35% of insertions and a triplet only 5% of the time. The technique for fiber density determination differs slightly from jitter measurements. The SFEMG needle is manipulated so as to obtain maximal amplitude from the first single fiber action potential that is obtained. Once that is accomplished, the number of single fiber potentials, regardless of size, that are time linked to the index potential is counted. This is done for at least an additional 19 potentials. The total number of fiber potentials is then divided by the number of test sites. For example, if 30 potentials are identified at 20 sites, the fiber density will be 1.5. Fiber density is considered an index of successful reinnervation and differs from jitter, which in denervating diseases is considered an index of immature reinnervation. Contrasting jitter values with fiber density values is one way to estimate how complete the reinnervation process is. High fiber density values with normal jitter are an indication that the reinnervation process has matured. Normative values for fiber density again vary with patient age and muscle selected and are based on measurements made with SFEMG needles.

There is another form of SFEMG referred to as stimulated SFEMG. In this technique small electrical stimuli are delivered, by a needle electrode, to a nerve fiber within the tested muscle. Jitter is then recorded from a single muscle fiber innervated by the same nerve. There are both advantages and disadvantages of this technique. As it does not depend on voluntary muscle activation, it is more readily performed on those who cannot (or will not) cooperate. As the stimulus rate does not vary as opposed to voluntary activation, a spurious MCD value secondary to varying firing rates will not occur. The time-consuming effort of finding a fiber pair is removed from consideration. Drawbacks include the recognition that normal values for jitter are less than voluntary SFEMG. The optimal frequency of stimulation has to be adjusted to ensure accurate jitter measurements; too low a rate of stimulation will produce falsely high MCD values. There is also the possibility of falsely reduced jitter values if the muscle fiber is stimulated directly, eliminating neuromuscular transmission from the equation.

There are other EMG techniques that are uncommonly used in clinical settings. Macro EMG involves the use of a specialized needle with multiple recording ports. This allows waveform acquisition over a far wider recording radius than with conventional concentric or monopolar EMG needles. Macro EMG is used primarily in research settings to assess the size and distribution of SFMAP components of MUPs.

MUPs of increased duration and amplitude are often so strikingly different from normal MUPs that these may be readily identified by subjective means. The distinction between normal MUPs that are small and pathological MUPs that are reduced in amplitude and duration is more difficult to subjectively assess. MUP analysis or quantitation is a technique that has been used to objectively measure the average amplitude and duration of a population of MUPs. An abnormal result is determined by comparison of the average size of an MUP in a studied muscle to normative data. These norms account for MUP size variability based on patient age and muscle selected. MUP quantitation may be used as both a clinical and, more commonly, a research tool in laboratories that offer it.

THE PATHOPHYSIOLOGY OF NERVE INJURY—ELECTRODIAGNOSTIC AND CLINICAL CORRELATES

The pathophysiology of peripheral nerve lesions can be inferred from EDX data, as can the clinical symptoms that the pathophysiological process produces. Four different pathophysiologies can be considered from an EDX perspective, axon loss, and three forms of demyelination. The latter have been referred to as focal or uniform slowing, differential slowing also known as temporal dispersion, and conduction block. More than one of these mechanisms may coexist with any given disease or injury. There is a fifth pathophysiology of nerve to consider from at least a theoretical if not a practical basis, that being disordered function of ion channels. Certain marine toxins and potentially some drugs such as phenytoin may affect peripheral nerve adversely by this mechanism.

Loss of CMAP and SNAP amplitudes are the primary nerve conduction manifestations of axon loss. With axon loss, conduction slowing may occur if the largest, fastest

conducting axons degenerate. Conduction slowing tends to be modest in primarily axon loss disorders. In pure axon loss, focal conduction abnormalities do not occur. The needle examination in axon loss is characterized by abnormal spontaneous activity within 1–3 weeks of disease-onset, reduced motor unit recruitment immediately and enlarged, reinnervated MUPs within a matter of months. Axon loss leads to muscle atrophy and weakness, loss of all sensory modalities, and loss of deep tendon reflexes within the territories of nerves that are affected.

Demyelination may cause uniform slowing of nerve conduction. Conceptually, in uniform slowing, conduction is slowed equally in all fibers within the affected segment of nerve. As all impulses traverse the affected portion of nerve synchronously, the only clinical consequence of such a lesion is paresthesia, with or without pain. Uniform slowing may occur in a focal segment of nerve as a consequence of mechanical injury. It is a common EDX signature of carpal tunnel syndrome and some ulnar neuropathies. It may occur along the entire course of multiple nerves in the hereditary demyelinating and dysmyelinating disorders. It may occur as a consequence of disordered ion channel function as well. Historically phenytoin, a sodium channel blocker, was identified as the cause of peripheral neuropathy. This association seems to be based predominantly, if not solely, on the basis of slowed nerve conduction velocities. Clinical neuropathy associated with phenytoin use seems to be a rare event.

Differential slowing and demyelinating conduction block are always associated with acquired nerve disease and occur in either a focal or a multifocal distribution. Conceptually, differential slowing results from different degrees of slowing within different nerve fibers within the same segment of nerve. Again, all impulses traverse the damaged segment of nerve successfully. As a result, the CMAP waveform broadens and becomes dispersed, with a resulting loss of amplitude and lengthening of duration. Typically, the waveform takes on a serrated rather than smooth contour (Fig. 2–16). Theoretically, as all axons are conducting and all muscle fibers

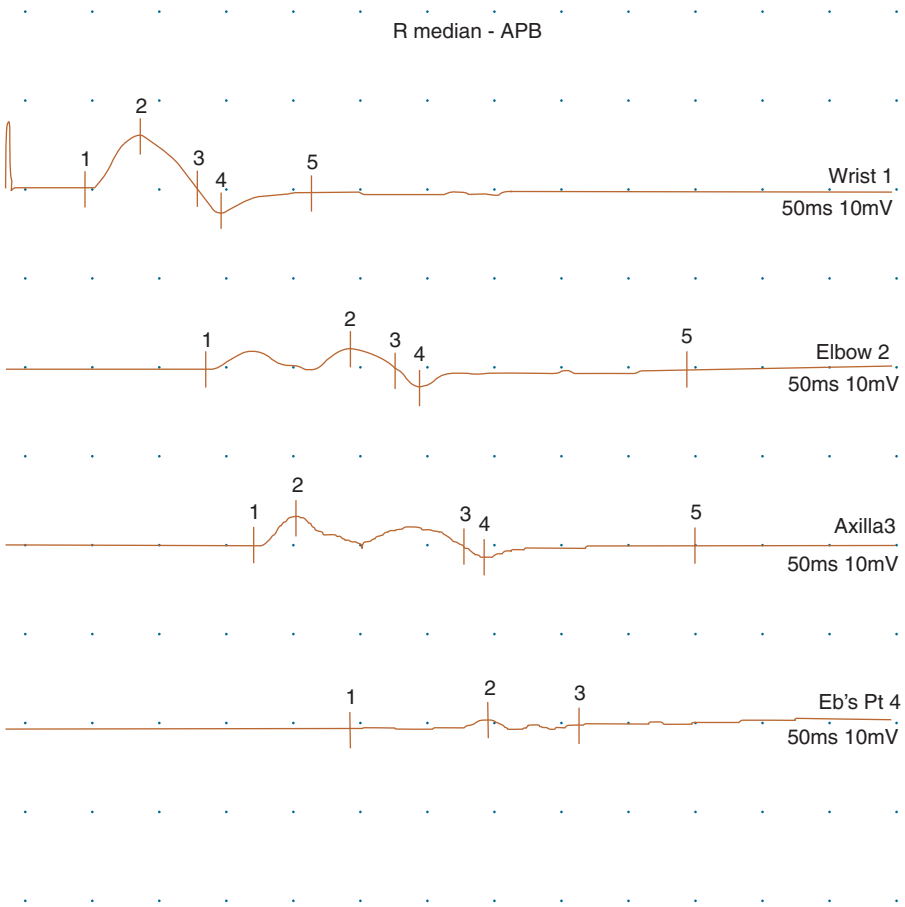


Figure 2–16. Motor nerve conduction with differential slowing (temporal dispersion) in patient with multifocal motor neuropathy.

activated, the area under the curve remains the same. Differential slowing may occur either from mechanical nerve injury in a mononeuropathy or in a multifocal fashion in the acquired demyelinating polyradiculoneuropathies such as GBS and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Clinically, differential slowing primarily affects modalities that require synchronous impulse transmission, notably deep tendon reflexes and vibratory perception.

Conduction block usually implies demyelination affecting consecutive myelin internodes to the extent that impulse transmission is actually blocked in a variable population of fibers within a given nerve. It is most accurately recognized when stimuli can be delivered sequentially over short segments of nerve. When a nerve is stimulated below the affected area, the CMAP amplitude is normal as the nerve distal to the lesion remains unaffected as long as the pathology is exclusively demyelinating. Above the block, the CMAP amplitude drops off proportionate to the number of fibers affected (Figure 2–2). This same phenomenon may also occur prior to overt demyelination, presumably on the basis of immune-mediated ion channel dysfunction, as most ion channels exist at internodes.

Clinically, conduction block produces neither significant muscle atrophy, loss of the so-called small fiber modalities including autonomic functions, nor perception of pain and temperature. Significant atrophy does not occur as the trophic influence of preserved axons remains. The latter functions are preserved as small poorly myelinated or unmyelinated fibers remain relatively unscathed, as demyelinating lesions have little or no influence on these fiber types. Conduction block is the only type of demyelinating pathology that results in muscle weakness.

THE VALUE AND LIMITATIONS OF EDX

EDX studies are very helpful in certain circumstances and of limited utility in others. In essence, these can, with varying degrees of confidence, determine the following:

- The existence of a problem within the neuromuscular system.
- Where within an individual nerve the problem lies.
- The geographic pattern of that problem, e.g., single nerve, single root, length-dependent, etc.
- The pathophysiology of the problem and the expected clinical consequences.
- Insight into the severity and, to a lesser extent, the prognosis of the problem.

Although disease etiology may be implied by the electrodiagnostic findings, it is rarely, if ever, defined as a direct result of EDX interpreted in isolation. Although the EDX examination is fairly sensitive and can provide support for most neuromuscular disorders, there are notable exceptions. One of these is the increasingly accepted concept of small fiber peripheral neuropathy, typically presenting with burning, hypersensitive feet. Conventional EDX techniques exclusively test large myelinated fibers and do not adequately assess disorders that exclusively affect small myelinated or unmyelinated fibers producing distortions in perception of pain and thermal sense with or without impaired autonomic function. Other tests, described later in this chapter and in the subsequent chapter on histological testing, have been used in attempts to assess small fiber integrity.

Another arena in which EDX is inadequately sensitive is in certain muscle disorders. Myopathies in which the pathology consists solely of myofiber atrophy or nondestructive internal changes of myofiber architecture can be particularly difficult. Certain endocrine, congenital, and mitochondrial myopathies are examples of this. In the myopathy of excessive corticosteroid use characterized by type II myofiber atrophy, the abnormal type II MUPs are not detectable, as these are obscured by their initially recruited type I counterparts.

As previously mentioned, an additional drawback of EDX is the time required for the full complement of EDX abnormalities to develop following nerve injury. In addition with traumatic injuries, EDX cannot adequately distinguish between complete severance of axons with preservation of the connective tissue sheath and complete nerve transaction. This is of pragmatic importance as the current standard of care would be to attempt primary nerve reanastomosis acutely if complete nerve transaction had occurred.

ELECTRODIAGNOSTIC LOCALIZATION WITHIN THE NEUROMUSCULAR SYSTEM

EDX is capable, in many cases, of clarifying or reinforcing the localization of the pathological process within the neuromuscular system. The strategy is similar to the same pattern recognition methodology used clinically at the bedside. Differential diagnosis is greatly facilitated in nerve disease by identifying the problem as a mononeuropathy, a monoradiculopathy, a polyradiculopathy, a polyradiculoneuropathy, a plexopathy, a multifocal neuropathy, a length-dependent neuropathy (LDPN), or a motor or sensory neuronopathy. Neuronopathy refers to a disorder affecting the cell body in the anterior horn or dorsal root ganglion, respectively. Both myopathies and DNMT have fairly distinctive EDX signatures that allow localization to these structures as well (Table 2–3).

Regarding localization within a nerve, there are a number of considerations. There are essentially three

▶ TABLE 2–3. ELECTRODIAGNOSTIC LOCALIZATION (TYPICAL PRESENTATIONS)

Diagnosis	CMAP Amp	Cond Slow	Disp/CB	SNAP Amp	Fibs/PW	Other Abnl Spon Act	Prsp dnrv	MUP size	MUP No.	Pattern
Mononeuropathy	↓	+/–	+/–	↓	Yes	+/–	No	↑	↓	Single nerve
Multifocal neuropathy	↓	No	+/–	+/–	Yes	+/–	No	+/–	↓	Multiple nerves
LD polyneuropathy	+/–	+/–	No	↓↓	Yes	No	No	↑	↓	LD symmetric LE > UE
Polyradiculoneuropathy (demyelinating)	↓	No	Yes	↓	+/–	No	+/–	+/–	↓	Diffuse non-LD
Monoradiculopathy	+/–	No	No	NL	Yes	+/–	Yes	↑	↓	Monosegmental
Polyradiculopathy	↓	No	No	NL	Yes	+/–	Yes	↑↑	↓	Polysegmental
Plexopathy	↓	No	No	↓↓	Yes	Occ Myk	No	↑↑	↓	Multiple nerves and roots in single extremity
Sensory neuropathy	NL	No	No	↓↓	No	No	No	NL	NL	Diffuse non-LD
Motor neuron disease	↓↓	+/–	No	NL	No	+/–	Yes	↑↑	↓↓	Diffuse non-LD
Presynaptic DNMT	↓↓	No	No	NL	+/–	No	+/–	↓	NL	Diffuse
Postsynaptic DNMT	NL	No	No	NL	+/–	No	+/–	↓	NL	Diffuse
Myopathy without abnormal spont act	+/–	No	No	NL	No	No	No	↓	NL	Diffuse or proximally predominant
Myopathy with fibs and positive waves	+/–	No	No	NL	Yes	No	Yes	↓	NL	Diffuse or proximally predominant
Myopathy with myotonia	+/–	No	No	NL	+/–	Myt	+/–	↓	NL	Diffuse, may affect facial and distal muscles

Amp, amplitude; Slow, slowing; Disp, dispersion; CB, conduction block; Abnl spon act, abnormal spontaneous activity; Prsp dnrv, paraspinal denervation; LD, length dependent; LE, lower extremity; MYT, myotonic potentials; MYK, myokymic potentials; OCC, occasional; UE, upper extremity; +/–, may or may not occur depending on severity or pathophysiology (e.g., axonal or demyelinating) of disorder.

means to predict where within the peripheral nerve the pathology lies. The first revolves around the presence or absence of conduction abnormalities within the sensory and motor nerve fibers. Sensory nerve conductions are abnormal in axon loss lesions affecting the dorsal root ganglion, the plexus, or the peripheral nerve. They are normal in disorders of the anterior horn, the neuromuscular junction, and muscle, as they are not affected by pathology that occurs exclusively in these locations. They are usually normal as well in disorders affecting nerve roots, despite clinical sensory symptoms in the segment tested. The reason for this is not intuitive. An axon separated from its nucleus will degenerate. In disorders of the dorsal root, this Wallerian degeneration takes place in a centripetal fashion, i.e., toward and within the posterior column of the spinal cord. As a result, the peripheral sensory axon remains viable and capable of conducting impulses in a normal fashion, even within symptomatic regions. A normal SNAP in a clinically affected territory implies that the patient's sensory symptoms are attributable to small fiber involvement, which cannot be detected by standard NCS techniques; that the patient is feigning symptoms; or that the pathology is proximal to the dorsal root ganglia. Conversely, abnormal CMAP amplitudes with spared SNAPs imply a localization to anterior horn, ventral root, neuromuscular junction, muscle, or those uncommon disorder that affect motor nerve fibers exclusively. The latter possibility is most readily defined by the identification of demyelinating features confined to motor nerves.

The second and most precise means of localization occurs when a focal demyelinating lesion exists and is detectable. The latter is dependent on being able to stimulate the nerve both above and below the lesion site. For these reasons, localization may be impaired not only by the pathophysiology of the nerve lesion but by the limits of anatomy as well. Deeply situated nerves in proximal locations are in large part inaccessible. If the lesion is purely axonal, or if the lesion is in an area that is difficult to access with NCS, nerve conductions will be able to localize the problem to the nerve but not within the nerve.

The third localization opportunity occurs in axon loss lesions in which localization can be inferred by the pattern of denervation. Here the electromyographer is hampered by at least three aspects of anatomy. Localization is limited by the anatomical location and distribution of branch points to individual muscles and their location along the course of a given nerve. In the ulnar nerve, for example, branches occur only in the hand and at the elbow, with none in the arm and forearm segments. A second problem is the tendency for fibers designated for certain muscles to be sequestered in selected fascicles. For example, it is common for ulnar forearm muscles to be spared with ulnar neuropathies occurring at the elbow. The presumption is that the fascicles containing the fibers supplying forearm muscles are rendered less vulnerable to nerve entrapment or compression by their position within the nerve. Lastly, most muscles are innervated by multiple roots. This benefits the patient but confounds the electromyographer. This overlap may make it difficult to provide single root localization. As an example, most muscles innervated by the C5 myotome are also innervated by the C6 myotome and vice versa, making discrimination between these two mononeuropathies challenging.

A mononeuropathy is defined by both conduction study and EMG abnormalities confined to a single nerve. Typically, mononeuropathies are caused by external nerve compression or by entrapment within a normally existing anatomical structure rendered abnormal from mechanical or other factors. Mononeuropathies may be associated with all of the pathophysiological processes defined above, often in combination, with the possible exception of ion channel dysfunction. Prognosis is determined by the type and relative degree that each pathophysiological process provides.

A monoradiculopathy is defined when sensory conductions are normal and denervation exists in a myotomal or segmental pattern. In other words, all affected muscles should share the same root innervation but include innervations from more than one peripheral nerve. For example, in a C7 radiculopathy, denervation might be expected in both the triceps and the flexor carpi radialis. Both have significant C7 innervation, but one is supplied by the median nerve while the other is supplied by the radial nerve. CMAP amplitudes are usually spared in monoradiculopathies for the following reasons. Many of the commonly affected nerve roots, particularly in the upper extremities, do not correspond to the same segments as the routinely performed conduction studies. In addition, most muscles have multiple root innervations. Even if there is significant axon loss within a given segment, potential loss of CMAP amplitude is buffered by the contribution(s) of other unaffected segments.

Conceptually, all mono- or polyradiculopathies, which have some degree of axon loss injury and affect ventral roots, should manifest paraspinal denervation. In reality, this may be hard to demonstrate. The electrodiagnositician should not be dissuaded if paraspinal denervation cannot be demonstrated if the pattern of denervation and preserved SNAPs occur in the appropriate clinical context. For the most part, monoradiculopathies are most readily recognized when there is axon loss. As demyelination can only be inferred when the lesion cannot be flanked by stimuli both proximal and distal to it, demyelinating radiculopathies can only be inferred and may go unrecognized. This inference would be made by the demonstration of reduced recruitment in a segmental distribution at an interval in excess of 3 weeks after symptom onset. This pattern, suggesting a proximally

located demyelinating conduction block, would also require the absence of fibrillation potentials and MUP morphological change.

Polyradiculopathy is defined by denervation in the distribution of multiple segments and their corresponding paraspinal musculature. Again, sensory potentials should be spared. CMAP amplitudes are more likely to be affected than monoradiculopathies, as the buffering provided by multiple root innervations is not as pronounced. Polyradiculopathies are electrodiagnostically indistinguishable from early motor neuron disease, as in both cases the pathology exists proximal to any accessible conduction site.

Recently, it has been postulated that a purely sensory polyradiculopathy affecting dorsal roots exists, presenting with multifocal sensory symptoms including sensory ataxia.[20] In these cases, the localization was postulated based on imaging, somatosensory-evoked potential abnormalities, and/or dorsal rootlet biopsy result occurring in absence of SNAP abnormalities in the symptomatic regions. The results of H reflexes were not reported, the one aspect of EDX that might be abnormal in exclusively dorsal root pathology affecting S1 segments. Motor conduction studies and needle examination were normal in the majority of patients in keeping with the proposed dorsal root localization.

Polyradiculoneuropathy differs from polyradiculopathy only in that the pathology extends centrifugally from nerve root into nerve. The concomitant dorsal root ganglia or peripheral nerve involvement results in SNAP abnormalities in addition to paraspinal denervation. Although there are a number of potential etiologies, the most readily recognized causes of polyradiculoneuropathies are the acquired inflammatory demyelinating neuropathies, i.e., GBS and CIDP. In these disorders, motor conduction studies are commonly replete with demyelinating features, including uniform and differential slowing (temporal dispersion) and conduction block. Some degree of axon loss is common. Sensory conductions are affected although "sural sparing" may occur. Denervation, when present, occurs on a generalized basis without length dependency and affects the paraspinal muscles.

Plexopathies are typically defined when both clinical and EDX sensory and motor abnormalities affect more than one nerve and nerve root distribution confined to a single limb. There are exceptions. Specific etiologies of plexopathy such as acute brachial plexus neuritis may affect more than one limb, in either a clinically evident or an occult basis. Plexopathies affect both SNAP and CMAP amplitudes, SNAPS almost always to a greater extent. When the CMAP amplitudes are affected disproportionately to the SNAPS, concomitant involvement of the ventral roots should be considered. Alternatively, CMAPs may be disproportionately affected in disorders such as acute brachial plexus neuritis if pure motor nerves like the anterior and posterior interosseous or long thoracic are preferentially involved. In this disorder, the pattern may actually conform more to multifocal neuropathy confined to the upper limb, rather than to an anatomically defined plexopathy. The pattern of denervation in plexopathy varies with etiology. A plexopathy is best defined electrodiagnostically when the pattern of abnormalities identifies and is only explained by pathology in a distinct plexus element, e.g., the upper trunk of the brachial plexus. In traumatic and inflammatory plexopathies, localization to a single plexus component is the exception rather than the rule. In a true anatomic plexopathy, sparing of paraspinal musculature is expected. In acute brachial plexus neuritis, the pathology may extend beyond the boundaries of the brachial plexus to involve other nerves such as the recurrent laryngeal and phrenic.

Polyneuropathies will be discussed here in four categorical domains: multifocal neuropathy, LDPN, sensory neuronopathy, and motor neuronopathy, a.k.a. motor neuron disease. Although motor neuron disease is not typically considered a polyneuropathy, sensory neuronopathies are. As it is conceptually difficult to discuss disorders affecting motor nuclei from those affecting their sensory counterparts, and as their clinical manifestations overlap with traditional neuropathy phenotypes, both will be discussed in here.

Multifocal neuropathy is diagnosed when EDX abnormalities occur in multiple nerve distributions, typically in an asymmetric fashion. Typically, there is both sensory and motor involvement, although both pure motor and perhaps pure sensory variants exist. When multifocal neuropathies are either pure motor or sensory, distinction from the neuronopathies may be difficult. As multifocal neuropathy is typically due to disorders that either infarct or infiltrate nerve, the pathophysiology is usually axonal. Multifocal neuropathy may also result from presumed immune-mediated demyelination or hereditary predisposition accompanied by distinctive demyelinating markers, e.g., multifocal-acquired demyelinating sensory and motor neuropathy (MADSAM or the Lewis–Sumner syndrome). Electrodiagnostic definition of multifocal neuropathy often requires an extensive examination with fastidious attention to detail.

LDPN is the most common polyneuropathy phenotype. As implied by the name, signs and symptoms first occur in the most distal aspects of the longest nerves, typically in a symmetric fashion. Etiologies are usually toxic, metabolic, or hereditary in nature. An axonal pathophysiology usually predominates. Hereditary neuropathies are the most common cause of a predominantly demyelinating length-dependent pattern. Most LDPNs involve both sensory and motor fibers. Again, SNAPs are typically affected earlier and to a greater extent than their CMAP counterparts. Abnormalities on needle examination are length dependent as well.

Many LDPNs appear to be purely sensory from a clinical perspective. Electrodiagnostically, the majority are sensory-motor. This confusing discrepancy can be theoretically explained on an anatomic basis. At onset, involvement of sensory nerve endings in the toes commonly produces symptoms that are typically positive (paresthesias) and are therefore easily perceived. Conversely, detection of motor abnormalities in the intrinsic foot muscles is rendered difficult by the duplicate function of leg muscles, which also promote toe flexion and extension. Only toe abduction/adduction, a function difficult to clinically assess, is controlled solely by intrinsic foot muscles. An LDPN is defined by reduction or loss of SNAP amplitude in the plantar, sural, and superficial peroneal nerves bilaterally. If the SNAPs are affected in the upper extremities, these should be affected to a lesser extent in all but the most severe of neuropathies. CMAP amplitudes in the tibial and peroneal nerves may or may not be symmetrically or near-symmetrically affected as well, depending on the severity of the neuropathy. Abnormalities in the needle examination also occur in a length-dependent, symmetric pattern. For example, if denervation occurs in the tibialis anterior, it should be proportionate to the ipsilateral medial gastrocnemius and the contralateral tibialis anterior but far greater than the more proximal tensor fascia lata, which shares an L5 myotomal innervation. The value of needle EMG of intrinsic foot muscles is controversial. In the estimation of the authors', denervation of intrinsic foot muscles is a sensitive marker of early neuropathy and a valuable means to define a length-dependent pattern.

Sensory neuronopathies or dorsal root ganglionopathies, as these are sometimes called, are typically caused by toxic, inflammatory, or infectious mechanisms. Although there is a tendency toward length dependency, asymmetric and often subtle non-length-dependent areas of abnormality are key to their detection, either by clinical or by EDX means. Multifocal reductions in SNAP amplitudes are the hallmark of these disorders. Both motor conduction and needle EMG abnormalities are by definition absent.

Motor neuronopathies or motor neuron diseases are commonly degenerative, hereditary, or infectious. The pattern of weakness varies with cause. Sensory conductions are normal in the absence of concomitant pathology. The pathophysiology appears to be that of axon loss, occurring in a multifocal or diffuse pattern. Early on if weakness is geographically limited in distribution, the pattern of denervation may be recognized as polysegmental. Denervation occurring in a nerve distribution pattern should suggest the far less commonly occurring motor neuropathies. From an EDX localization perspective, there are no reliable ways to distinguish diffuse ventral root disease from motor neuron disease.

Presynaptic DNMTs are usually clinically and electrodiagnostically diffuse in their geographic distribution. Their hallmark is reduced CMAP amplitudes with SNAP sparing. As described above, CMAP amplitudes should increase after brief exercise or in response to repetitive stimulation at rates of 5 Hz or more. A decremental response to slow repetitive stimulation may be demonstrated if sought for. Fibrillation potentials occur in botulism but are infrequent in the Lambert–Eaton myasthenic syndrome (LEMS). MUPs may be normal or reduced in size, i.e., small in amplitude, short in duration, and polyphasic in configuration. Recruitment may be concomitantly increased.

Postsynaptic DNMTs have an electrodiagnostic signature that overlaps its presynaptic counterpart. The major discriminator is that CMAP amplitudes are typically normal at rest except in the most severe cases. Decremental responses are initially sought for, without, or if necessary with, 1 minute of exercise. If demonstrated, these can be repaired by the same EDX techniques that are used to produce an increment in presynaptic disorders. Alternatively, these can be repaired with edrophonium infusion. As described above, a clinically weak muscle in MG will demonstrate a decremental response to 2–5 Hz repetitive stimulation. This may be easy to demonstrate in generalized MG but elusive in patients whose signs and symptoms are restricted to the oculomotor system. As the decremental response is the analog of muscle weakness, failure to demonstrate a decrement in a clinically weak muscle excludes MG from consideration. As in case of presynaptic DNMT, MG spares sensory potentials and may be associated with small MUPs. Fibrillation potentials are uncommon but may occur when receptor sites are damaged to the extent of effective denervation.

EDX AS A PROGNOSTIC TOOL

EDX assessment of prognosis can be ascertained in many different ways.[21] In general, demyelinating lesions are likely to resolve quickly (weeks to months) and completely if their cause is eliminated. There are certain disorders such as radiation injury and multifocal motor neuropathy (MMN) in which conduction block may become persistent. The prognosis for axon loss lesions is more uncertain and depends on the degree and location of the injury. The severity of the lesion is best judged by the amplitudes of the SNAP and CMAP responses. Reinnervation is most successful when there are many residual axons to sprout and few muscle fibers to reinnervate. Prognosis is also determined in axon loss lesions by the distance between the injury and the target. For example, in brachial plexus injuries, improvement in biceps and deltoid function is common whereas significant return of hand function is far more tenuous.

Rapid disease progression in ALS correlates with at least three recognized electrodiagnostic patterns. These are patients with an abundance of fibrillation potentials

and modest changes of chronic denervation and reinnervation, patients with prominent MUP variability, and patients with rapid declines in MUP estimates over time.[15]

Prognosis in the GBS had been linked to a composite of CMAP amplitudes. Although reduced CMAP amplitudes could represent demyelinating conduction block in terminal nerve twigs between the distal point of nerve stimulation and muscle, these are more likely to represent axon loss with the more pessimistic prognosis for rapid recovery that it portends.[22]

▶ QUANTITATIVE SENSORY TESTING

QST is used in both clinical and research settings, in an attempt to provide measurements of small myelinated and unmyelinated nerve function.[23–25] Peripheral neuropathies are usually pathologically indiscriminate and affect peripheral nerve fibers of all sizes and functions. The concept of small fiber neuropathy (SFN) recognizes the existence of a select group of neuropathy patients in whom the signs and symptoms suggest preferential injury to small poorly myelinated (A-delta) or unmyelinated (C) peripheral nerve fibers less than 7 microns in diameter.[26–28] As mentioned above, conventional EDX does not assess small fiber viability and function and is therefore of limited utility in SFN unless larger myelinated fibers are concomitantly affected. Quantitative sensory techniques represent an attempt to fill this diagnostic gap as well as to provide a potential tool for epidemiologic studies and therapeutic trials and potentially to screen for subclinical neuropathy in industry where the potential for neurotoxic exposure exists.[23,24,29] Two other techniques that may also be used in SFN assessment, autonomic testing and the assessment of intraepidermal nerve fiber density (INFD) through skin biopsy, will be discussed in the next section and next chapter, respectively. The latter technique is reported to have a sensitivity of 88% and a specificity of 91% in the diagnosis of SFN.[30] This sensitivity may exceed that of QST and ANST although the test results may not be concordant, implying the potential benefit of using multiple testing modalities in SFN suspects.[30,31]

Clinically, SFN is typically a symmetric LDPN, as discussed in detail in Chapter 20, representing perhaps 5% of the LDPN population in whom sensory symptoms predominate.[27,31,32] It has been hypothesized that the natural history of SFN is to evolve into a more typical LDPN phenotype with both small and large fiber involvement.[30] Other patterns of SFN involvement are suspected, although there is no current diagnostic gold standard to define the limits of phenotypic expression. Typically, patients complain of painful, often burning paresthesias with associated cutaneous hypersensitivity. In its purest form, the only abnormalities on clinical examination in SFN, if any, are diminished perception of thermal sensation and either diminished or enhanced response to painful stimuli. Vibratory perception is either normal for age or diminished mildly at the toes. Motor, reflex, and EDX examinations are commonly normal unless large fiber involvement is also present.[26,31,32]

QST is a psychophysical test whose accuracy is dependent on optimal control of multiple environmental variables including patient understanding and cooperation.[24] Understandably, there are certain patient populations in whom testing is unlikely to succeed. Although the stimuli delivered are quantified, the patient responses are largely subjective. There are numerous testing algorithms, used by different commercial vendors, that have been developed in an attempt to make QST as accurate, reproducible, and efficient as possible.[33] It is not clear which existing algorithm achieves these goals with the most success. Results are very much dependent on the patient population studied, the environment in which they are studied, as well as the equipment and testing algorithm used.[24,34] QST should not be used as the sole means to detect nerve pathology nor should it be relied upon for dispute resolution in a medical–legal venue.[35]

It is beyond the scope of this chapter to provide a detailed discussion of QST algorithms. There are a number of different paradigms used in terms of both stimulus threshold and reproducibility of result. Threshold algorithms include the smallest stimulus intensity perceived, the smallest difference in stimulus intensity perceived, or the lowest stimulus intensity that provides a given magnitude of response, e.g., pain. Reproducibility algorithms include dynamic testing, which involves ramping stimulus intensity up or down until identical thresholds are identified. Thresholds are considered abnormal when these exceed 95% of age-matched norms. In contrast to dynamic testing algorithms, static stimuli are delivered as individual stimuli of set duration and intensities. Either flanking or forced choice algorithms can be used. The 4-2-1 paradigm is the most frequently used flanking algorithm. If a stimulus is perceived, the stimulus is reduced by four orders of magnitudes at a time until no longer perceived, then increased by two levels of magnitude until recognized, and then reduced by one order of magnitude. In a sense, the process "zeros in" on the threshold. The forced choice paradigm provides paired stimuli, one of which is null. The true stimulus varies in intensity, and the null stimulus varies randomly in its order of delivery.[34]

The most commonly used QST testing algorithms assess thresholds for cooling and vibration, particularly in a diabetic population.[36] In SFN, the expectation is that thermal thresholds would be affected disproportionately to those for vibration. Although QST it is used predominantly for suspected peripheral neuropathy, one of its limitations is that it tests the entirety of the somatosensory system. Accordingly, abnormal test results have no localizing value. One potentially beneficial, although

unvalidated, application of QST is its use in topographical areas not readily accessible to conventional EDX.[37] For example, it may provide a means to evaluate sensory complaints of the genitalia.

QST has been studied in a number of clinical applications. Thermal testing may be abnormal in diabetic patients before the onset of symptoms or abnormal EDX.[29,38,39] In uremic patients, altered vibratory thresholds seem to be more prevalent than their thermal counterparts in presumed neuropathy.[40] Conversely, impaired thermal threshold may be the first abnormality to occur, and the paradoxical heat perception resulting from a cold stimulus may also occur in the uremic population.[41,42] QST is frequently applied in the evaluation of the frequently painful distal sensory neuropathy in the HIV population.[35,43]

In studies conducted to date, QST sensitivity for the detection of SFN has ranged from 60% to 85%. In general, this sensitivity in the detection of small fiber pathology is similar to both quantitative sudomotor axon reflex testing (QSART) discussed below and epidermal nerve fiber density discussed in the following chapter.[26] At least one study has suggested that INFD provides a more sensitive means to confirm small fiber involvement.[31] As QST abnormalities may reflect either peripheral or central nervous system pathology, and in consideration of their apparently similar thresholds for detection of abnormalities within the peripheral nervous system, abnormal QST coupled with normal epidermal nerve fiber density should raise provoke consideration of central nervous system pathology.[27]

▶ AUTONOMIC NERVOUS SYSTEM TESTING

Detecting pathological involvement of the autonomic nervous system provides at least three potential applications in the evaluation process of patients with neuromuscular disease. It indicates small myelinated (A-delta) or unmyelinated (C) nerve fiber involvement in SFN suspects. It also aids in the differential diagnosis of peripheral neuropathy. Traditionally, the extensive list of potential etiologies of somatic peripheral neuropathy is whittled down by the process of pattern recognition, both by the identification of fiber types affected and by the topographic distribution of the signs and symptoms produced by their involvement. Peripheral neuropathy may affect somatic fibers alone, autonomic C-fibers alone, or both fiber types concomitantly.[20,44,45] As there are a limited number of diseases in the latter category, ANST can aid in this strategic approach (Table 2–4).[46–50] Finally, the coexistence of dysautonomia with somatic peripheral neuropathy provides potential prognostic insight. In diabetic neuropathy in particular, dysautonomia significantly contributes to morbidity and the potential for premature mortality.[51]

▶ TABLE 2–4. CAUSES OF PERIPHERAL NEUROPATHY WITH ASSOCIATED DYSAUTONOMIA

Idiopathic
Immune mediated
• Paraneoplasia
• Guillain–Barré syndrome
Infiltrative
• Primary systemic amyloidosis
Metabolic
• Porphyria
• Diabetes mellitus
Toxic
• *cis*-Platinum
• Vinca alkaloids
• Perihexilene
• Hexacarbons
• Thallium
• Arsenic
• Acrylamide
• Taxol
• Lead
• Pesticides
• Pyridoxine toxicity
Hereditary
• Familial amyloidosis
• Hereditary sensory and autonomic neuropathy types I–IV
• Fabry's disease
• Tangier's disease
• Mitochondrial disorders

The pharmacology of the autonomic nervous system is complex. In way of brief and simplified review, all preganglionic neurons of both the parasympathetic and the sympathetic nervous systems are thinly myelinated and use ACH as their primary neurotransmitter. The postganglionic receptors on which these work are populated by nicotinic receptors whose activation is blocked by hexamethonium. These ganglionic receptors are thought to represent the targets for circulating autoantibodies found in the serum of approximately half of autoimmune autonomic neuropathy patients.[52] Although nonautonomic cholinergic receptors on skeletal muscle are also nicotinic, these differ pharmacologically. These are blocked by curare and are the target of the anti-ACH receptor antibodies of MG. The postganglionic parasympathetic fibers transmit to muscarinic cholinergic receptors on the end organs that they innervate. There are at least three types of muscarinic receptors in the body. M1 receptors are found in the cerebral cortex and 5% of sympathetic ganglia, M2 receptors primarily in the heart, and M3 receptors in secretory glands.[53] Atropine is the primary blocking agent at these receptors.

The majority of postganglionic sympathetic neurons release norepinephrine as their primary neurotransmitter. The notable exceptions to this rule are sweat glands, smooth muscle fibers within the walls of blood vessels

populating skeletal muscle that promote vasodilatation, and some of the chromaffin cells of the adrenal medulla. All of these are cholinergic in nature. There are at least four types of adrenergic receptors, two alpha and two beta. Alpha-1 receptors mediate vasoconstriction, intestinal relaxation, and pupillary dilation, components of the primordial flight response. Alpha-2 receptors are presynaptic in location and inhibit norepinephrine release. Activation of beta-1 receptors, which may be induced by both epinephrine and norepinephrine, increases both heart rate and contractility. Beta-2 receptors are most receptive to the effects of epinephrine and are most prevalent in the smooth muscle of blood vessels within muscle. These result in vasodilatation when activated.

Symptoms that implicate dysautonomia can be classified as either cholinergic or adrenergic in nature. Orthostatic intolerance manifested as lightheadedness or fainting, fading of visual or auditory perception, and fatigue or nuchal discomfort are all symptoms that may result from impaired sympathetic vasomotor tone. In an older population, orthostatic intolerance may manifest as cognitive change without the perception of lightheadedness.[52] Other symptoms of impaired sympathetic function include ptosis, impaired ejaculation, and disordered sweating. The latter may manifest as dry feet or somewhat paradoxically by hyperhidrosis in unaffected areas in an attempt to compensate for hypohidrosis in other topographic distributions. Symptoms of cholinergic dysautonomia include blurred vision and photophobia from impaired pupillary constriction, impotence, resting tachycardia, the sicca complex of dry eyes and dry mouth, urinary retention, gastroparesis, and intestinal pseudo-obstruction.

In the subset of peripheral neuropathy presenting with painful feet suspected to have an SFN phenotype, autonomic symptoms are typically mild and usually restricted to the cholinergic domain. Disordered cholinergic sweat gland function may produce either hyperhidrosis initially or dry skin from impaired sweating. The sicca complex of dry mouth and dry eyes is common as is impotence in males. Skin vasomotor changes are also prevalent, manifesting as pallor alternating with rubor, cyanosis, and mottling. Orthostatic intolerance in this syndrome is uncommon.[52,54]

There is an extensive list of testing modalities that assess autonomic nervous system function.[34,55] A common menu includes heart rate response to deep breathing (Fig. 2–17), heart rate and blood pressure response to both the Valsalva maneuver (Fig. 2–18) and the tilt table testing, and QSART (Fig. 2–19).[48] Accurate responses to both the deep breathing and the Valsalva maneuver require a reasonable amount of patient cooperation. Blood pressure responses to the Valsalva maneuver and the tilt table, and QSART assess predominantly sympathetic function. Parasympathetic function is assessed by heart rate responses to deep breathing, tilt, and the Valsalva maneuver.

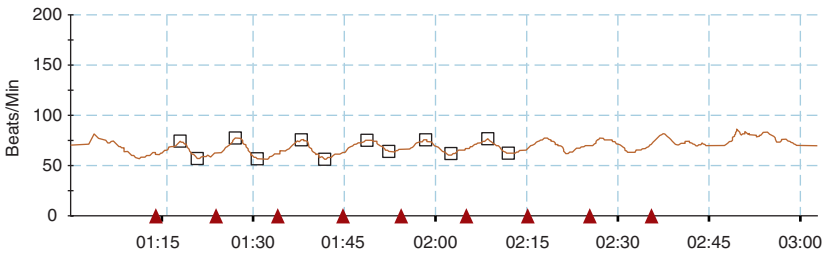
In normal individuals, the heart rate will accelerate in response to inspiration and increased venous return to the right heart and decelerate in response to expiration (sinus arrhythmia). This response will diminish as a normal consequence of aging. The afferent receptors for this reflex include pulmonary stretch receptors, cardiac mechanoreceptors, and possibly baroreceptors.[55] Sinus arrhythmia is a consequence of increased or decreased parasympathetic, cardiovagal tone. There are numerous protocols that address both the performance and the measurement of heart rate variability. Commonly the patient is positioned with the head up 30° from supine. The patient is asked to breath slowly and steadily at a rate of 6/min (5-second inspirations and 5-second expirations), usually for a period of 1 minute. Heart rate response to deep breathing can be measured either by the greatest difference between the fastest and slowest rate that occur during this interval or by the calculation of an *E* (expiration) to *I* (inspiration) ratio. The latter is done my measuring the shortest (*I*) and longest (*E*) intervals between QRS complexes (R–R interval) as singular, summed, or averaged values. As the heart rate is the slowest during expiration, the R–R interval increases accordingly resulting in an $E{:}I$ ratio of >1. There are published, age-matched normative data for both of these parameters. The mean heart rate variation in heart rate in a teenager is 30 beats per minute (bpm) with the 5th to 95th percentile range being 14 to 41 bpm. Between 60–69 years of age, the mean heart rate variation is closer to 18 with the 90% of normals being in the 7–27 bpm range.[45,46]

The Valsalva maneuver is more complex. The patient is asked to sustain a constant expiratory pressure of 40 mm Hg for approximately 15 seconds into a mouth piece attached to a manometer with a slow leak in the system. Both heart rate and blood pressure responses are monitored during and in the immediate aftermath of this maneuver. Four distinct phases are discernable, the first and third and the first part of the second phase (IIA) being mechanical in nature and phase IIB and IV resulting from autonomic nervous system responses. During the first phase, there is a transient increase in blood pressure resulting from strain and its effect of producing increased intrathoracic pressure resulting in compression on the aorta. Phase IIA also takes place during strain and is defined by a drop in blood pressure occurring from the reduced venous return also promoted by increased intrathoracic pressure. Phase IIB is normally identified by rising blood pressure that approaches baseline. This is promoted by increased vasomotor tone mediated by increased sympathetic and alpha adrenergic output. During the entirety of phase II, there is an increasing heart rate as a result of cardiovagal withdrawal. Phase III is initiated with glottic release and a resultant decline in intrathoracic pressures. Blood pressure transiently declines as intrathoracic venous structures can now readily refill. During phase IV, blood pressure rises and pulse declines under normal circumstances and over- and

Test Results

Analysis Type : HRDB **Analysis** ID : 423
Analysis Date : 08/25/2006 **Analyst** : HRDB
Analysis Comments:

Max Rate	Min Rate	Rate Difference
75.0	58.0	17.0
78.0	57.0	21.0
76.0	58.0	18.0
76.0	65.0	11.0
76.0	62.0	14.0
77.0	63.0	14.0
	Avarage HR Difference:	15.8

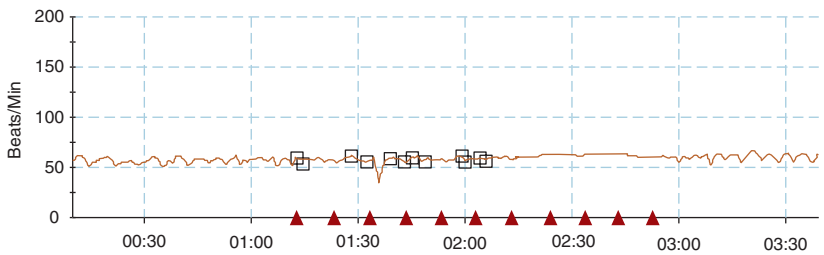


A

Test Results

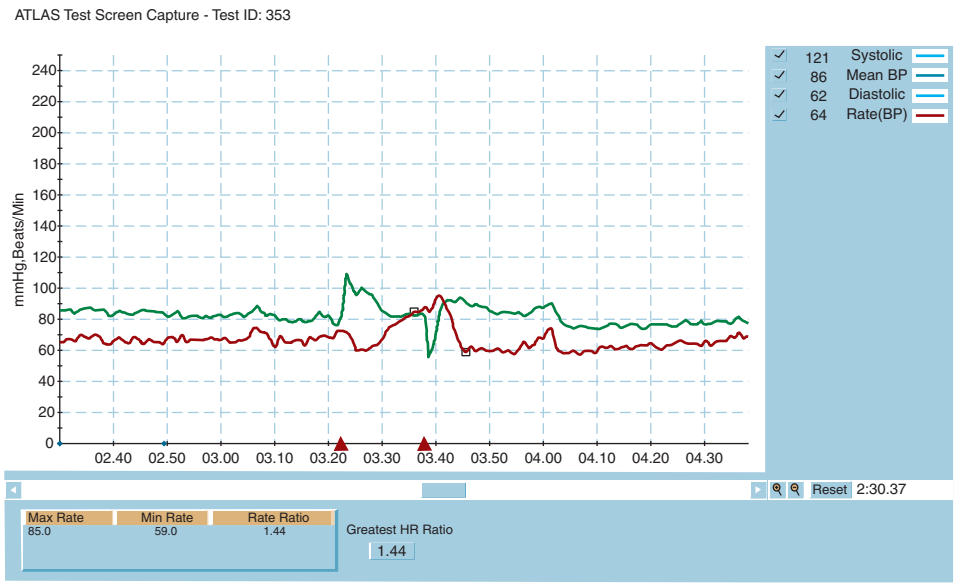
Analysis Type : HRDB **Analysis ID** : 63
Analysis Date : 01/31/2007 **Analyst** : HRDB
Analysis Comments :

Max Rate	Min Rate	Rate Difference
61.0	52.0	9.0
62.0	54.0	8.0
59.0	55.0	4.0
60.0	56.0	4.0
60.0	57.0	3.0
59.0	57.0	2.0
	Average HR Difference:	5.0

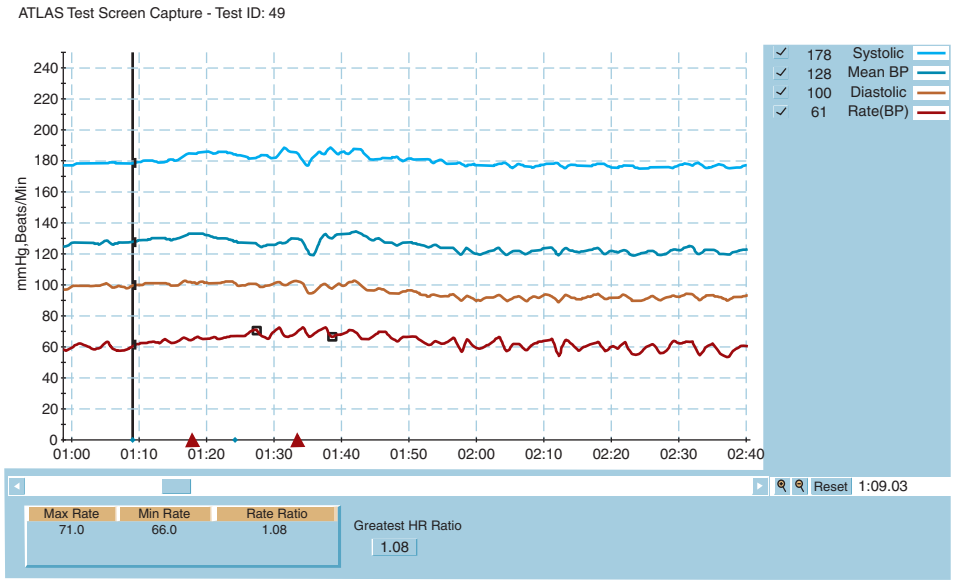


B

Figure 2–17. Normal (average heart rate difference 15.8) (A) and abnormal (average heart rate difference 5.0) (B) heart rate responses to deep breathing.



A



B

Figure 2–18. Normal (A) and abnormal (B) responses to the Valsalva maneuver. Pink line—heart rate, green line—mean arterial blood pressure. First pink triangle—glottic closure, second pink arrow—glottic release.

undershoots their respective baseline values. The increasing blood pressure is due to increased venous return and cardiac output coupled with the persistent effects of increased, sympathetically mediated vasomotor tone. The cardiovagal effects that are measured during the Valsalva maneuver can be quantitated by calculating the Valsalva ratio, the fastest heart rate during phase II divided by the slowest rate recorded during phase IV. Normative data for the Valsalva ratio are readily available.[45] The ratio does not change as dramatically with age and gender as do other autonomic parameters. A normal ratio averages 1.6 for males and 1.5 for females during their teenage years. Abnormal sympathetic responses are best identified by a failure of both blood pressure rise during phase IIB and blood pressure overshoot during phase IV to occur.[55]

Tilt table testing is used to assess heart rate and blood pressure responses to standing in a controlled but somewhat artificial environment. Its primary goal is to explore potential mechanisms of syncope or near syncope. Normally, despite a 25–30% shift in venous blood from central to peripheral compartments, rapid

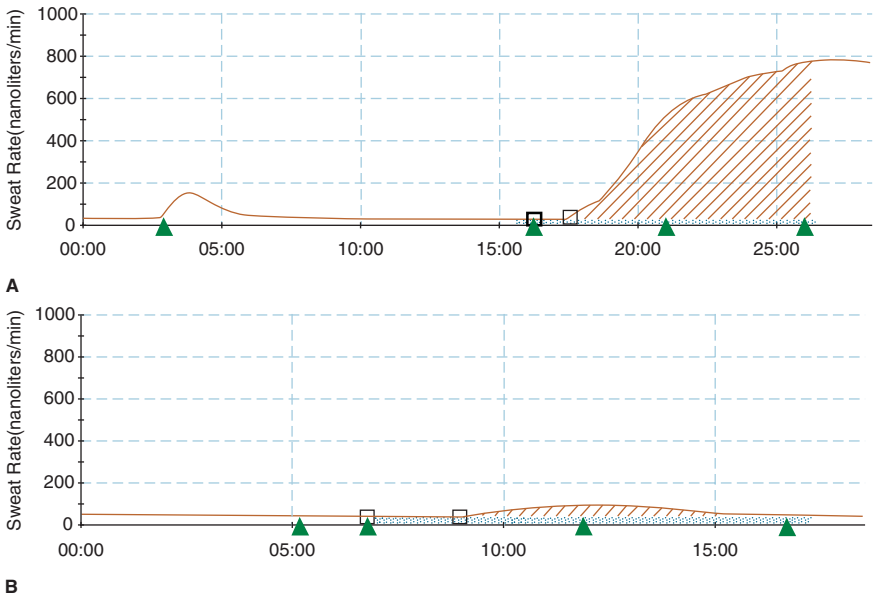


Figure 2–19. Normal (A) and abnormal (B) responses to quantitative sudomotor axon reflex testing. First green triangle, ACh injection; second green triangle, 2 mA stimulus begins; third green arrow, stimulus ceases; fourth green arrow, 5 minutes post stimulus cessation.

compensatory responses from the autonomic nervous system preclude major changes in either pulse or blood pressure.[55] Orthostatic hypotension is frequently defined as a drop in either systolic blood pressure of 20 or diastolic blood pressure of 10 mm Hg. Typically, symptoms do not develop until systolic blood pressure drops of 30 or diastolic pressures of 15 mm Hg occur. Orthostatic hypotension usually occurs either immediately or within a few minutes of standing. A drop in blood pressure with an associated tachycardia suggests hypovolemia of whatever cause. A drop in blood pressure without compensatory tachycardia implicates dysautonomia due to either disease or drugs. Symptomatic tachycardia with a heart rate greater than 30 bpm above baseline without a significant drop in blood pressure is the signature of the postural orthostatic tachycardia syndrome. Finally, prolonged tilt table monitoring is done in an attempt to reproduce symptoms in patients believed to suffer from neurocardiogenic syncope (vasovagal syncope). In these patients, symptoms of impaired CNS blood flow are accompanied by hypotension and paradoxical bradycardia.

QSART is a means to assess cholinergic, postganglionic sympathetic small fiber function. It is particularly attractive as a test for SFN and other LDPN with dysautonomic components, as it can be applied in numerous topographical locations and may provide support for a length-dependent pattern of abnormality. Typically, QSART is performed by placing sweat capsules in four standardized locations: the dorsum of the foot, shin, thigh, and forearm. These capsules measure the humidity produced by sweat production emanating from the tested skin surface in response to an injected intradermal cholinergic stimulus. The sensitivity of QSART in the detection of SFN has been quoted as being 60–80%, similar to QST.[26,31,54,56–58] In diabetic patients, there are similar rates of both sensitivity and concordance regarding results of the heart rate response to deep breathing, the Valsalva maneuver, and QSART.[59] Normative data for QSART also varies by gender, age and area tested. Reference 45. Mean values range between 1 and 3 microliters/centimeter squared.

ANST, perhaps more than any other testing modality, requires adequate control of environmental variables that may readily confound the accuracy of test results. Normative data vary considerably with patient age. Ideally, testing would be performed in some who is adequately hydrated, has not eaten for 8 hours, smoked tobacco, drank ethanol or caffeine, and has not been recently physically or emotionally stressed. Drugs that potentially react with adrenergic or cholinergic receptors are to be avoided if possible, including those with indirect autonomic effects such as insulin. Extremes of temperature or pressure stockings can adversely affect the outcome of testing procedure.[45]

▶ TESTING DONE ON BLOOD

ROUTINE LABORATORY (BLOOD) TESTING

There is a limited evidence basis from which to determine a sensitive, specific, and cost-effective laboratory evaluation for most neuromuscular syndromes. Laboratory evaluations for specific neuromuscular syndromes

will be addressed in detail in subsequent chapters of this book and will be mentioned here only in summary terms. An ideal test would be cost effective, noninvasive, and accurate in identifying or excluding a specific disorder in a large percentage of the tested population. There are few tests that resemble this description, anti-ACH receptor binding antibodies (ACHRBA) being arguably the best example.

Peripheral neuropathy is the most common neuromuscular syndrome with an extensive differential diagnosis. Numerous publications and clinical experience indicate that a significant number of these individuals will go undiagnosed despite extensive evaluation. Understandably, there is an incentive to extensively test in an attempt to fill in this gap. There have been a number of attempts to clarify which tests come closest to meeting the criteria outlined in the first paragraph.[17,36,60,61] This includes a practice parameter being currently constructed by the American Academy of Neurology. In summary, there is a low diagnostic yield for any routine blood test in the detection of an abnormality that is causally related to a patient's neuropathic symptoms.

Deficiency of vitamin B1, B6, B12, and E are potentially causally related to peripheral neuropathy. In addition, a sensory neuropathy/neuronopathy may occur with vitamin B6 toxicity in daily doses that are estimated to exceed 200 mg.[62] Testing for vitamin deficiency is generally not recommended on a routine basis[61] and is generally reserved for those patients perceived to be at higher risk. This group would include patients with a sensory predominant neuropathy who are at risk of nutritional deficiency due to alcoholism, dietary anomalies, isoniazid exposure, and malabsorption from bariatric surgery or enteral disease such as celiac sprue. The onset of symptoms in the hands may indicate a myeloneuropathy, which is a common presentation of vitamin B12 deficiency. Measurements of serum levels of methylmalonic acid and/or homocysteine may improve detection of this latter disorder.

An increased incidence of serum monoclonal proteins (MCPs) in patients with polyneuropathy has been recognized for decades. Most MCPs associated with peripheral neuropathy will initially be designated as being of unknown significance (MGUS). The neuropathy associated with MGUS may vary depending on MCP type but is typically a nonspecific, sensory > motor, and length dependent phenotype with primarily EDX axonal features.[63,64] The association between the neuropathy and MGUS in these cases is strictly statistical, a causal relationship being difficult if not currently impossible to prove. The MGUS that is most likely to have a causal relationship to peripheral neuropathy and has the most homogenous phenotype is that associated with an IgM kappa MCP. This is in turn often associated with antibodies directed toward myelin-associated glycoprotein in a significant percentage of cases. These antibodies will be discussed further in the following section.

A small percentage of patients at the time of initial evaluation and a larger percentage subsequently will have an MCP associated with a secondary disorder. Multiple myeloma, amyloidosis, lymphoma, cryoglobulinemia, or POEMS syndrome are noteworthy examples. A lambda, rather than a kappa, light chain increases the probability of a secondary cause of an MCP. Peripheral neuropathies associated with secondary causes of MCPs have, with the exception of the IgM kappa-related demyelinating sensory-predominant neuropathy, more distinctive phenotypes than MGUS-related neuropathies. For example, polyneuropathy, organomegaly, endocrinopathy, monoclonal protein and skin changes (POEMS) syndrome often associated with a motor-predominant, demyelinating, nonlength-dependent CIDP phenotype. Amyloidosis may manifest as a small fiber phenotype with prominent dysautonomia.[65] MCPs or light chains can be detected in these disorders in serum or urine by immunoelectrophoresis or immunofixation. The latter is more sensitive but is also more labor intensive. For these reasons, it is not used as a default screening procedure by many laboratories.

Diabetic neuropathy is common and is associated with multiple phenotypes. It is estimated to be the cause of neuropathy in 15–30% of North American patients.[60,61,66] The diagnosis of diabetic neuropathy is dependent on the fulfillment of criteria outlined by the American Diabetes Association in association with one or more of the characteristic clinical and EDX diabetic neuropathy phenotypes. The diagnosis is made by association. A direct causal relationship cannot be readily proven. Although thickening of the basal membranes of the vaso nervorum demonstrable by nerve biopsy is characteristic of diabetes, it is unknown what role it plays, if any, in the pathogenesis of diabetic nerve injury. Alternative causes of peripheral neuropathy should always be considered in diabetic patients, particularly if the phenotype is atypical in the diabetic population. The American Diabetes Association criteria include either an elevated (fasting blood sugar) ($\geq$124 mg/dL) or an abnormal 2-hour (glucose tolerance test) ($\geq$200 mg/dL).[67] Tests of glycosylated hemoglobin are usually employed for assessment of diabetic control rather than for initial detection of diabetes. Traditionally, neuropathy was not readily attributed to diabetes unless the diagnosis of diabetes had been established for years. More recently, a statistical association has been demonstrated between impaired glucose tolerance (FBS 110–125 mg/dL or GTT 140–199 mg/dL) and the SFN phenotype.[68–71]

Measurement of serum creatine kinase (CK) is a valuable adjunct in the evaluation of patients with neuromuscular disease. Although considered to be primarily a marker of muscle disease, increased serum CK levels commonly occur in ALS and other motor neuron diseases. Conversely, elevated CK levels do not occur in all myopathies. Normal CK levels vary with gender, race,

age, muscle mass, and physical activity. In normal individuals, levels may reach 5× the upper limits of normal following EDX or other invasive medical procedures and perhaps as high as 50× the upper limits of normal in extreme, protracted exercise. Levels increased by any of these inducements should return to normal by 1 week after the event.[72] The level of CK does not appear to correlate with the degree of muscle destruction or weakness.

Elevations of serum CK may occur in asymptomatic individuals. There are multiple inherited neuromuscular conditions in which elevated serum CK levels precede the development of recognizable signs and symptoms of the disorder. It is possible that many, if not all, of these patients with "idiopathic hyperCKemia" harbor mutations for which testing does not currently exist or is not considered.

DNA MUTATIONAL ANALYSIS

DNA mutational analysis is an evolving and complex diagnostic tool for neuromuscular disease. There are certain key general principles that currently apply. Although these tests are highly specific, identification does not predict phenotypic expression. Although most mutations are highly penetrant, these are not universally so. In addition, not all mutations, particularly polymorphisms, are necessarily pathological. Genotype–phenotype correlations are complex. Many similar, if not identical, phenotypes arise from mutations arising from different genes on multiple chromosomes. Conversely, allelic mutations commonly manifest themselves with widely disparate phenotypes. Detection of pathologic mutations may be rendered difficult for a number of reasons. We do not know all of the pathologic mutations for most phenotypes. Even with known genotypes, there are multiple types of mutation, not all of which may be identified by the technology used by the laboratory called upon to detect it.

DNA mutational analysis is most commonly employed to diagnose symptomatic individuals. These tests may also be applied to individuals who are at risk, or at times simply fearful, of being presymptomatic from a heritable disease. When used in these latter situations, it is incumbent upon the ordering physician to be fully cognizant of all potential ramifications of the testing result. This would include both positive or negative results and the potential impact not only on the tested individual but also on other family members whose genotype may be inadvertently illuminated. The tested individual should be counseled on all conceived consequences of test result before testing proceeds. Both patient and physician should be aware that these costly tests are often not reimbursed by third party payers in presymptomatic individuals.

In the neuromuscular realm, mutational analysis is commercially available for selected genotypes of motor neuron disease, hereditary spastic paraplegias, a number of the muscular dystrophies, dystrophic and nondystrophic myoptonias, periodic paralysis, a few mitochondrial disorders, several metabolic myopathies, some of the hereditary neuropathies characterized as Charcot–Marie–Tooth (CMT) disease, and the transthyretin-related familial amyloid polyneuropathies. These disorders are listed in more detail in Table 2–5 and in other chapters covering these subjects in subsequent chapters of the book. Other mutational analyses may be available in research laboratories, which can be accessed from the www.genetests.org.

CMT disease or hereditary motor sensory neuropathy is subcategorized largely on the basis of inheritance pattern and axonal or demyelinating pattern of conduction slowing in the upper extremities with EDX testing. CMT1 is dominantly inherited and demyelinating. As there are few other chronic demyelinating neuropathies, most notably CIDP and the rare adult-onset leukodystrophies, the clinical diagnosis is straightforward in most cases. DNA mutational analysis is available for many of these patients but is arguably of little current pragmatic value in most. Conversely, CMT2 is dominantly inherited but with axonal characteristics on EDX testing. As the differential diagnosis of chronic axonal neuropathies is much more extensive than their demyelinating counterparts, and as other affected family members are not always evident, clinical diagnosis is often problematic. It is in this population where DNA mutational analysis would be potentially the most helpful. Unfortunately, DNA mutational analysis options for the CMT2 phenotype will currently identify only a small proportion of affected individuals. Even if testing were available for all CMT2 genotypes, the inability to distinguish between them clinically would require analyses for all possible mutations. This is not currently financially pragmatic for most patients and physicians.

There are a number of inherited syndromes in which neuromuscular involvement occurs either as the dominant feature or as the component feature of the illness and for which genetic mutational analysis is not currently commercially available. These include seven recognized mutations producing five different phenotypes of hereditary sensory and autonomic neuropathy,[73] the hereditary motor neuropathies (distal spinal muscular atrophy), and familial brachial plexus neuropathies.

BIOCHEMICAL TESTING FOR INBORN ERRORS OF METABOLISM

There are a seemingly endless number of uncommon inherited metabolic diseases, many of which may have neuromuscular components. Peripheral nerve axons and

TABLE 2–5. COMMERCIALLY AVAILABLE DNA ANALYSES FOR NEUROMUSCULAR DISEASE AS OF 8/07 (BLOOD)

Disease Category	Type	Gene Location	Gene Product
Motor neuron disease	fALS	AD21q	Superoxide dismutase 1
	SMA I-IV	AR5q	Survival motor neuron gene 1
	X-linked spinobulbar muscular atrophy	X11q	Androgen receptor gene
Muscular dystrophy	Duchenne/Beckers	X21p	Dystrophin
	Limb girdle 2A	AR15q	Calpain 3
	Limb girdle 2B	AR2p	Dysferlin
	Limb girdle 2C	AR13q	gamma Sarcoglycan
	Limb girdle 2D	AR17q	alpha Sarcoglycan
	Limb girdle 2E	AR4q	beta Sarcoglycan
	Limb girdle 2F	AR5q	delta Sarcoglycan
	Limb girdle 2I	AR15q	Fukutin-related protein
	Limb girdle 1B	AD1q	Lamin-A/C
	Limb girdle 1C	AD3p	Caveolin 3
	Myotonic DM1	AD19	Dystrophica myotonia protein kinase
	Myotonic DM2	AD3	Zinc finger protein 9
	FSH	AD4q35	Unknown
	Oculopharyngeal	AD14q	Polyadenylate-binding protein nuclear 2
	Emery Dreifuss	X28q	Emerin
		AD1q	Lamin-A/C
Channelopathies	Myotonia congenita	AD7q	Chloride channel protein—CLCN1
	Paramyotonia congenita	AD17q	Sodium channel protein type 4 subunit alpha
	Hyperkalemic periodic paralysis	AD17q	Sodium channel protein type 4 subunit alpha
	Hypokalemic periodic paralysis 1	AR1q	Voltage-dependent L-type calcium channel subunit alpha-1S
	Hypokalemic periodic paralysis 2	AD17q	Sodium channel protein type 4 subunit alpha
Glycogen storage myopathy	McArdle's	AR11q	Myophosphorylase
	Pompe's	AR17q	Acid alpha 1-4 glucosidase
Lipid storage myopathy	Carnitine palmitoyltransferase deficiency IA	AR11q	Carnitine palmitoyltransferase I
	Carnitine palmitoyltransferase deficiency II	AR1p	Carnitine palmitoyltransferase 2
Mitochondrial myopathies	Kearns–Sayre syndrome	Maternal mtDNA	
	Progressive external ophthalmoplegia	Maternal mtDNA	SLC25A4, encoding ANT1 PEO1, encoding twinkle POLG1, encoding the catalytic subunit of mtDNA polymerase
	MERFF	Maternal mtDNA	Mitochondrial tRNA lysine
	MELAS	Maternal mtDNA	NADH-ubiquinone oxidoreductase chain 5 or Mitochondrial tRNA leucine 1
	MNGIE	AR ECGF1	Thymidine phosphorylase

(*continued*)

▶ TABLE 2–5. (CONTINUED) COMMERCIALLY AVAILABLE DNA ANALYSES FOR NEUROMUSCULAR DISEASE AS OF 8/07 (BLOOD)

Disease Category	Type	Gene Location	Gene Product
Neuropathy	CMT type 1A	AD17p	Peripheral myelin protein 22 (duplication)
	CMT type 1B	AD1q	Myelin protein 0
	CMT type 1C	AD16p	Lipopolysaccharide-tumor necrosis factor-alpha factor
	CMT type 1D	AD10q	Early growth response protein 2
	CMT type 1E	AD17p	Peripheral myelin protein 22
	CMT type 1F	AD8p	Neurofilament triplet L protein
	CMT type 2E/1F	AD8p	Neurofilament triplet L protein
	CMT type 2I	AD1q	Myelin protein 0
	CMT type 2J	AD1q	Myelin protein 0
	CMT type 2K	AD8q	Ganglioside-induced differentiation-associated protein-1
	CMT type 4C	AR5q	SH3 domain and tetratricopeptide repeats containing protein 2
	CMT type 4F	AR19q	Periaxin
	X-linked	Xq	Connexin 32
	HNPP	AD17p	Peripheral myelin protein 22 (deletion)
Familial amyloid polyneuropathy		AD18q	Transthyretin
Mitochondrial neuropathy	Neuropathy, ataxia, and retinitis pigmentosa	Mitochondrial nucleotide 8993	MT ATP6

fALS, familial amyotrophic lateral sclerosis; SMA, spinal muscular atrophy; FSH, facioscapulohumeral; MERRF, myoclonic epilepsy and ragged red fibers; MELAS, mitochondrial encephalomyopathy, lactic acidosis and strokelike episodes; CMT, Charcot–Marie–Tooth; HNPP, hereditary liability to pressure palsy; SPG, spastic paraplegia gene; MNGIE, mitochondrial neurogastrointestinal encephalomyopathy for contemporary listing of available gene test, refer to www.genetests.org.

their surrounding myelin sheaths appear to be particularly vulnerable to an unfriendly metabolic mileux. This is presumably due to their configuration and the complex metabolic requirements necessary to maintain the health of a structure that may exceed 1 m in length.[73] Although these are inherited disorders for which DNA mutational analysis may be applied, diagnostic confirmation is currently most expeditiously achieved by biochemical or at times by pathological means. In many cases, reduced levels of the gene product are sought, e.g., reduced alpha-galactosidase levels in Fabry's disease. In other cases, elevated levels of a substance resulting from the "synthetic or degradation road block" created by the deficient gene product may be the means by which the diagnosis is achieved. Phytanic acid buildup due to phytanic acid oxidase deficiency in Refsum's disease is an example of the latter phenomenon. The major inherited disorders that may associate with peripheral neuropathy and the most common means to achieve diagnostic confirmation are summarized in Table 2–6. DNA mutational analysis for many of these disorders are available only through research laboratories. Again, www.genetests.org is a valuable resource in this regard.

Biochemical testing to confirm the diagnosis of an inherited neuromuscular disorder is not confined to the realm of peripheral neuropathy. Western blot for dysferlin may be performed on peripheral monocytes for evaluation of LGMD2B or Miyoshi myopathy. Dried blood spot analysis for alpha-glucosidase activity is an outstanding screening test for Pompe disease (acid maltase deficiency). Some advocate that this test should be done routinely on all newborns, as there is now enzyme replacement therapy available for this lethal disease. The test should be considered for all children and adults with prominent respiratory failure or limb-girdle pattern of weakness.

SEROLOGICAL TESTING

The commercial availability of antibody testing has provided both diagnostic opportunity and confusion in the evaluation of patients with neuromuscular disease. These tests vary widely in their ability to provide sensitive and specific diagnostic support for specific neuromuscular phenotypes. As in any test, the specificity of

▶ TABLE 2–6. INHERITED METABOLIC DISEASES ASSOCIATED WITH PERIPHERAL NEUROPATHY (KLEIN, 2007)

Category	Disorder	Locus	Gene Product	Test*
Familial amyloid polyneuropathy		AD18q11	Transthyretin	• DNA sequencing • Tissue diagnosis
		AD11q23	Apolipoprotein A-1	• Tissue diagnosis
		AD9q34	Gelsolin	• Tissue diagnosis
Leukodystrophy	Metachromatic	AR22q13	Arylsulfatase	• Arylsulfatase A deficiency in leukocytes • Sulfatide excretion in urine • Tissue deposition of metachromatic lipid deposits • DNA sequencing or targeted mutation analysis
	Krabbe	14q31	Galactocerebrosidase	• Galactocerebroside deficiency in leukocytes • DNA sequencing or targeted mutation analysis
	Adrenal	XR	ATP-binding cassette subfamily D member 1	• C26–C22 long chain fatty acid ratio • DNA sequencing or duplication/deletion analysis
Peroxisomal	Refsum	AR10pter-p11.2	Phytanoyl-coa hydroxylase (90%)	• Phytanic acid • Phytanoyl-coa hydroxylase enzyme activity (fibroblasts) • DNA sequencing
		AR6q22-q24	PEX7 (10%)	
	Fabry	XRq22	alpha Galactosidase A	• alpha Galactosidase A • DNA sequencing
Lipoprotein deficiency	Tangiers	XR9q22	ATPase-binding cassette 1	• ↓ HDL • ↑ triglycerides
	Cerebrotendinous xanthomatosis	AR2q33	CYP27A1	• ↑ cholestanol • ↓ cholesterol • ↑ bile alcohols • DNA sequencing
	Abetalipoproteinemia			• ↓ beta-lipoproteins, LDL, and VLDL
Porphyria	Acute intermittent	AD11q	Porphobilinogen deaminase	• ↑ urinary delta amino levulinic acid/porphobilinogen • Erythrocyte hydroxymethylbilane synthase/porphobilinogen deaminase activity • DNA sequencing and mutation scanning
Defective DNA maintenance	Xeroderma pigmentosa	AR3p25	XPC	• DNA sequencing
	Ataxia telangiectasia	AR11q22	ATM	• ↑ alphafetoprotein • ATM protein immunoblotting • DNA sequencing and mutation scanning
Mitochondrial	MNGIE	AR ECGF1	Thymidine phosphorylase	• ↑ thymidine • ↓ thymidine phosphorylase (leukocytes) • DNA sequencing
Miscellaneous	Giant axonal neuropathy	AR16q24	Gigaxonin	• Nerve biopsy • DNA sequencing
	Neurofibromatosis type 1	AD17q11	Neurofibromin	• Protein truncation testing • DNA sequencing • Nerve biopsy
	Neurofibromatosis type 2	22q12	Merlin	• DNA sequencing • DNA mutation scanning • Nerve biopsy

*All tests use blood unless otherwise designated
MNGIE, mitochondrial neurogastrointestinal encephalomyopathy; HDL, high density lipoprotein; LDL, low density lipoprotein; VLDL, very low density lipoprotein.

antibody testing is increased when a hypothesis-driven approach is used. e.g., a specific test ordered to support or confirm a diagnosis that is clinically suspected. When large panels are ordered indiscriminately, an opportunity facilitated by industry marketing practices, the probability of a false-positive result increases.[32,38,74] This section will address those antibody tests that are commercially available, appear to represent legitimate markers of specific neuromuscular phenotypes, and have a sensitivity adequate to warrant their judicious use in the appropriate clinical setting. Tests with limited sensitivity and/or specificity are purposefully omitted. In the patients with peripheral neuropathy, antibody tests will have the highest diagnostic yield in those individuals with subacute evolutions, multifocal distributions, and manifestations restricted to a motor, sensory, or autonomic domain. Chronic neuropathies that are length dependent, predominantly axonal, and sensorimotor in their characteristics are less likely to associate with abnormal serological tests of diagnostic significance.

Current evidence would support the aforementioned phenotypically targeted approach. In one study of 79 patients with cryptogenic polyneuropathy, 6% were found to have significant titers of one of four commonly tested antibodies (anti-Hu, anti-GM1, anti-MAG, and antisulfatide).[75] Two of these five individuals had generic phenotypes not typically correlated with the detected antibody and these were considered to be false-positive results. With neurologic paraneoplastic antibodies, significant antibody titers were found in less than 1% of cases considered to be at high risk of paraneoplastic syndromes.

Paraneoplastic Antibodies

In general, the presence of a paraneoplastic antibody predicts the existence, and to a lesser extent the type of cancer, rather than a specific neurologic syndrome.[74] Hu refers to an antigen found within the nuclei of dorsal root ganglia, the central nervous system, the myenteric plexus, and certain cancers, most notably small cell carcinoma of the lung.[76] Anti-Hu or antineuronal nuclear antibodies type 1 are most closely aligned with this malignancy.[44,77,78] Despite the concurrence of the Hu antigen distribution and clinical syndromes referable to destruction of these targets, the weight of evidence does not currently support a direct pathogenetic role for anti-Hu antibodies.[76] Their existence predicts a >90% sensitivity in identifying an underlying malignancy, which may or may not be initially detectable by conventional imaging methods. Conversely, anti-Hu antibodies will be found in the serum of 90% or more of patients with a sensory neuronopathy and malignancy. From a neuromuscular perspective, anti-Hu antibodies correlate best with a sensory neuronopathy phenotype, i.e., a non-length-dependent multifocal syndrome of sensory loss that frequently includes pain and sensory ataxia. Intestinal pseudo-obstruction, cerebellar degeneration, and limbic and brainstem encephalitis are other notable Hu-related syndromes.[79] Electrodiagnostically, a certain percentage of anti-Hu-related neuropathy cases will be found to have a sensorimotor neuropathy in which the motor component is not clinically evident. Testing for anti-Hu antibodies is recommended in the appropriate clinical context, i.e., a subacute sensory syndrome occurring in a smoker, with or without other suggestive paraneoplastic symptoms.

Antibodies directed against the collapsing response-mediator protein 5 or anti-CV2 have an even more diverse association with neurologic and non-neurologic syndromes.[65] These include cerebellar degeneration, MG, uveitis, optic neuropathy, chorea, and dysgeusia/dysosmia. Again, their presence correlates best with small cell lung cancer, although these have been reported in association with thymoma as well.[80] From a neuromuscular perspective, these are most closely associated with a sensory neuropathy. Unlike the anti-Hu syndrome, sensory axons rather than sensory nuclei within the dorsal root ganglia appear to be the target of the suspected immune-mediated injury.[81] Antibodies directed against N-type voltage-gated channel antibodies, distinct from the P/Q type associated with the LEMS, may represent a marker for paraneoplastic neuropathy as well.[52]

Antibodies Directed Toward Glycolipid and Glycoprotein Components of Peripheral Nerves

IgM antibodies directed against the GM1 ganglioside, first described in 1984, correlate with the syndrome of MMN, with or without detectable demyelinating conduction block.[82–87] In high titer, these appear to be fairly specific for this disorder.[9,43,88,89] Their specificity declines in low titer, being detectable in motor neuron disease, inflammatory demyelinating neuropathy, and normal individuals. The utility of anti-GM1 antibody testing is greatest in the clinical setting of a lower motor neuron syndrome in which neither a defining pattern of weakness nor a demyelinating conduction block can be demonstrated. Presumably, identification of high titer of IgM anti-GM1 antibodies in this population will identify a treatable motor neuropathy and distinguish it from a treatment-resistant, degenerative, or hereditary motor neuron disease. Although the sensitivity of this test has been quoted to be as high as 85% using specific technologies, their absence does not preclude treatment responsiveness as their sensitivity is generally quoted to be in a more modest 40–50% range.[85,90] Testing for anti-GM1 antibodies in lower motor neuron syndromes accompanied by definite upper motor neuron and/or bulbar features is not generally recommended.

IgG anti-GM1 antibodies as well as antibodies to other gangliosides have been linked to GBS as well as to specific organisms such as *Campylobacter jejuni* that are thought to act as an antigenic trigger to the neurologic syndrome.[9] In general, the low sensitivity of these tests offers little, if any, advantage over the conventional clinical, EDX, and CSF analysis by which GBS has been historically diagnosed.

Testing for antibodies directed against the GQ1b ganglioside has significant value. As the differential diagnosis of acute ophthalmoparesis can be confounding, a sensitive and specific marker for GBS with ophthalmoparesis and its Miller–Fisher variant provide considerable diagnostic benefit. The presence of these antibodies has both sensitivity and specificity in detecting and defining inflammatory demyelinating neuropathies associated with ophthalmoparesis.[52,91,92] They are found in the serum of 80–100% of patients with the Miller–Fisher variant of a sensitive and specific marker for GBS.[93,94] The apparent relevance of anti-GQ1b antibodies is made even more attractive by the demonstration that this antigen is abundantly expressed in the paranodes of the cranial nerves affecting oculomotor function.[92]

Of the antibody tests currently used in neuropathy diagnosis, antibodies directed against myelin-associated glycoprotein, first described in 1980, are associated with the greatest body of evidence, implicating a direct role in disease pathogenesis.[95] Immunofluorescent staining has detected radiolabeled antibody bound to peripheral nerve myelin, associated with the distinctive pathological feature of separation of myelin membranes. These antibodies are found in 50–70% of patients with a slowly progressive, demyelinating, sensory-predominant LDPN phenotype associated with an IgM kappa MCP.[96–98] Tremor, sensory ataxia, and generalized hypo- or areflexia are common features. The majority (approximately 85%) of patients with this phenotype and anti-MAG antibodies will have a detectable IgM MCP.[99] The presence of anti-MAG activity does not seem to define a different natural history or treatment responsiveness.[9,50] For these reasons, it can be argued that testing for anti-MAG antibodies is superfluous in patients who have the characteristic clinical syndrome, EDX pattern, and IgM MCP. If anti-MAG activity is sought, it is important to be aware of the potential for false-positive test results for the enzyme-linked immunosorbent assay (ELISA) screening technique. Conversely, the specificity for the Western Blot confirmatory test has been reported to be as high as 80–90%.[99,100]

Antibody Testing for DNMT

The basis for antibody testing in MG has evolved from the initial pathogenetic observations of Patrick and Lindstrom in 1973.[101] Antibody testing directed at various components of the nicotinic, postsynaptic anti-ACH receptor remains the most accurate of neuromuscular antibody tests. These antibodies, unlike most if not all described elsewhere in this chapter, have an unequivocal pathogenetic role in the disease with which these are associated. There are five different antibodies that are commercially available, have potential diagnostic relevance for autoimmune MG, and are related directly or indirectly to disease pathogenesis. These include ACHRBA, blocking and modulating antibodies, antibodies directed against muscle-specific kinase (MuSK), and antistriated muscle antibodies. The role of each of these antibodies will be briefly discussed.

ACHRBA antibodies are the primary means by which the diagnosis of autoimmune MG is serologically confirmed. Detection of these antibodies in serum is a highly specific and reasonably sensitive test. The incidence of false-negative testing varies depending in large part on two variables. The sensitivity of this test is in general proportionate to the severity of the illness. The incidence of ACHRBA in generalized myasthenia is estimated at approximately 80–90%, whereas the incidence in ocular myasthenia is quoted to be in the 50–70% range.[28,102] This provides an unfortunate dilemma whereby the incidence of false-negative tests is the greatest in a myasthenic population most difficult to diagnose by other means. The accuracy of ACHRBA detection is also dependent on the type of assay and source of receptor antigen used. Radioimmunoprecipitation and human ACH receptor harvested from amputated limbs are the current preferred methodologies.[103,104]

False-positive ACHRBA tests are uncommon but have been reported to occur. These may be found in LEMS, graft vs. host disease, autoimmune hepatitis, healthy relatives of patients with myasthenia, patients with thymoma, and rare patients with lung cancer and motor neuron disease.[102] There is no correlation between antibody titer and the severity of the disease nor is there a difference in phenotype or treatment responsiveness between seronegative and seropositive individuals. ACHRBAs have no utility in monitoring treatment response, as titers do not reliably decline coincident with successful treatment and as antibodies may remain in patients who enjoy clinical remission. Occasionally, patients with MG will seroconvert so that repeating the test in someone who is initially seronegative may be of potential value.

Anti-ACH receptor blocking and modulating antibodies have limited clinical utility. It is generally estimated that the latter may be detected in a significant titer in approximately 5% of patients seronegative for ACHRBAs.[102] In view of cost and this low figure, it is reasonable to postpone ordering this test until after the ACHRBA and EDX evaluation fail to confirm the diagnosis. This test is reported on a percentage basis and should be considered significant only when present at a high percentile. Minimally positive test results in normal

patients are not uncommon. Anti-ACH blocking antibodies are highly specific. False positives have rarely been reported in the LEMS and in patients exsposed to curare-like drugs. These are essentially never present in isolation. Accordingly, these are not used as a screening test for MG, and their only practical role is to aid in the identification of a potential false-positive result.[102]

Antistriated muscle antibodies or striational antibodies are not typically used to diagnose myasthenia, although their presence in otherwise seronegative individuals in the appropriate clinical context is suggestive. Striational antibodies are present in approximately 80% of myasthenics with thymoma and have their greatest utility in the detection of this tumor.[105] Antistriated muscle antibodies cross-react with a number of different striated muscle components including actin, actinin, myosin, the ryanodine receptor, and titin (connectin).[106] The specificity of these antibodies is somewhat limited. These may occur in patients with MG without thymoma, thymoma without MG, LEMS, and autoimmune liver disease, or in those treated with penicillamine.[107] Striational antibodies are of probable limited utility in patients with evidence of thymoma on imaging. Their sensitivity in detecting thymoma has been reported to be similar to that of computed tomography (CT) imaging of the chest.[108] Following titers of antistriated muscle antibodies in an effort to detect recurrent tumor in patients who have had thymectomy is a rational but unproven strategy.[109] Anti-titin antibodies are also found in the sera of 80% of patients with thymoma and 11% of patients with MG but without thymoma. In the latter group, disease onset is essentially always after the age of 60 years.[37] Anti-titin antibody testing is not currently commercially available.

As seronegative MG appears to be an autoimmune disease based on alterations of ACH receptor morphology, passive transfer experiments, and equivalent responses to immunomodulating treatments, other antibodies have been sought to fill this diagnostic gap.[28,110,111] Such tests would be of significant clinical utility in that a positive result would not only distinguish MG from other neuromuscular causes of weakness, but also distinguish acquired autoimmune MG from rarer hereditary, congenital forms of this disease. In 2001, antibodies directed against muscle-specific tyrosine kinase (MuSK) were found in the serum of some patients with "seronegative myasthenia."[112] The incidence was reported to be between 40% and 70% in these patients.[69,113–115] Unlike ACHRBA MG, the severity of anti-MuSK MG appears to correlate with antibody concentration.[116] Initially, these antibodies were thought to exist only in the sera of seronegative patients,[117] but an overlap is now known to exist, at least in some ethnic groups.[118] MuSK appears to have a role in the clustering of nicotinic ACH receptors during embryogenesis.[103] Although anti-MuSK antibodies appear to be a specific marker for the MG phenotype,[112] it has yet to be demonstrated that these alter either the anatomy or the physiology of the neuromuscular junction or are causally related to weakness produced by this or other mechanisms.[103,119]

Rippling muscle syndrome is a rare disorder often found in patients with inherited myopathies, particularly the limb-girdle dystrophy phenotype associated with caveolin deficiency. It may also occur as an acquired disorder in association with MG, thymoma, and ACHRBA.[120,121]

LEMS is an autoimmune disorder of presynaptic neuromuscular transmission. It may occur as an isolated disorder, or most frequently as a paraneoplastic condition, usually but not always associated with small cell carcinoma of the lung. The incidence of a detected underlying carcinoma has been reported to be between 43% and 69%.[122] Autoantibodies directed against the P/Q type of voltage-gated calcium channels are pathogenetic and represent a highly sensitive and specific marker for this disease. These do not block calcium channels but rather bind to them, resulting in downregulation through endocytosis. This in turn reduces the number of active zones and diminished quantal release. These antibodies were originally estimated to occur in high titer in virtually 100% of paraneoplastic LEMS and in greater than 90% of LEMS occurring independent of any underlying malignancy.[123] Predictably, further experience would indicate that sensitivity, although still impressive, is more in the 85% range.[124] As in seronegative MG, seronegative LEMS appears to be an antibody-mediated autoimmune disorder as the phenotype can be induced by passive transfer experiments in animals.[122] False-positive test results are rare and usually occur in low titer, reported in MG, motor neuron disease, other neurologic paraneoplastic syndromes, and small cell lung cancer without an associated neurological syndrome.[102,123]

Serological Testing for Muscle Disease

Antibody testing to aid in the diagnosis of suspected inflammatory myopathies is commercially available.[102,125] There are varying opinions regarding its value. There are typically other more specific and expeditious means to make a diagnosis. There is a frequently prolonged interval between specimen acquisition and result availability. As an anecdotal impression, these tests appear to be used more frequently by rheumatologists than neurologists. Although autoantibodies have been reported to occur in 60–80% of patients with idiopathic inflammatory myopathies, a select few appear to be "myositis specific" and occur far less frequently.[102,125] Their potential value includes the distinction between potentially treatable, acquired, immune-mediated muscle disease and other myopathies including some that are hereditary in which histological evidence of inflammation may occur. In addition, the presence of specific types of antibodies

(e.g., Jo-1 antibodies) may predict patterns of organ involvement in addition to skeletal muscle, particularly interstitial lung disease; response to treatment; and therefore prognosis. Only those selected antibodies will be described here.

Autoantibodies to amino-acyl-tRNA synthetase appear to correlate with a constellation of symptoms known collectively as the "antisynthetase" syndrome. Polymyositis, polyarthropathy, pulmonary fibrosis, Raynaud's phenomenon, and scaling and cracking of the lateral fingers constitute the major manifestations of this phenotype. The presence of anti-tRNA synthetases predicts a chronic condition with moderate responsiveness to immunomodulating treatment.[126] One of these six antisynthetases, anti-histidyl-tRNA synthetase or Jo-1, is found in 20–30% of patients with polymyositis or dermatomyositis. It correlates with the presence of interstitial lung disease in approximately 75% of these patients. Anti-Jo-1 essentially precludes the diagnosis of inclusion body myositis, although this distinction is usually readily made by clinical and histological means. Antibodies directed against signal recognition protein occur infrequently in patients with polymyositis but serve to identify a subgroup that is disproportionately black, with acute-onset, prominent cardiac involvement and poor responsiveness to immunomodulating treatment.[127] The presence of anti-Mi-2 antibodies conversely are seen predominantly if not exclusively in a small percentage of pediatric and adult dermatomyositis cases and typically predict treatment responsiveness.[128] Anti-PM-Scl and anti-Ku antibodies, unlike those already addressed, are myositis associated rather than myositis specific. These typically occur in individuals with other connective tissue diseases, with or without an associated myositis. These are usually associated with good treatment responsiveness.[125]

Serological Testing for Infectious Causes of Neuromuscular Disease

Lyme disease is a cause of a number of neuromuscular syndromes, including cranial neuropathy and polyradiculopathy.[129] Serology is the primary testing method for confirmation due to the difficulties inherent in the culture of the *Borrelia burgdorferi* spirochete. There are a number of controversial issues. In most laboratories, initial screening is performed on serum by the ELISA, a test with high sensitivity but limited specificity.[130–133] ELISA is estimated to have a 5% false-positive rate. Seroconversion takes place within 2–8 weeks and may be aborted by antimicrobial exposure. By the time neurological manifestations occur in the early disseminated phase of the disease, false-negative results are unexpected. If the ELISA screen is positive, confirmation is achieved by Western blot detection of IgM and IgG antibodies directed at specific Lyme antigens.[134] There is no recognized role for Western blotting in the setting of a negative ELISA screen. Although providing specificity, Western blotting lacks perfect sensitivity. The use of Western blotting alone without ELISA screening provides some risk of a false-negative result. Polymerase chain reaction, C6 ELISA antigen detection in urine and detection of immune complex disruption, and B lymphocyte chemoattractant have either not been adequately tested or not achieved adequate levels of sensitivity and/or specificity to be routinely applied to either serum or CSF.[135] In the CSF, demonstrating IgG and IgM Lyme antibodies in concentrations greater than those found in serum is currently the recommended means to confirm central nervous system involvement. The detection of Lyme antibodies in the spinal fluid may lack sensitivity, and CSF pleocytosis and/or elevation of protein levels in the appropriate clinical context is considered sufficient by some to identify CNS Lyme disease.[136–138] Rare cases of seronegative CNS Lyme detectable only with CSF examination have been reported.[129]

HIV is a neurotropic virus with a number of potential neuromuscular manifestations.[139–141] Serological testing is based on the detection of IgG antibodies directed against the p24 nucleocapsid and gp41 and 120 envelope proteins. These antibodies appear within 6 weeks in the majority of infected individuals and within 6 months in 95% and persist for life.[142,143] A positive test requires detection of two of these three antigens and has a detected sensitivity and specificity of over 99%.[144] As in Lyme disease, serological testing for HIV typically consists of an ELISA screen followed by Western blot confirmation. HIV antigens can be detected in the CSF in patients with CNS involvement.[145]

Other Serological Tests in Neuromuscular Disease

Neuropathy is estimated to occur in approximately 10% of patients with Sjögren's and/or the sicca syndrome, associating with multiple potential phenotyes.[146] A sensory neuronopathy syndrome, clinically similar to paraneoplastic neuropathy, is the most notorious of these. SFN phenotype may be the most common neuromuscular. Multifocal neuropathy, multiple cranial neuropathies, or trigeminal sensory neuropathy, with or without an associated sensory neuropathy, may occur as well.[147] Anti-Ro (SS-A) and Anti-LA (SS-B) antibodies represent a reasonable screening test in patient's with sicca symptomatology or a suggestive neuropathic phenotype. These are detectable in approximately 60% of patients with Sjögren's syndrome.[52] The diagnosis of seronegative Sjogren's or sicca-related neuropathy is dependent on tissue analysis, usually provided by lip biopsy, revealing an inflammatory response directed against minor salivary glands.

The presence of ganglionic acetylcholine receptor autoantibodies in the serum appears to define a group of patients with dysautonomia whose phenotype includes orthostatic hypotension, erectile dysfunction in males and some combination of sicca symptoms, abnormal pupillary responses, gastroparesis, and neurogenic bladder.[46,79,148] These may be detected in approximately 50% of patients with an acute, presumed immune-mediated autonomic neuropathy.[9]

The potential association between celiac sprue and polyneuropathy is controversial.[149,150] A sensory-predominant, axonal, length-dependent phenotype has been most frequently associated with this disorder.[151,152] Antigliadin, antitransglutaminase, and endomysial antibody tests are all potential screening tests for this disorder, the former having the least specificity. When these are detected in neuropathy patients, it is usually in individuals with sprue.[149] Their specificity and sensitivity in patients without enteral symptoms remain uncertain. Neuropathy response to dietary and immunomodulating treatment has been disappointing to date, suggesting that the neuropathy is due to alternative mechanism than sprue, or that nerves are damaged beyond repair.

Vasculitic neuropathy may occur in a multifocal neuropathy or an apparent LDPN pattern. The latter may represent the confluence of a multifocal neuropathy syndrome. Neuropathy occurs with the greatest prevalence in vasculitis due to polyarteritis, Churg–Strauss syndrome, or Wegener's granulomatosis and can be the presenting manifestation of these disorders. *p*-Antineutrophilic cytoplasmic antibodies (ANCA) or antibodies directed against myeloperoxidase represent a marker for the former two disorders. The presence of c-ANCA or antibodies directed against antiproteinase 3 provide high specificity in support for a diagnosis of Wegeners.[52] In one series, 8% of 166 neuropathy patients had positive blood tests for ANCA.[153] Approximately half of these patients were found to have systemic vasculitis, the disorder for which this test is most commonly used as a screening procedure. As this series was derived from a major peripheral neuropathy referral center, it is not clear whether its application to a more general neuropathy population would result in a similar yield. Vasculitis and neuropathy may also occur as a consequence of rheumatoid arthritis. Although titers of rheumatoid factor tend to be high in general in rheumatoid vasculitis, the presence of these antibodies represents a marker of the underlying disease and does not define the cause of neuropathy. Predictably, the yield and accuracy of ANCA and rheumatoid factor testing will be greatest in patients with acute to subacute painful and frequently multifocal neuropathy patterns who additionally have signs and symptoms of an underlying systemic disease process.

Antibodies directed against voltage-gated potassium channels occur in a large percentage of patients with acquired neuromyotonia or Issacs' syndrome, both in serum and in CSF. As in LEMS, Issacs' syndrome is an autoimmune disorder that can occur in isolation, in association with other autoimmune diseases or as a paraneoplastic syndrome.[124,154,155]

▶ CSF ANALYSIS

CSF analysis is a potentially helpful if not routine test performed in the evaluation of select groups of patients with suspected neuromuscular disease. From an anatomic perspective, abnormal CSF results imply the existence of pathology in the central nervous system or within the nerve roots. As such, these are diagnostically helpful from a number of different perspectives. Abnormal CSF may suggest the existence of a disorder that affects both the central and the peripheral nervous system and limit the differential diagnosis in that manner. Abnormal CSF may aid in the localization within the neuromuscular system and narrow differential diagnostic considerations in that manner as well. Lastly, CSF analysis may provide an exact diagnosis in neuromuscular disorders such as neoplastic meningitis or motor neuron disease caused by West Nile or other viruses by cytological or serological analysis.

An elevated CSF protein level in the absence of a cellular response in the setting of a peripheral neuropathy implies demyelination of nerve roots, as characteristically seen in both the acute and the chronic inflammatory demyelinating neuropathies. This same formula is also characteristic of mitochondrial disorders, which may produce a number of neuromuscular phenotypes as well in a certain percentage of patients with ALS. A lymphocytic pleocytosis in the setting of an acute motor neuron syndrome suggests a West Nile, poliomyelitic, or other neurotropic enteroviral infection. A lymphocytic pleocytosis occurring in the setting of an apparent polyradiculopathy with both sensory and motor involvement would suggest neoplastic, inflammatory, or chronic infection causes of meningitis. Lyme disease and sarcoidosis are two notable examples of the latter two categories.

▶ NERVE AND MUSCLE IMAGING

Imaging of nerve and muscle is being used with an increasing frequency in the evaluation of patients with neuromuscular disorders.[156,157] Arguably, this role will continue to evolve as resolution of the images and neurologist's familiarity with the benefits of a number of different applications expand. Although both computerized axial tomography (CAT) and ultrasound have been used, magnetic resonance imaging (MRI) is currently the imaging modality of choice in most circumstances. The current role of imaging is undoubtedly influenced by

individual experience and biases. Potential applications include:

- In muscle disease
  - detect signal change/atrophy within/of muscle suggesting myopathy, particularly when muscle involvement is subclinical, e.g., dermatomyositis without weakness;
  - define a pattern of muscle involvement to provide an etiologic diagnosis or refine the differential diagnosis in myopathy;
  - reveal muscle involvement in syndromes of multiple causes, e.g., paraspinal muscle atrophy in camptocormia;
  - identify muscle(s) suitable for biopsy.
- In nerve diseases
  - detect nerve enlargement indicative of nerve tumor or hypertrophic nerve, particularly in areas that have limited EDX accessibility;
  - define a pattern of signal change within specific muscles that may define specific nerve injury (may precede analogous changes on EDX)[147];
  - detect nerve enhancement suggestive of an acquired, inflammatory neuropathy, e.g., MMN and acute brachial plexus neuropathy, particularly in areas that have limited EDX accessibility;
  - identify focal, structural nerve pathology superimposed upon and disguised by a more diffuse peripheral nerve disorder.
- In nerve or muscle disease, monitor response to treatment.

This section will emphasize the direct imaging of nerve and muscle. Other pathologies that indirectly affect nerve or muscle through direct compression or infiltration (e.g., retroperitoneal hematoma, Pancoast tumor, and rhabdomyosarcoma) will not be discussed. Ideally, future imaging techniques will allow us to track the progress of reinnervation and allow determination of the efficacy of treatment on a more expeditious basis.

Ultrasonography is of potential value as a diagnostic tool in that it is readily available, relatively inexpensive, quick, and painless.[158] It is limited by the specificity of the changes it may demonstrate and its ability to assess deep structures or those in an obese population. It is capable of detecting altered echogenicity within muscle indicative of pathology as well as the existence and pattern of muscle atrophy or hypertrophy. Arguably, it is a diagnostic tool best applied to children and/or to identify an ideal muscle to biopsy.[157] Ultrasound has been used to identify nerve transaction and has demonstrated an 89% sensitivity and 95% specificity under experimental conditions.[159]

The role of CT in neuromuscular disease has been, in large part, usurped by MRI except in those who cannot have or tolerate MRI due to size, claustrophobia, or metallic implants. CT can differentiate nerve from muscle disease, not only based on the pattern of muscular involvement but based on the basis of X-ray attenuation changes within individual muscles as well.[89] CT has been demonstrated to be 85% sensitive in detecting neuromuscular pathology, using muscle histology as the comparative gold standard.[160]

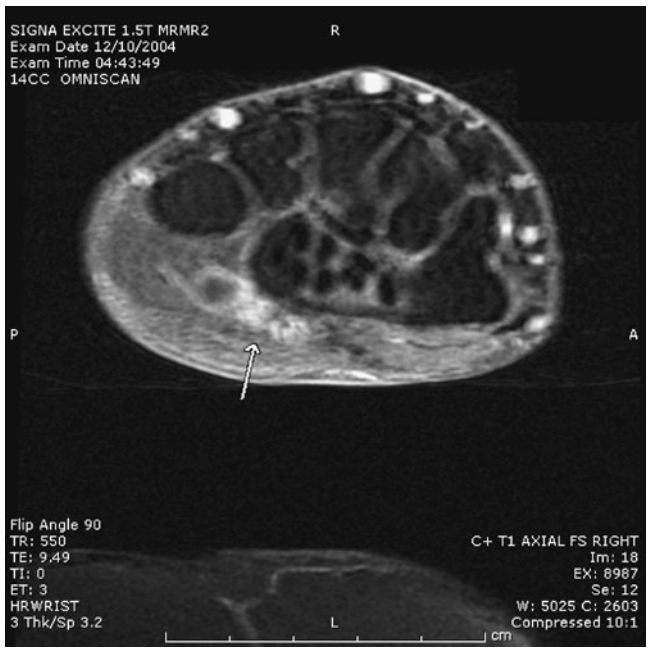


Figure 2–20. MRI (T1 sequence with gadolinium) demonstrating enhancing mass (arrow) in Guyon's canal (ganglion cyst) in a young female presenting with painless weakness and atrophy restricted to intrinsic right-hand muscles innervated exclusively by the ulnar nerve.

MRI has certain inherent advantages over CT. Figs. 2–20 to 2–22 provide three representative examples where MRI aided significantly in the diagnosis of nerve (Figs. 2–20 and 2–21) and muscle (Fig. 2–22) disease. MR image resolution exceeds that of both US and CT. MRI images can be obtained in multiple planes without repositioning the patient or reformatting data with the loss of associated resolution. The contrast agent used with MRI is noniodinated, resulting in far fewer adverse reactions. MRI images can also be obtained with numerous different weightings, allowing emphasis on different tissue characteristics. For example, chronic nerve and muscle diseases are both associated with fatty replacement of muscle manifesting as increased signal in T1-weighted images. Acutely denervated muscle will demonstrate little if any signal change with T1 sequencing.[161] T2-weighted images accentuate the signal produced by water. Increased T2 signal occurs within acutely denervated muscle. It is generally felt to correlate with the pathological features of edema, inflammation, and myofiber necrosis.[88,108,115,162–166] Muscle hypertrophy is not usually associated with tissue signal changes.

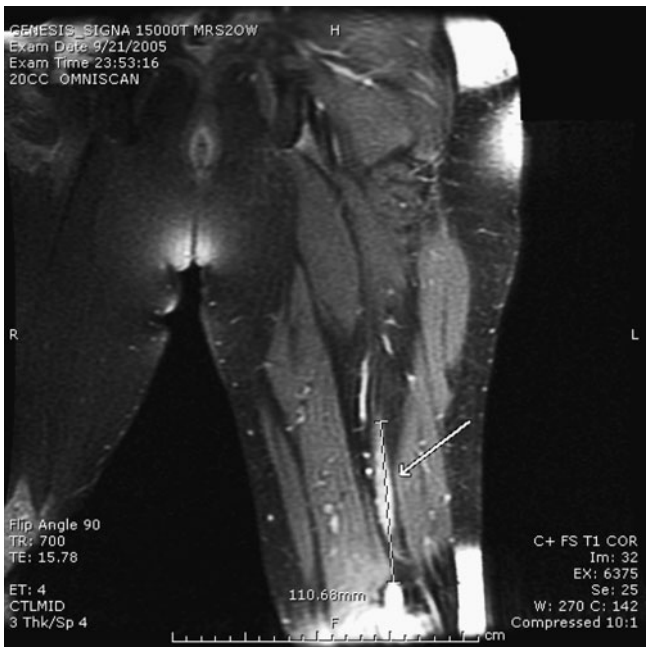
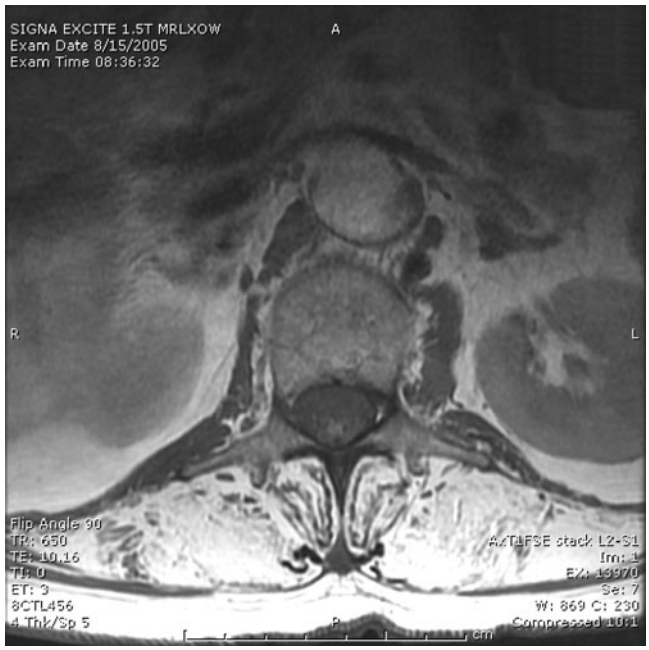


Figure 2–21. MRI (T1 sequence with gadolinium) demonstrating enhancing mass (arrow) in the distal left sciatic nerve (Schwannoma) in a young male with slowly progressive weakness of foot plantar flexion and sensory loss on the sole of the foot.



A

B

Figure 2–22. (A) MRI (T1 sequence) demonstrating fatty replacement and atrophy of the lumbar paraspinal musculature in (B) an older woman with bent spine syndrome.

MRI has numerous potential roles in the assessment of muscle disease.[167,168] It is the diagnostic test of choice for muscle infarction. Abnormal, but currently nonspecific signal changes can be seen in various metabolic muscle disease. MRI has been reported to be 89–97% sensitive and 89% specific in detecting abnormalities in the inflammatory myopathies.[108,162] Signal changes have also been documented to occur coincident with treatment responsiveness in these disorders.[162,169] As in EDX, it has been used to detect asymptomatic muscle involvement in patients with characteristic rashes and to aid in the distinction of muscle weakness due to steroids as opposed to the underlying disease.[88,162] Distinct patterns of muscle involvement have the potential to be diagnostic, most notably in inclusion body myositis.[108] Although of limited pragmatic benefit, rhabdomyolysis is associated with a diffuse pattern of increased signal on T2 or short tau inversion recovery (STIR) sequences.[115,170] Gadolinium has a limited role in MRI of muscle and is used predominantly for the assessment of suspected primary or metastatic muscle tumors.[167]

MRI has a number of beneficial applications in nerve disease as well. Normal nerve is isointense with muscle on both T1- and T2-weighted sequences. An axonal nerve injury will have increased signal characteristics on cross-sectional images using STIR sequences and T2 fast spin echo sequences both at and distal to axon loss injury and will enhance with gadolinium.[161] STIR enjoys the benefit of more intense signal characteristics and fat signal suppression but does not provide the image resolution of its T2 fast spin echo counterpart. Acutely denervated muscle will also have increased signal characteristics on STIR and T2 fast spin echo sequences that may precede the development of acute denervation on the EDX examination. Signal changes do not take place in muscles in which nerve injuries appear to be purely demyelinating.[156]

MRI imaging has been used to detect focal nerve entrapment or compression syndromes. In the case of

carpal tunnel syndrome, it has not usurped the traditional role of EDX in most institutions.[171] One potential benefit of MRI imaging in this context is its potential ability to identify a secondary pathology as a contributor to the syndrome, e.g., a ganglion cyst within the tunnel. There is the potential for a greater role for MRI in the evaluation of ulnar neuropathy at the elbow than in carpal tunnel syndrome. Carpal tunnel syndrome has demyelinating pathophysiology in most cases and is therefore readily localizable to the wrist. It has been estimated that up to one-half of ulnar neuropathies have a predominantly axonal pathophysiology, which usually precludes precise lesion localization. MRI has been shown to identify increased signal in areas consistent with ulnar nerve injury at least in some cases and may do so even when EDX is normal.[172] MRI has been reported to be occasionally beneficial in other less frequent and at times controversial mononeuropathies including thoracic outlet, piriformis syndromes, and tarsal tunnel syndromes, as well as posterior interosseous and peroneal neuropathies.[156] It would be prudent to interpret subtle imaging abnormalities cautiously in these aforementioned contexts and to accept their validity only when congruent with clinical and EDX data.

Ideally, MRI could accurately identify nerve transaction or avulsion in traumatic injury to expedite surgical intervention in these cases. Unfortunately, current imaging resolution and evolution of signal changes within nerve and muscle do not provide this service. With both axonotmetis (axonal transaction with preservation of nerve sheath continuity) and neurotmetis, there is increased signal on STIR and T2 fast spin echo images in the nerve distal to the injury that persists but is eventually resolved. In both cases, chronic denervation produces fatty infiltration of denervated muscle, which does not allow for distinction between the two types of injury.[156]

MRI is the current diagnostic modality of choice to identify nerve sheath tumors. Virtually all of these, regardless of histology, demonstrate gadolinium enhancement. Benign histology cannot reliably be distinguished from its malignant counterpart by MRI, although positron emission tomography may be helpful in this regard. A potentially vexing clinical problem, the separation of recurrent tumor vs. radiation-induced plexus injury, may be solved in some cases by different MR characteristics. Recurrent tumor tends to be focal, irregular, and enhancing. Radiation-induced nerve injury tends to produce either uniform enlargement or focal atrophy.[156]

MRI is capable of identifying areas of presumed inflammation, edema, and demyelination in the acquired inflammatory demyelinating neuropathies, including MMN, GBS, and CIDP,[173–177] and in brachial plexus neuritis.[178] In some cases, nerve root are preferentially involved in keeping with known pathological data.[173] T2 signal abnormalities in brachial plexus elements may be seen in both CIDP and MMN.[177] Other than for symmetry, these changes are identical. These may be of considerable utility, however, allowing for the discrimination of MMN and other, presumed degenerative and untreatable lower motor neuron syndromes. Although insightful in the appropriate clinical context, neither the location, signal characteristics, nor the morphology of imaging abnormality predict pathology in these disorders. Similar changes, particularly in nerve roots, may be seen in infectious, neoplastic, or other inflammatory diseases (e.g., sarcoidosis) with affinity for peripheral nerve.[157] MRI may be capable of identifying hypertrophic nerves seen in conditions such as CMT disease,[179] particularly within the spinal canal where these may lead to the clinical syndrome of neurogenic claudication.

In summary, imaging has a definite and undoubtedly expanding role in the evaluation of neuromuscular disease. What its role and indications are in comparison with the other diagnostic techniques described in this and in the subsequent chapter is an evolving question undoubtedly influenced by personal experience and bias. As the potential applications of MRI in nerve and muscle disease increase, e.g., the use of superparamagnetic iron oxide to mark and follow macrophage migration into damaged peripheral nerve,[161] the utility of imaging in the evaluation of patients with nerve and muscle disease can only expand as well.

▶ SUMMARY

This chapter has attempted to provide an even and practical description of the many ancillary tests that are available to the neuromuscular clinician. It has attempted to fairly emphasize both the strengths and the weaknesses of each modality. Again, these tests represent a proverbial double-edged sword that may achieve either a desired or an undesired effect, dependent on the skill, knowledge, and judgment of the hand that wields it.

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CHAPTER 3

Muscle and Nerve Histopathology

▶ INTRODUCTION

Muscle and nerve biopsies can be extremely useful in the evaluation of patients with myopathies and neuropathies. That said, not everyone suspected of having a muscle or nerve disorder needs a biopsy. In this chapter, we discuss the indications and limitations for muscle and nerve biopsies, how specific muscle or nerves are selected for biopsy, and various aspects of specimen handling. Further, we discuss the routine stains that are performed on muscle and nerve tissue, other stains or studies that can be performed on the tissue, and when to order them. We also discuss the role of skin biopsy to assess epidermal nerve fibers in the evaluation of patients with peripheral neuropathy. This chapter is not designed to make the reader a neuropathologist. However, clinicians who take care of patients with neuromuscular disease and order biopsies should have at least a working knowledge of muscle and nerve histopathology.

▶ MUSCLE BIOPSIES

Muscle biopsies are studied through a combination of enzyme histochemistry, electron microscopy (EM), and molecular biology.[1–5] It is important to correlate the histopathological findings with the clinical history, the neuromuscular examination, and the electrodiagnostic findings.

INDICATIONS FOR MUSCLE BIOPSY

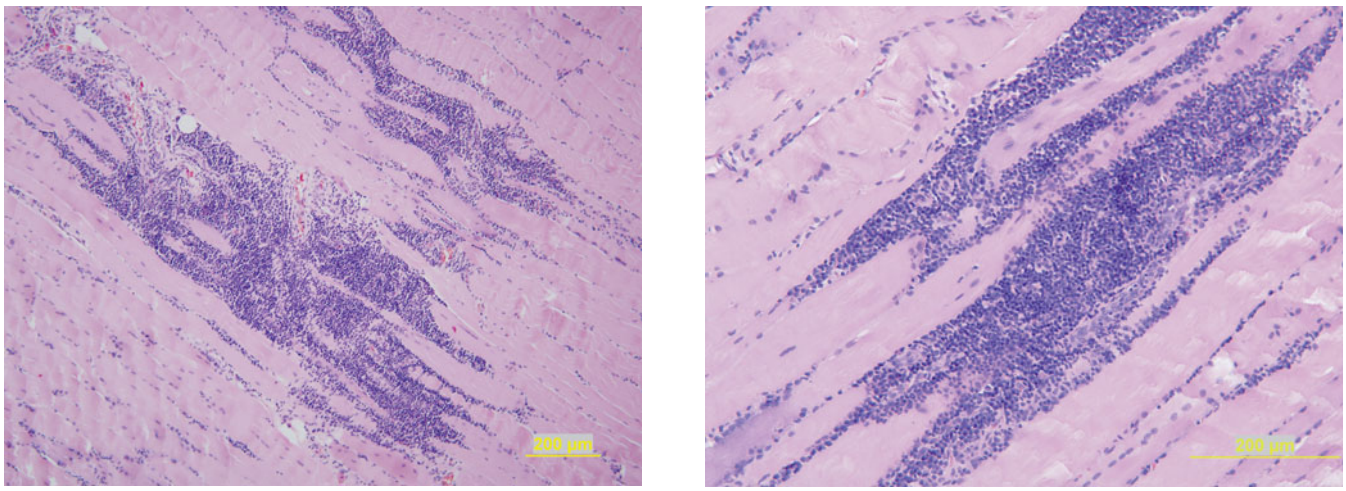
A muscle biopsy may be helpful when the patient has objective muscle weakness, abnormal muscle enzymes (e.g., elevated serum creatine kinase levels), abnormal skeletal muscle magnetic resonance imaging, or myopathic electromyographic findings (EMG). These findings may point to a myopathy but not the exact etiology, and therefore a muscle biopsy may be indicated. That said, if the diagnosis is suspected based on the phenotype and can be made by less invasive means, we generally opt for this first. For example, in a young boy with proximal weakness and large calves, we would first do genetic testing for a dystrophinopathy. Muscle biopsies are less helpful in evaluating patients with only myalgias, subjective weakness, or mild isolated elevations of creatine kinase (CK) in absence of objective abnormalities.[6]

TECHNIQUES

Muscle tissue can be obtained through an open (minor surgical procedure) or needle biopsy. A larger sample of tissue can be biopsied by the open surgery technique, and we prefer this method in patients who may have patchy pathology (e.g., inflammatory myopathies) or myopathies that require metabolic analysis (e.g., mitochondrial disorders or glycogen storage diseases), molecular studies (e.g., Western blotting and direct genetic analysis), or electron microscopy (EM). Needle biopsy can also be technically difficult in patients with substantial subcutaneous tissue or whose muscles are atrophic and/or fibrotic. However, the yield of a needle biopsy can be quite high in laboratories that are experienced in handling the small amount of tissue obtained by this technique.[7–10] The advantage of a needle biopsy is that it allows for examination of multiple sites within the muscle and it is a less invasive procedure than an open muscle biopsy.

We select the specific muscle to biopsy based on the clinical examination, or occasionally based on skeletal muscle magnetic resonance imaging or EMG guidance. If the requesting physician is not the person who performs the surgery (the usual situation), communication between the two is essential to ensure that the proper site is chosen. Preferably, one should biopsy a mildly weak muscle in the Medical Research Council grade 4/5 range to increase the yield. If the muscle is too weak (i.e., Medical Research Council grade 3 or less), the tissue typically has end-stage damage. It is often impossible to discern a myopathic process from severe neurogenic atrophy under these conditions. In patients with little, if any, weakness on examination, or those who might only have weakness in muscles that are not easily assessable to biopsy (e.g., iliopsoas muscle in a patient with only hip flexor weakness), needle EMG or skeletal muscle magnetic resonance imaging are used to select the muscle to biopsy. However, it is important to biopsy the contralateral muscle to the needle examination in order to avoid artifact from needle EMG.

We find that the easiest muscle to biopsy with open surgery is the biceps brachii and is our first choice if clinically affected. Other muscles that are commonly biopsied are the deltoid, triceps, and quadriceps. The peroneus brevis muscle is useful to biopsy along with the overlying superficial peroneal nerve in patients



A B

Figure 3–1. Paraffin sections are useful because large, longitudinal segments of muscle fibers can be cut and stained compared to frozen sections. Marked endomysial inflammatory cell infiltrate in this biopsy of a patient with polymyositis (A). On higher power, inflammatory cell infiltrates can be seen to invade the necrotic segments (B). Paraffin sections, hematoxylin and eosin (H&E).

suspected of having vasculitis. In patients with suspected distal myopathies, we have found the tibialis anterior, gastrocnemius, and extensor digitorum easy to biopsy. Otherwise, we tend to avoid the gastrocnemius or tibialis anterior muscle, because asymptomatic radiculopathies or unrelated axonal polyneuropathies may give a false impression that the primary abnormality is a neurogenic process and therefore overshadow an underlying myopathy.

In adults, muscle biopsies are performed under local anesthesia, but young children require sedation or general anesthesia. The biopsies are taken from the belly of the muscle, and it is important to avoid the region of the tendon. Each specimen should be about 1–2 cm in length and 0.5 cm in width. The specimens should be wrapped in slightly moist gauze and placed in separate labeled sterile containers until they reach the laboratory. The tissue should be processed immediately. Because muscle disorders can be multifocal (e.g., inflammatory myopathies), we obtain at least two separate specimens, which are immediately frozen in isopentane cooled in liquid nitrogen. The frozen tissue is then sectioned and stained for routine histochemistry. In patients with prominent myalgias and tenderness, we may biopsy a piece of the overlying fascia to assess for fasciitis. Separate specimens may also be taken and again frozen immediately for biochemical analysis (e.g., for glycogen or lipid storage disorders and mitochondrial myopathies), mitochondrial DNA analysis, or for Western blot (e.g., in various forms of muscular dystrophy).

In addition, a separate piece of muscle tissue is fixed in formalin or Bouin's fluid for paraffin sections. Paraffin sections can be particularly useful in inflammatory myopathies and vasculitis, as it allows for the examination of a somewhat larger piece of tissue than that used for histochemistry in cross section and longitudinal section and assesses inflammatory cells and vasculature more effectively (Fig. 3–1). However, due to shrinkage of the muscle tissue associated with the processing, the muscle fibers in paraffin sections are often appear cracked and are not ideal for evaluation of histochemical abnormalities. Finally, an additional piece of muscle should be taken for possible ultrastructural examination with EM. This small piece of muscle tissue is secured on a clamp or stretched out by suturing the muscle over a tongue blade, in order to prevent hypercontraction artifact. This tissue is fixed in glutaraldehyde for plastic (resin) embedding for EM.

A standard battery of histochemical stains are used for light-microscopic evaluation of frozen sections.[1–5] Hematoxylin and eosin (H&E) and modified Gomori-trichrome stains assess the size and shape and cytoarchitecture of the muscle fibers, presence of internalized nuclei, destruction of fibers (e.g., necrosis) and regeneration, as well as the supporting connective tissue (e.g., dystrophic features) and vasculature (vasculitis) (Figs. 3–2 and 3–3). Inflammatory cell infiltration is easily appreciated with these stains. In addition, some specific abnormalities are well demonstrated with modified Gomori-trichrome stain (e.g., ragged red fibers associated with mitochondrial myopathies, nemaline rods, tubular aggregates, and rimmed vacuoles) (Fig. 3–4).

The myofibrillar adenosine triphosphatase (ATPase) is typically performed at three pHs, 4.3, 4.6, and 9.4, in order to assess the size and distribution of different muscle fiber types (Table 3–1 and Fig. 3–5). Individual

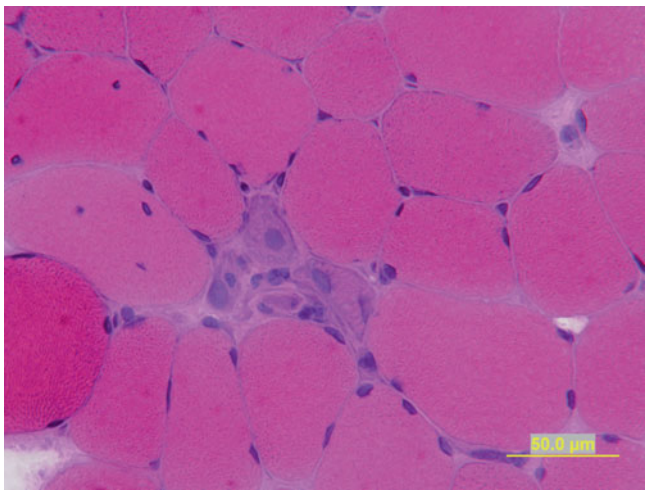


Figure 3–2. A cluster of regenerating muscle fibers are apparent on this H&E stain.

muscle fibers can be classified into four different fiber types based on their staining characteristics and physiologic properties: types 1 (slow twitch, fatigue resistant, and oxidative metabolism), 2A (fast twitch, intermediate fatigue resistance, and oxidative and glycolytic metabolism), 2B (fast twitch, poor fatigue resistance, and glycolytic metabolism), and 2C (undifferentiated and embryonic). In adults, only about 1–2% of muscle fibers are the undifferentiated type 2C fibers.[11] The specific muscle fiber type is determined by the innervating motor neuron. The different muscle fiber types are normally distributed randomly, forming a so-called checkerboard pattern. Alterations in the random distribution of fiber such as seen with fiber-type grouping are a sign of a neurogenic process with subsequent reinnervation. Some

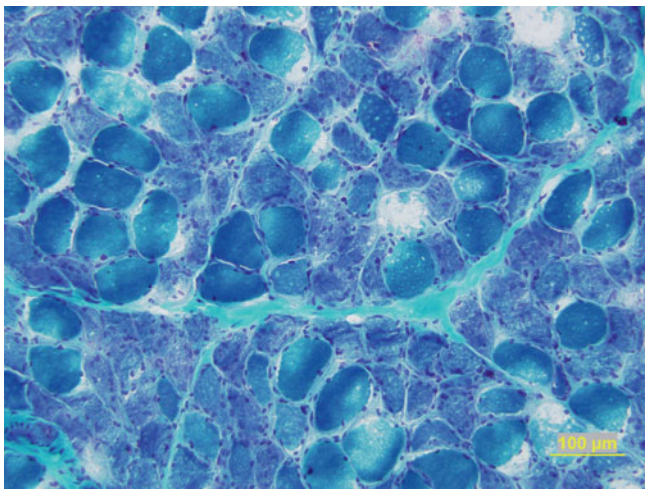


Figure 3–3. Muscle biopsy in a patient with acute quadriplegic myopathy reveals marked atrophy degeneration of muscle fibers on this modified Gomori-trichrome stain.

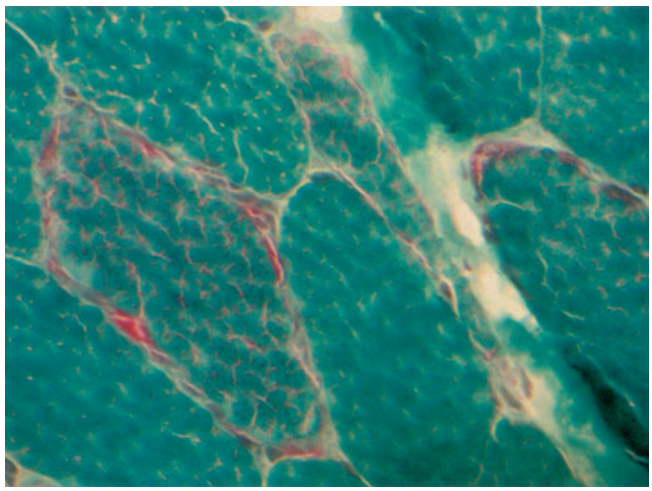


Figure 3–4. Modified Gomori-trichrome stain reveals a ragged red fiber in a patient with a mitochondrial myopathy.

myopathies are associated with a predominance of one fiber type or another as well as atrophy of specific fiber types. For example, some congenital myopathies are associated with a predominance of type 1 fibers, which are also smaller in diameter than normal. Disuse and steroid myopathy are associated with preferential atrophy of type 2B fibers.

Periodic acid Schiff (PAS) stain is used to assess glycogen content, which may be increased in the glycogen storage disorders (Fig. 3–6). If there is abnormal PAS staining then a PAS with diastase should be performed, as glycogen is removed with diastase but more complex carbohydrates (such as polyglucosan bodies) are resistant to digestion with diastase. Loss of some enzyme activities associated with some metabolic myopathies can be detected by specific staining protocols (e.g., myophosphorylase and phosphofructokinase). Acid phosphatase stains can highlight lysosomes that are increased in certain disorders (e.g., Pompe disease) as well as macrophages that may be present in muscle tissue. In addition, oil red O or Sudan black can evaluate lipid content, which may be increased in patients with lipid storage myopathies (Fig. 3–7). Oxidative enzyme stains (nicotinomide adenine dinucleotide-tetrazolium reductase or NADH-TR, succinate dehydrogenase or SDH, cytochrome-C oxidase or COX) are useful for identifying mitochondrial and intermyofibrillar network abnormalities (Fig. 3–8). Target fibers suggestive of denervation are particularly well seen with the NADH-TR stain. Various stains (Congo red, crystal violet, cresyl violet, and Alcian blue) can be performed to assess for amyloid deposition (Fig. 3–9).

Immunohistochemistry is important in evaluating for specific types of muscular dystrophies (e.g., dystrophin staining for Duchenne and Becker muscular dystrophy; merosin and alpha-dystroglycan staining for

▶ **TABLE 3–1. MUSCLE FIBER TYPE CHARACTERISTICS**

	Type 1	Type 2A	Type 2B
Gross appearance			
Color	Dark	Dark	Pale
Capillary density	High	High	Low
Muscle fiber diameter	Smallest	Large	Largest
Comparative histochemical activity			
ATPase 4.3	Strong	Weak	Weak
ATPase 4.6	Strong	Weak	Strong
ATPase 9.4	Weak	Strong	Strong
Adult myosin heavy chain—fast	Weak	Strong	Strong
Adult myosin heavy chain—slow	Strong	Weak	Weak
NADH-TR	Strong	Strong	Weak
SDH	Strong	Weak	Weak
Cytochrome oxidase	Strong	Weak	Weak
Glycogen content	Low	High	High
Glycogen phosphorylase	Weak	Strong	Strong
Myoglobin content	High	High	Low
Lipid content	High	High	Low
Modified Gomori trichrome	Strong	Weak	Weak
Electron microscopy			
Mitochondria	Numerous	Numerous	Few
Z-disc	Intermediate	Wide	Narrow
Physiologic characteristics			
Twitch speed	Slow	Fast	Fast
Fatigability	Resistant	Resistant	Susceptible
Axons			
Diameter	Smallest		Largest
Conduction velocity	Slowest		Fastest
Other classifications			
	Intermediate (Red)	Red	White
	S	FR	FF
	SO	FOG	FG
	B	C	A

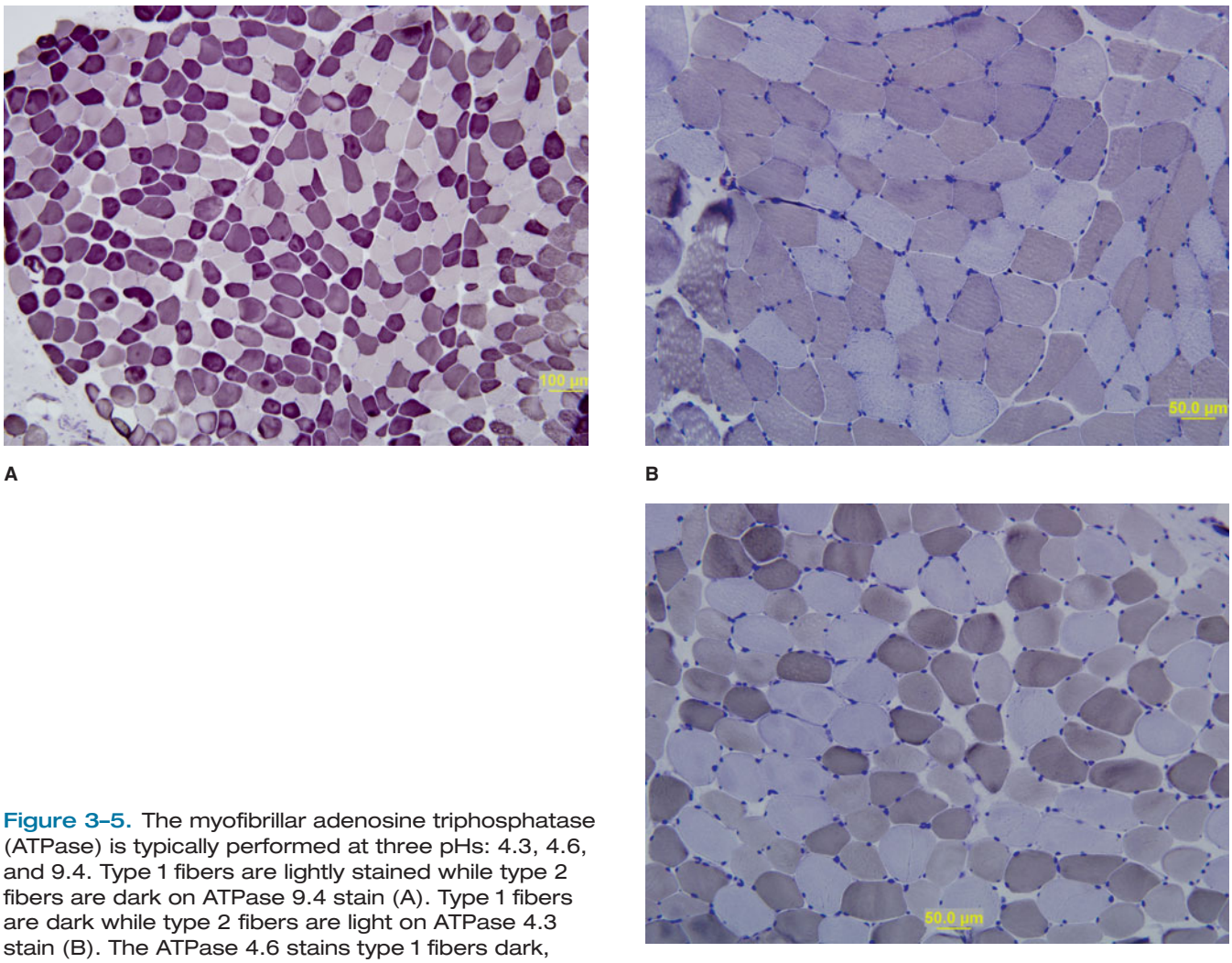
FR, fast, resistant; FF, fast, fatigable; S, slow; FOG, fast, oxidative glycolytic; FG, fast, glycolytic; SO, slow oxidative; NADH-TR, nicotinomide adenine dinucleotide-tetrazolium reductase.
Modified with permission from Carpenter S, Karpati G. Pathology of Skeletal Muscle, 2nd edn. New York: Oxford, 2001, Fig. 3.2, p. 45.

congenital muscular dystrophy; sarcoglycans, caveolin, telethonin, and dysferlin for limb girdle muscular dystrophies; and emerin for Emery–Dreifuss muscular dystrophy) (Fig. 3–10). Immunohistochemistry can also be valuable in inflammatory myopathies and vasculitis (e.g., stains for major histocompatibility antigens, complement, membrane attack complex, immunoglobulins, and appropriate inflammatory cell markers) (Fig. 3–11).

EM is used to assess the ultrastructural components of muscle fibers (e.g., the sarcolemma, sarcomeres, nuclei, and mitochondria) and vasculature (e.g., tubulofilaments in capillaries in dermatomyositis) (Fig. 3–12).[12] Various myopathies have specific ultrastructural abnormalities that are more readily characterized by EM (e.g., vacuoles, central cores, nemaline rods, myofibrillar degeneration, proliferation of abnormal appearing mitochondria, and filamentous inclusions in nuclei and sarcoplasm).

STRUCTURE OF NORMAL SKELETAL MUSCLE

Skeletal muscles are syncytial tissue composed of individual muscle fibers with multiple nuclei. The connective tissue within muscles include the endomysium that surrounds individual muscle fibers, the perimysium that groups muscle fibers into primary and secondary bundles (fasciculi), and the epimysium that envelops single muscles or large groups of fibers. Normally, myonuclei are located adjacent to the muscle membrane (sarcolemma) and are oriented parallel to the length of the fiber. These are oval in shape and contain evenly distributed chromatin and inconspicuous nucleoli. In approximately 3% of normal adult fibers, the myonuclei lie more internal within the cytoplasm (sarcoplasm). Increased internalized nuclei are a nonspecific abnormality, as these are seen in different types of myopathies as



A

B

C

Figure 3–5. The myofibrillar adenosine triphosphatase (ATPase) is typically performed at three pHs: 4.3, 4.6, and 9.4. Type 1 fibers are lightly stained while type 2 fibers are dark on ATPase 9.4 stain (A). Type 1 fibers are dark while type 2 fibers are light on ATPase 4.3 stain (B). The ATPase 4.6 stains type 1 fibers dark, type 2A fibers light, and type 2B fibers in between (C).

well as in neurogenic disorders. Satellite cells are present next to the sarcolemma and are enveloped by basement membrane that surrounds the muscle fibers. Most of the sarcoplasm of the muscle fiber contains myofilaments, which form the contractile apparatus and supporting structures. Individual muscle fibers contain repeating units (sarcomeres) of interlaced, longitudinally directed thin filaments and thick filaments and perpendicularly oriented Z bands to which the thin filaments are connected. The sarcomere is connected to the sarcolemma via filamentous actin. The sarcolemma is composed of various protein complexes and is connected to the extracellular matrix. Greater detail of the sarcolemmal proteins and extracellular matrix is discussed in Chapter 24 devoted to Muscular Dystrophies.

The T tubules are composed of invaginations of the sarcolemmal membrane into the interior of the muscle fibers. Their course is parallel to the Z bands and they are surrounded on each site by the sarcoplasmic reticulum. The T tubules allow for rapid depolarization of muscle membrane deep within muscle fiber cells and the accelerated release of calcium from the sarcoplasmic reticulum during excitation.

Adult muscle fibers are polygonal in appearance but are more rounded in shape in infancy and early childhood. The cross-sectional diameter of individual fibers varies depending on the specific muscle, fiber type, and age of the individual. The motor neuron and the muscle fibers it innervates comprise the motor unit. The individual muscle fibers of a motor unit are normally randomly distributed as previously mentioned, within a sector approximating 30% of the muscle's cross-sectional diameter.

The percentages of type 1, 2A, and 2B fibers differ in various muscle groups, and it is important to be aware of the normal percentages of these fibers in the biopsied muscle for accurate assessment.[13] The most commonly biopsied muscles (i.e., biceps brachii, triceps, and quadriceps) have approximately equal amounts of the three major fiber types, although the deltoid muscle has

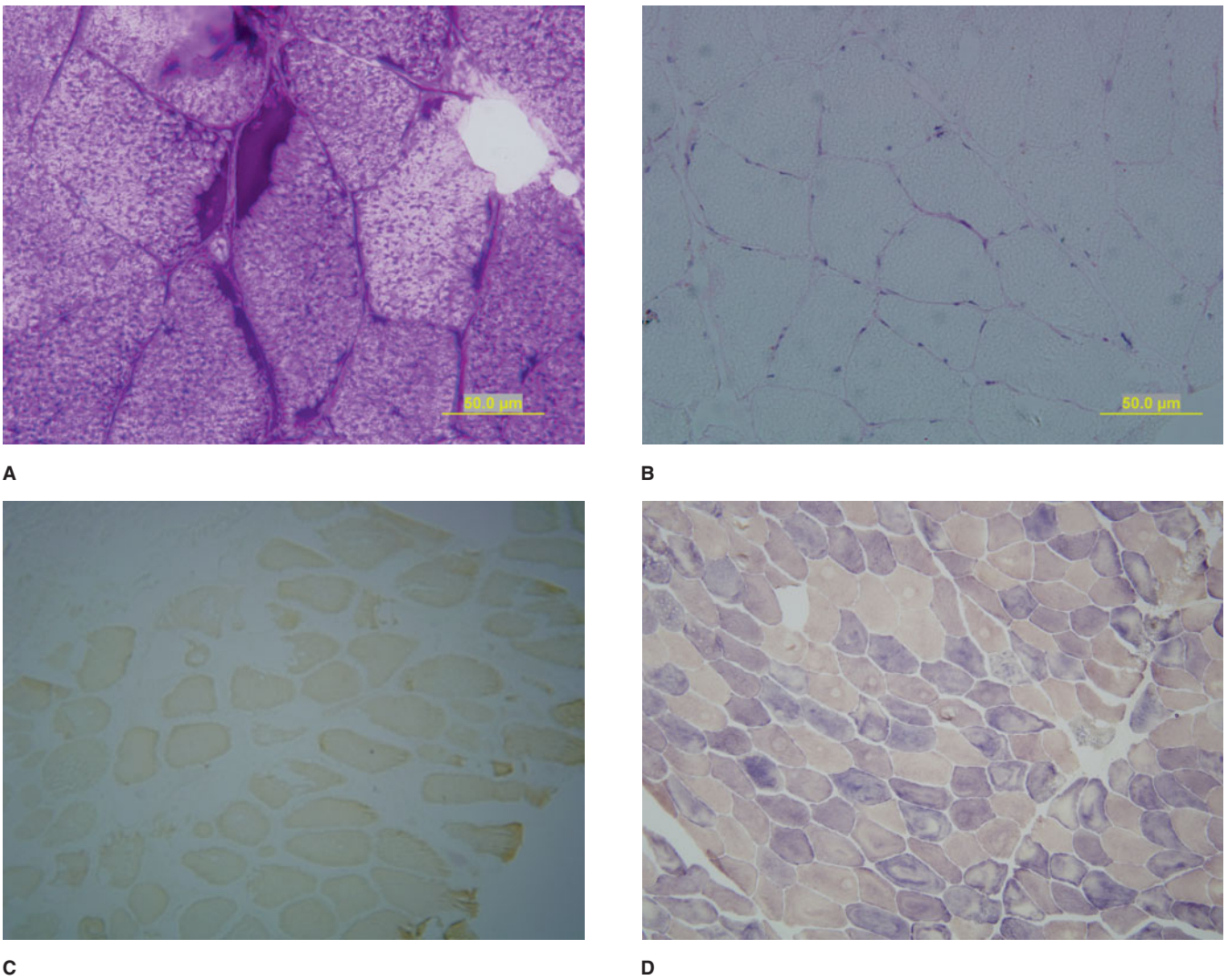


Figure 3–6. Scattered muscle fibers have small foci of increased glycogen deposition in subsarcolemmal regions in a patient with McArdle disease (A), periodic acid Schiff (PAS) stain. When diastase is added to the PAS stain the abnormal accumulations are no longer evident, suggesting that the deposits were glycogen (B). Myophosphorylase stain demonstrates absent myophosphorylase activity (C). (D) Shows myophosphorylase activity in a healthy control biopsy. Type 2 fibers that contain more myophosphorylase stain are darker than type 1 fibers.

more type 1 fibers than type 2A and 2B. Because muscle fibers from a single motor unit are randomly distributed among muscle fibers of different motor units and fiber types, a checkerboard or mosaic pattern is appreciated on ATPase stains.

Although ATPase stain is primarily used to assess fiber type, we can often ascertain the fiber types from other standard stains (Table 3–1). For example, type 1 fibers stain more intensely with modified Gomori trichrome, lipid, and oxidative enzyme stains than type 2 fibers because of the increased number of mitochondria and oxidative metabolism associated with type 1 fibers. In contrast, type 2 fibers, which are involved with glycolytic metabolism, stain more intensely with PAS, as these contain more glycogen but are lighter staining on modified Gomori trichrome, lipid, and oxidative enzyme stains.

The diameters of individual muscle fibers are assessed in order to characterize their size. Quantitative analysis is performed by measuring the mean and range of the diameters for each different fiber type.[14–17] Importantly, the diameters of muscle fibers increase to a point during childhood until the early teens. At 1 year of age the mean muscle fiber diameter is approximately 16 µm. The size increases by about 2 µm/yr until the age of 5 years and subsequently by 3 µm/yr until 9 years of age. By 10 years of age, mean muscle diameters range from 38 to 42 µm. Normal adult size is reached between the ages of 12 and 15 years.[17] There is usually less than 12% difference in the largest mean fiber diameters between

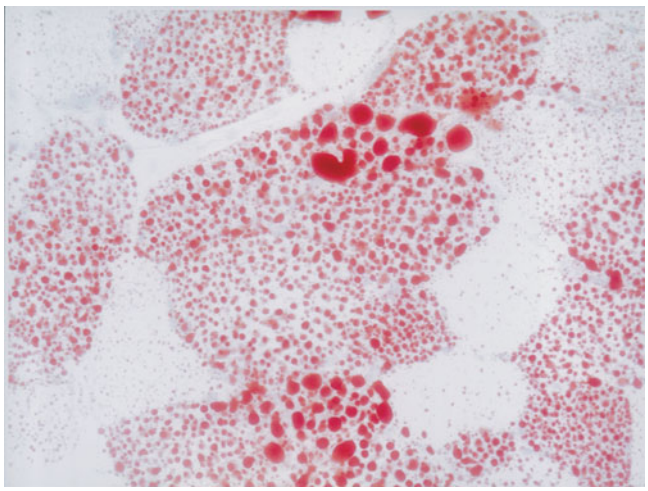


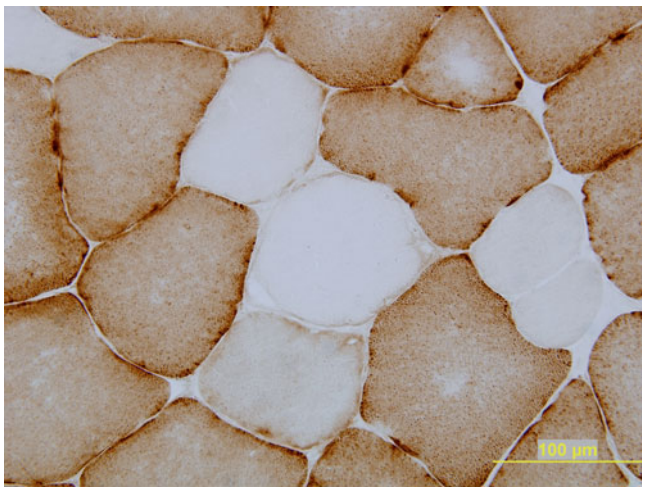
Figure 3–7. Increased lipid droplets in muscle fibers are evident on this oil red O stain in a case of a lipid storage myopathy.

the major fiber types. Both types 1 and 2 adult muscle fibers are larger in men than in women. Type 2 fibers are usually larger than type 1 fibers in men; type 1 fibers are larger than type 2 fibers in women. The diameter of muscle fibers is also dependent on the specific muscle biopsied. For example, in the biceps brachii, the diameters of muscle fibers are as follows: type 1 fibers 64.3 +/− 3.7 μm and type 2 fibers 72.7 +/− 5.3 μm in males and type 1 fibers 56.8 +/− 4.8 μm and type 2 fibers 54.6 +/− 7.0 μm in females. In the vastus lateralis, the diameters of muscle fibers are slightly different: type 1 fibers 59.5 +/− 6.4 μm and type 2 fibers 64.8 +/− 8.1 μm in males and type 1 fibers 58.8 +/− 6.1 μm and type 2 fibers 49.9 +/−6.2 μm in females.[14]

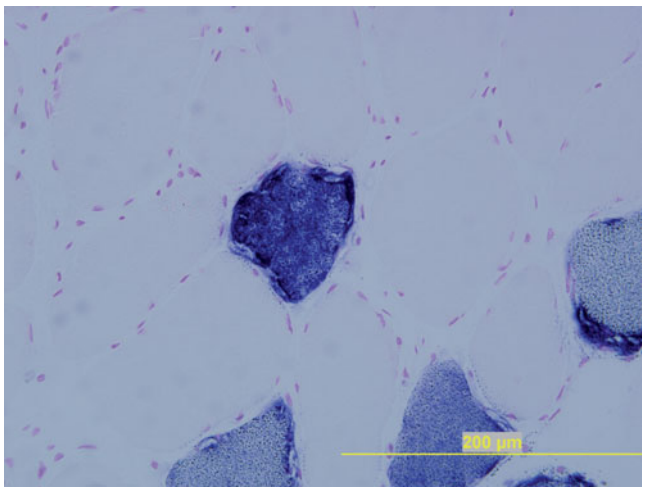
REACTIONS TO INJURY

Muscle abnormalities may be classified on histopathologic and etiologic grounds into three major categories: (1) neurogenic atrophy: a pattern of muscle pathology consequent to denervation and reinnervation; (2) myopathies: inherited and acquired diseases characterized by abnormalities in the muscle fiber itself; these include dystrophies, congenital, inflammatory, metabolic, and toxic myopathies; and (3) disorders of the neuromuscular junction. Patients with neuromuscular junction defects usually have only slight and nonspecific alterations apparent on routine light microscopy and are rarely biopsied except at very specialized centers.[1–5]

Upon review of muscle biopsy slides, specific features on various stains are important to note. It is essential to assess the size and variability of muscle fibers, the distribution of fiber types, the size and location of the myonuclei, the presence of necrosis, other alterations in the cytoarchitecture and organelles (e.g., the presence of target fibers, cores, vacuoles, tubular aggregates, and ragged red fibers), and any abnormal accumulation of glycogen or lipid. Besides the muscle fibers, we evaluate the surrounding vasculature (is there evidence of vasculitis and thickened basement membranes?) and the supportive tissue (is there increased endomysial connective tissue, edema, or amyloidosis?). One should characterize any inflammatory cell infiltrate making note of the type (macrophages, lymphocytes, plasma cells, eosinophils, and macrophages) and the location (endomysial,

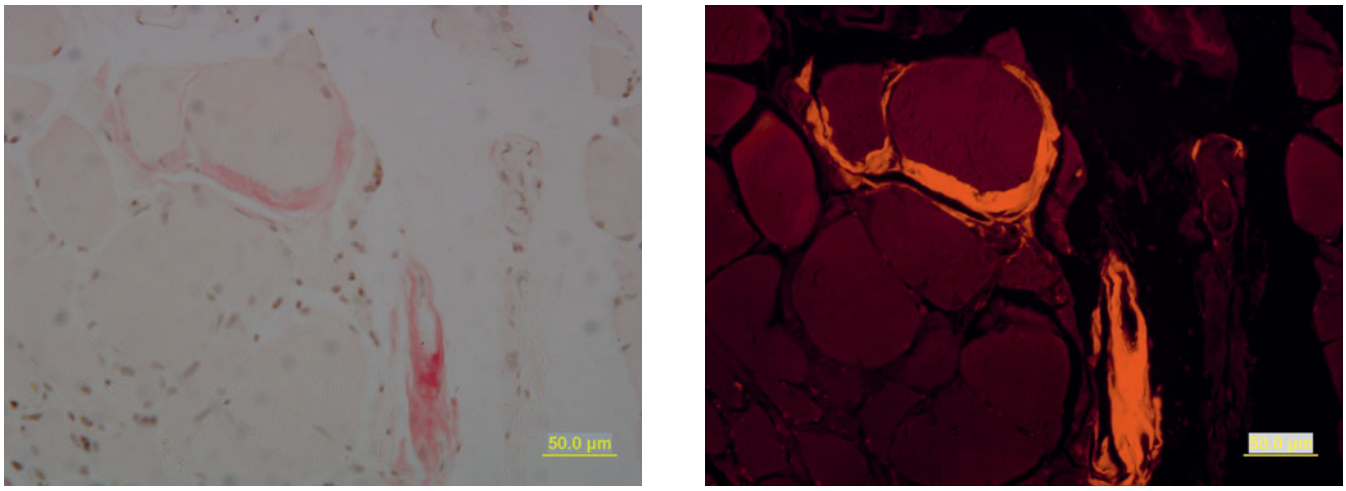


A



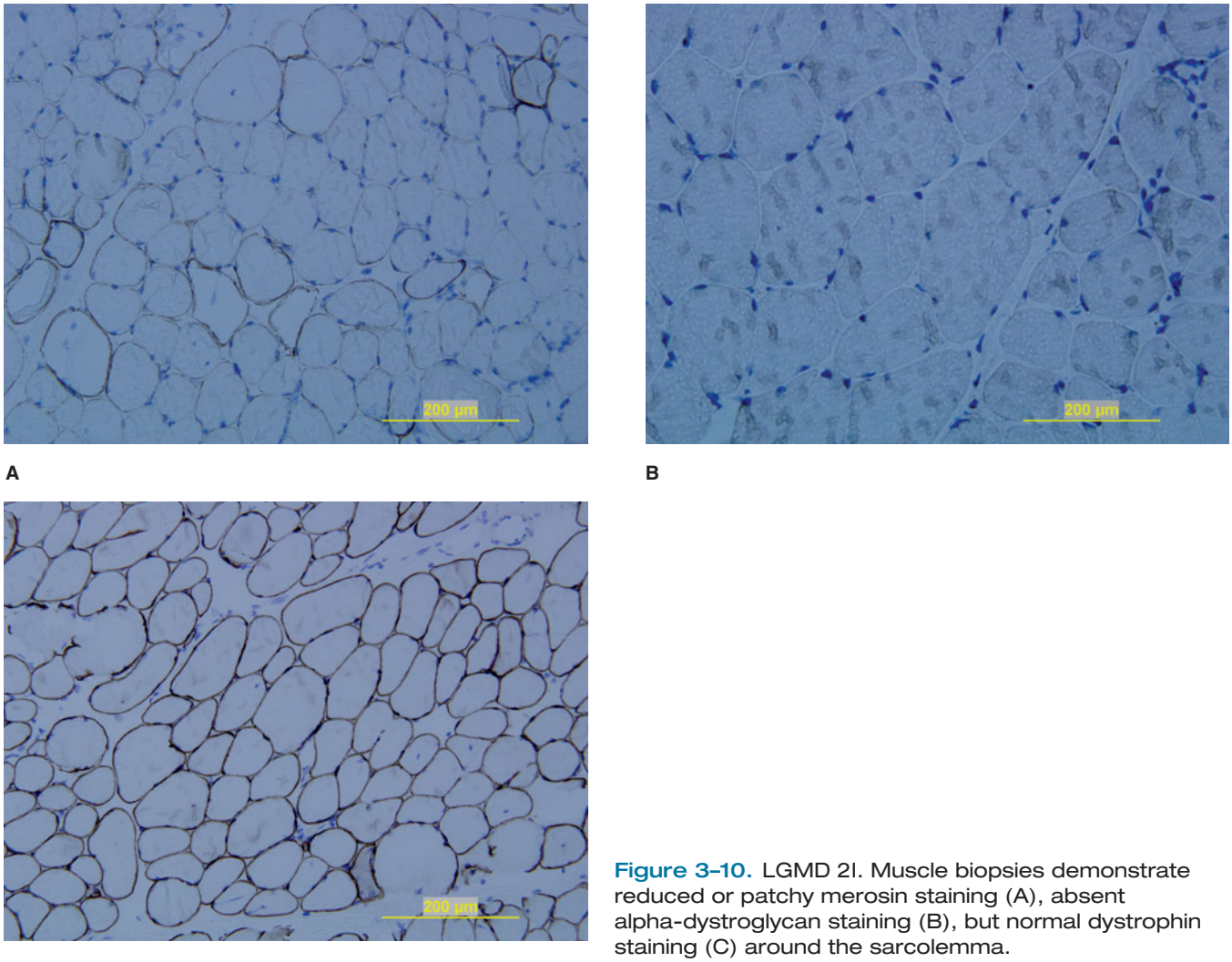
B

Figure 3–8. In addition to ragged red fibers seen on modified Gomori-trichrome stain (Fig. 3–4), mitochondrial myopathies may demonstrate muscle fibers with absent or reduced cytochrome oxidase staining (COX) (A) or increased succinic dehydrogenase staining (SDH) (B). Myopathies with ragged red fibers that are COX negative but SDH positive associated with mitochondrial DNA mutations.



A B

Figure 3–9. Congo red stain demonstrates amyloid deposition surrounding muscle fibers and blood vessels. Under routine light microscopy, the amyloid deposition is pinkish red staining (A), apple-green under polarized light, but is most easily appreciated as bright red using rhodamine optics (B).



A B C

Figure 3–10. LGMD 2I. Muscle biopsies demonstrate reduced or patchy merosin staining (A), absent alpha-dystroglycan staining (B), but normal dystrophin staining (C) around the sarcolemma. Immunoperoxidase stains.

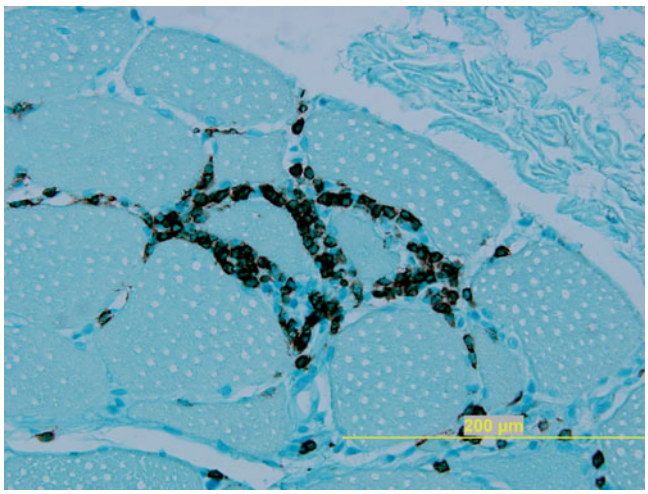
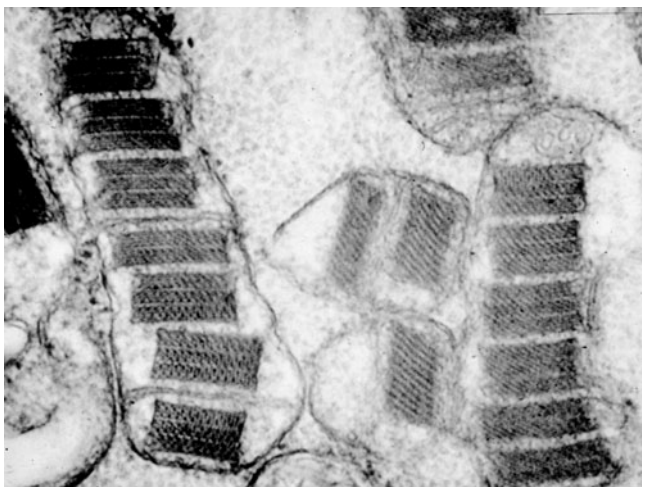


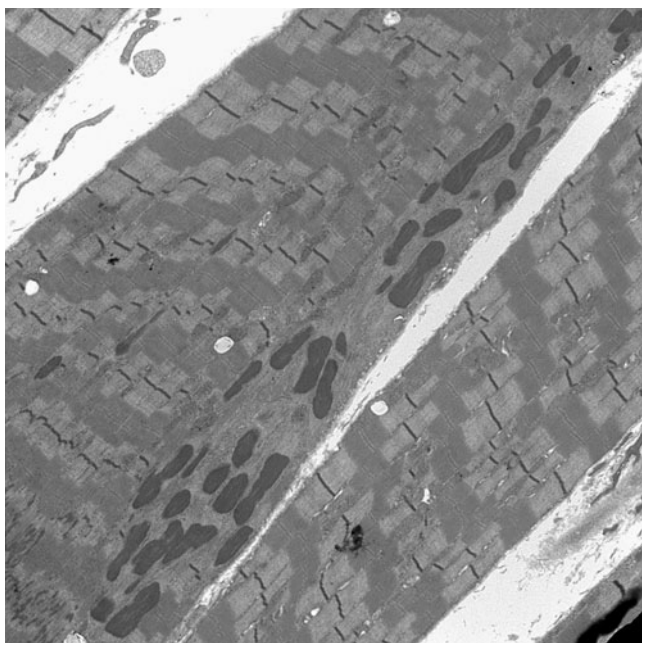
Figure 3–11. Specific types of inflammatory cells, in this case CD8+ T lymphocytes can be seen in the endomysium surrounding muscle fibers in polymyositis. Immunoperoxidase stain.

perimysial, and perivascular), and if there is cellular invasion of nonnecrotic or just necrotic appearing fibers. We discuss some of the common abnormalities seen on muscle biopsy in the following section, but in more detail in the subsequent chapters where specific disorders and their characteristic histological features are described.

In the setting of axonal degeneration, the muscle fibers within that motor unit lose their neural input and undergo denervation atrophy. This leads to decreased synthesis of myofilaments, degeneration of myofibrils, and a reduction in the size of the muscle fiber.[18] The atrophic fibers lose their polygonal appearance and look angulated in shape (Fig. 3–13). Neurogenic disorders affect motor nerves that innervate both type 1 or 2 fibers. Therefore, in early denervation, muscle biopsies reveal scattered, atrophic angulated muscle fibers of both fiber types. As more motor nerves degenerate, rather than seeing isolated atrophic angulated fibers, there are groups of adjacent muscle fibers that are atrophic (grouped atrophy). A feature of denervation is the presence of the so-called target fibers. Reorganization of the cytoarchitecture within muscle cells results in a rounded central zone of disorganized filaments that contain fewer mitochondrial and glycogen. Target fibers have three zones that are circumferentially oriented, which are best seen on NADH-TR staining (Fig. 3–14). The innermost zone is devoid of mitochondrial, glycogen, phosphorylase, and ATPase enzymatic activity; the second zone has increased enzymatic activity, while the third zone exhibits intermediate enzymatic activity. Targetoid fibers refer to similar appearing fibers without a distinct intermediate zone of enzyme activity. As with central cores, target and targetoid fibers preferentially affect type 1 fibers. In contrast to central core myopathy in which the cores are present in the majority of type 1 fibers, target and targetoid fibers are less abundant. These occur in neurogenic disorders in the course of reinnervation. Target and targetoid fibers

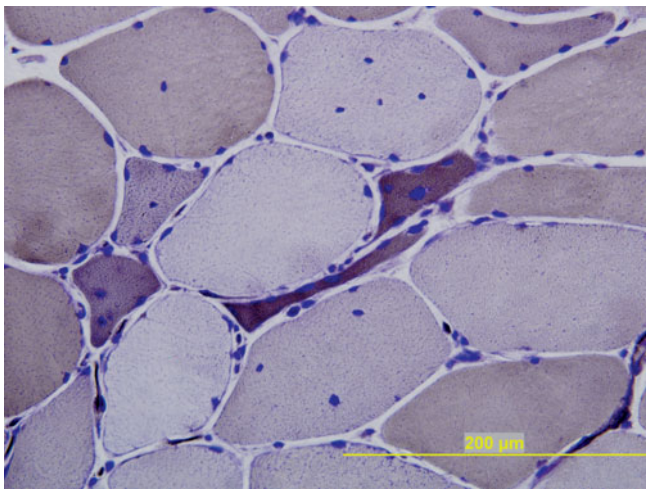


A

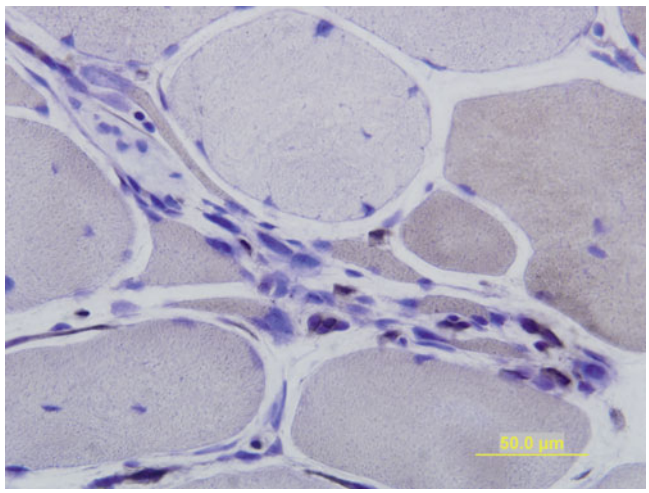


B

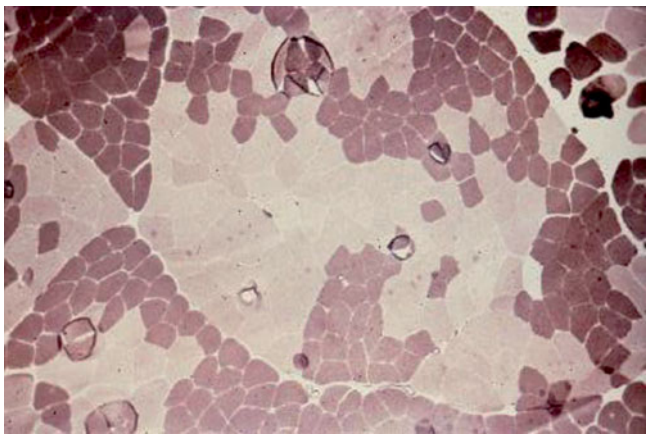
Figure 3–12. Electron microscopy is useful in assessing ultrastructural abnormalities such as proliferation of mitochondrial with abnormal paracrystalline inclusions in this muscle biopsy of a patient with mitochondrial myopathy (A) and rods as evident in a biopsy of a patient with nemaline myopathy (B).



A



B



C

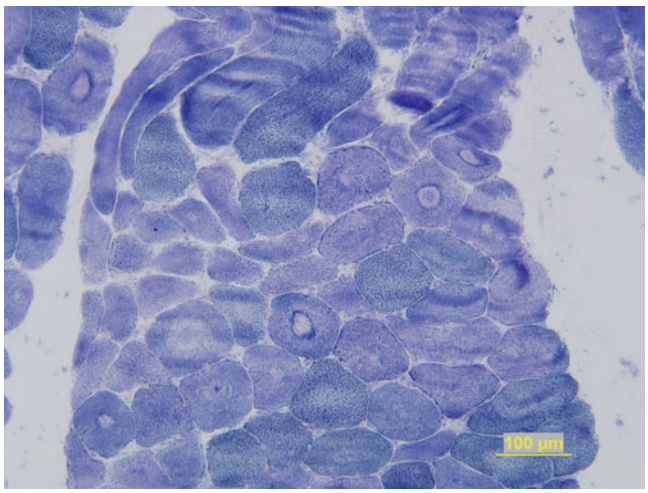
Figure 3–13. Neurogenic atrophy. Denervation results in muscle fibers becoming atrophic and angulated in appearance (A). Several atrophic and angulated fibers clustered together is referred to as group atrophy (B). If surrounding nerve fibers sprout and reinnervate nearby denervated muscle fibers, the newly reinnervated fibers assume the fiber type of the motor nerve that now innervates them. This leads to the loss of the mosaic pattern on ATPase stains and the appearance of fiber type grouping (C). ATPase 4.3.

can also be appreciated on other stains such as the ATPase and modified Gomori-trichrome stains.

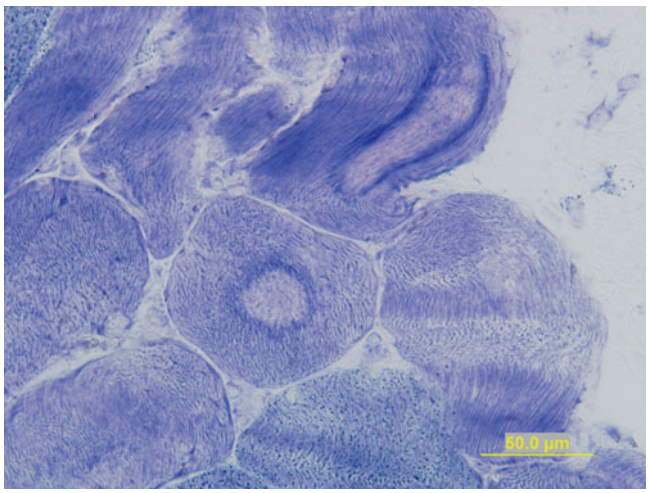
Denervated muscle fibers send out trophic signals that lead nearby unaffected axons to sprout collateral branches, in an attempt to reinnervate the newly denervated muscle fibers. Once successful reinnervation is accomplished, the newly reinnervated muscle fiber assumes the physiologic properties of the reinnervating neuron. This may lead a type 1 fiber to become a type 2A or a type 2B fiber to become a type 1 fiber. As a consequence, the normal checkerboard appearance of muscle tissue is replaced by large groups of single muscle fibers, all with the same fiber type (e.g., fiber-type grouping) (Fig. 3–13). If these larger motor nerves subsequently degenerate, large areas of atrophic fibers of the same fiber type are seen—a different type of grouped atrophy.

In contrast to neurogenic atrophy, myopathic disorders are associated with a wider spectrum of histopathologic alterations (Fig. 3–15). Remember that muscle is a syncytium formed from the fusion of thousands of myoblasts. Because of its syncytial nature, histopathological abnormalities may be focal rather than occurring along the entire length of a muscle fiber (e.g., segmental necrosis). Genetic disorders can manifest discrete abnormalities, with other regions of the single fiber appearing relatively normal. An example of this can be seen in mitochondrial myopathies in which the histopathological alterations are dependent on the degree of abnormal mitochondria, which in turn is a reflection of the percentage of mutated mitochondrial DNA in the region. Thus, when cut longitudinally, one may appreciate segments of the muscle fiber with a ragged red appearance, which do not stain with cytochrome oxidase, while other nearby segments of the same fiber may be normal. In dystrophies, one often sees scattered necrotic muscle fibers on the cross section. However, if the tissue is cut longitudinally, one sees that necrosis is segmental in nature. Likewise, inflammatory myopathies are multifocal, resulting in infiltrates surrounding and invading segments of muscle fibers along their length.

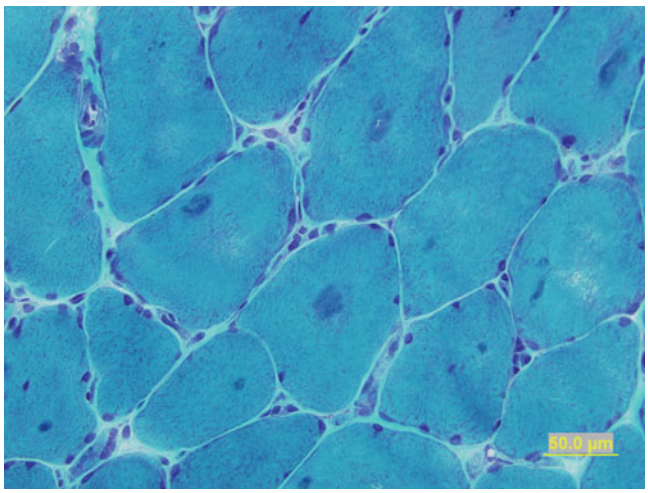
Myopathies are usually associated with a random loss of muscle fibers belonging to different motor units.



A



B



C

Figure 3–14. Target fibers. In the course of reinnervation, target fibers may develop. True target fibers have three zones in the center of the muscle fibers that are best seen on NADH-TR staining, at low power (A), and at higher power (B). The innermost zone is pale; the second zone has increased enzymatic activity, while the third zone exhibits intermediate enzymatic activity. Target fibers can also be appreciated on other stains such as the modified Gomori-trichrome stain (C). On the Gomori-trichrome stain the center of the target fibers stain dark and are surround by pale staining zone.

Atrophy of muscle fibers is a common histopathological feature in myopathies, but, rather than fibers becoming angular as in neurogenic atrophy, these usually become more rounded in appearance in myopathic disorders (Fig. 3–15). Small groups of atrophic fibers of similar type may be observed in myopathies due to muscle fiber splitting, degeneration, and regeneration; however, large areas of group atrophy or fiber-type grouping are more typical of neurogenic atrophy. Preferential atrophy or hypotrophy of type 1 fibers is seen in certain myopathic disorders (e.g. myotonic dystrophy and various congenital myopathies). On the other hand, preferential type 2 fiber atrophy can be seen in certain endocrine disorders (e.g., steroid myopathy), as well as a complication of disuse.

Besides atrophy of muscle fibers, hypertrophy can develop in response to increased load, either in the setting of exercise or in pathologic conditions where other muscle fibers are injured. Large fibers may divide along a segment (muscle fiber splitting) so that, in cross section, a single large fiber contains a cell membrane traversing its diameter. Because both chronic myopathic and neurogenic disorders can be associated with a mixture of atrophic and hypertrophic fibers, increased variability of muscle fiber size is a nonspecific abnormality.

Necrosis is a feature more common in myopathies, but it can also occur in denervated muscle fibers (Fig. 3–16). A single muscle fiber can undergo either total necrosis or segmental necrosis, but again, given the syncitial nature of muscle, atrophy along the entire fiber length is rare. The more common form of muscle tissue loss is referred to as segmental necrosis in which a relatively small segment of the single muscle fiber is affected. The site of necrosis may be somewhat focal at first, but it extends longitudinally along the muscle fiber with disease progression. Segmental necrosis is best appreciated on paraffin or semithin sections of muscle fibers cut longitudinally (Fig. 3–17). With segmental necrosis, the affected portion of the single muscle fiber becomes more rounded and the sarcoplasm begins to

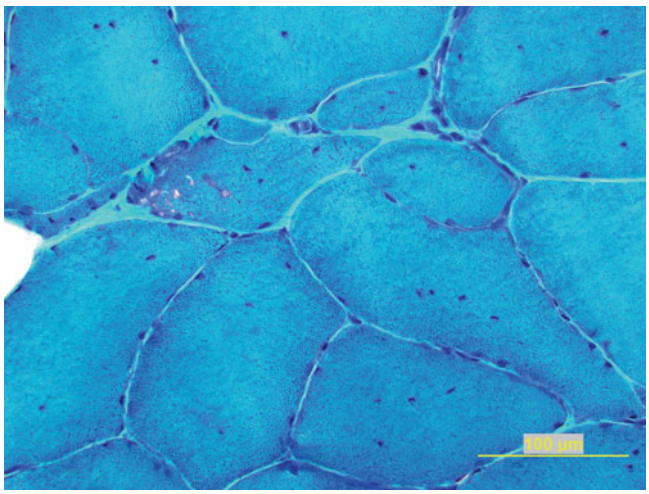


Figure 3–15. Variability in muscle fiber size, increased internalized nuclei, muscle fiber splitting, and small intracytoplasmic vacuoles are nonspecific myopathy features appreciated on this modified Gomori-trichrome stain.

have a featureless ground-glass appearance. Semithin and EM sections reveal degeneration of the Z disk and myofibrillar network as well as abnormal mitochondria. Macrophages are recruited into the area and infiltrate the necrotic segments in order to digest the disintegrating muscle tissue damaged tissue. In certain diseases (polymyositis and inclusion body myositis), macrophages and lymphocytes may invade nonnecrotic tissue such that a muscle fiber can be "severed" into distinct segments.

Repair of necrotic segments can occur and begins with the proliferation of adjacent satellite cells in the region of the destroyed portion of the fiber.[19] The satellite

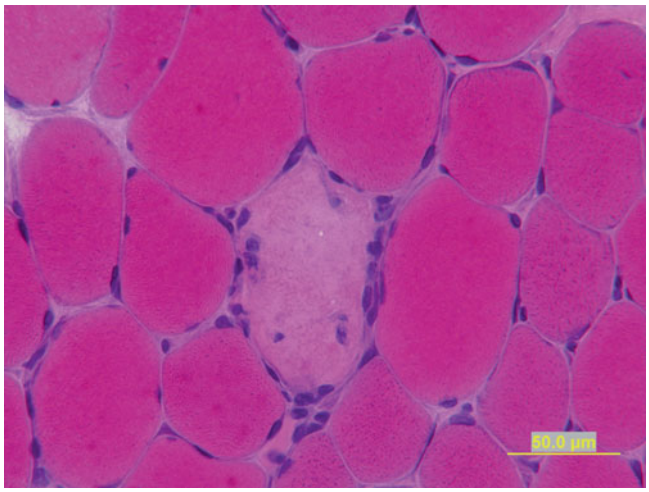


Figure 3–16. A necrotic muscle fiber is pale staining in comparison to surround muscle fibers on H&E stain. H&E stain.

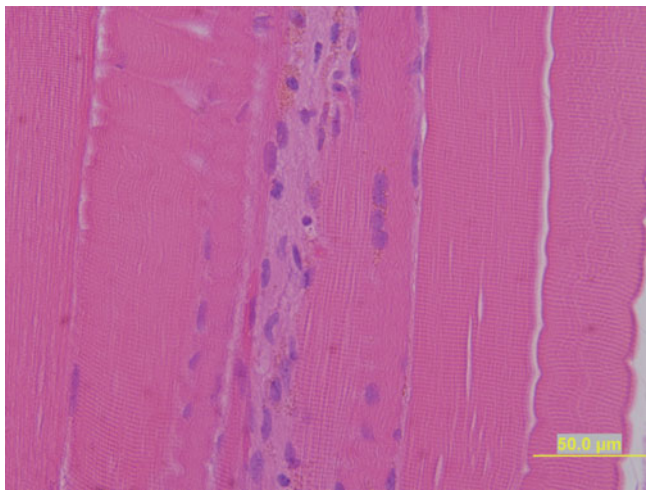


Figure 3–17. Segmental necrosis is best appreciated on paraffin sections in which large, longitudinal segments can be visualized. The striations of the sarcomeres can be appreciated in normal fibers while the necrotic segment of an adjacent fiber loses the striations. The necrotic segment is invaded by macrophages. Paraffin sections, H&E stain.

cells align next to each other to form myotubes. Several myotubes form per segment and adhere to the surrounding basal lamina. The expansion of myotubes occurs laterally and longitudinally, eventually reaching and fusing with the healthy muscle tissue stumps. The regenerating muscle fibers can be appreciated by their large internalized nuclei with prominent nucleoli, and their basophilic cytoplasm that is laden with ribonucleic acid (RNA) (Fig. 3–18). Old damage can be ascertained by the increase in the number of internalized nuclei (Fig. 3–15). Myonuclei,

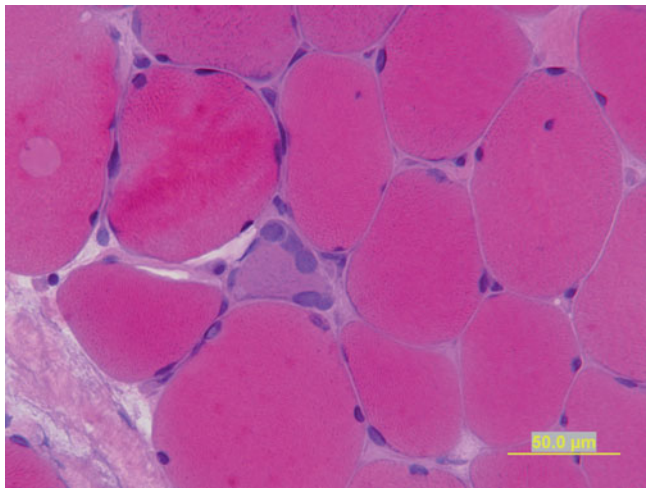


Figure 3–18. Regenerating muscle fibers are smaller and more basophilic than normal fibers and contain enlarged nuclei sometimes with nucleoli, as these are very active in trying to replenish necessary muscle proteins. H&E stain.

which usually lie along the subsarcolemmal membrane, are more internalized in regenerated segments.

Other characteristics of myopathic injury include alterations in structural proteins or organelles, formation of vacuoles, and accumulation of intracytoplasmic deposits. Increased endomysial connective tissue is a common feature of muscular dystrophies. Inflammatory cell infiltrates are seen in the different types of myositides but can also be seen in dystrophies and other types of myopathy and thus are not specific for an immune-mediated process. These various histopathologic abnormalities are discussed in more detail in subsequent chapters with the diseases in which these appear.

▶ NERVE BIOPSIES

As is true for muscle biopsies, the interpretation of a nerve biopsy requires correlation of histological changes, with clinical information including the results of electrophysiological investigations. Nerve biopsies are generally less useful than muscle biopsies because the pathologic abnormalities are often nonspecific and frequently do not help distinguish one form of peripheral neuropathy from another.[20–23] In addition, there is increased morbidity associated with the removal of a segment of sensory nerve, which leads to permanent numbness in the corresponding cutaneous distribution. Also, nerve biopsies can be complicated by significant neuropathic pain in the distribution of the nerve for several months and the potential for growth of painful neuromas. Therefore, we do not recommend nerve biopsies just because the patient has a generalized neuropathy of undetermined etiology despite an extensive laboratory evaluation. This situation is quite common, as discussed in Chapter 20 on Idiopathic Polyneuropathy.

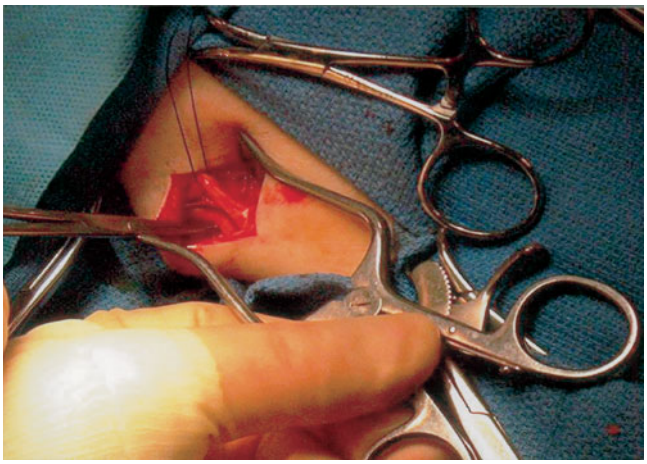
INDICATIONS FOR NERVE BIOPSY

The major indications for nerve biopsy are when vasculitis or amyloidosis are strongly suspected. Amyloidosis should be considered in patients with a monoclonal gammopathy, autonomic neuropathy, systemic signs of amyloidosis (e.g., renal insufficiency or cardiomyopathy), or a family history of amyloidosis. Vasculitic neuropathy is in the differential diagnosis in people presenting with a history of multiple mononeuropathies, particularly when of acute onset and painful, an underlying connective tissue disease (e.g., systemic lupus erythematosus and rheumatoid arthritis), eosinophilia or late-onset asthma (Churg–Strauss syndrome), renal failure or chronic sinusitis, hepatitis B or C, an elevated erythrocyte sedimentation rate, or antinuclear cytoplasmic antibody. Additional indications for nerve biopsy include other autoimmune inflammatory conditions (e.g., sarcoidosis), possible infectious processes (e.g., leprosy), and tumor infiltration (e.g., lymphoma and leukemia). Also, a nerve biopsy may be required for diagnosis of a tumor of the peripheral nerve (e.g., perineurioma). Less commonly, nerve biopsy may be warranted to diagnose uncommon forms of hereditary neuropathy when DNA testing is not available or is negative (e.g., giant axonal neuropathy and polyglucosan body neuropathy).

TECHNIQUES

We usually biopsy a superficial sensory nerve that is clinically affected and also abnormal on sensory nerve conduction studies. The most common nerve biopsied is the sural nerve. We prefer to biopsy the sural nerve in the mid-shin approximately one-third to one-fourth of the distance from ankle to knee, as opposed to the lateral ankle itself where the nerve may be more prone to trauma and healing may not be as good (Fig. 3–19). Patients should be warned that following the sural nerve biopsy, there is often pain for several months as well permanent loss of sensation on the lateral aspect of the ankle and foot.[20] A superficial peroneal nerve biopsy is particularly useful when vasculitic neuropathy is suspected because the underlying peroneus brevis muscle can also be biopsied through the same incision site, thereby increasing the diagnostic yield (Fig. 3–20). Biopsy of the superficial peroneal nerve will lead to numbness of the dorsum of the foot and again often neuropathic pain for several months.[20]If only the upper extremities are involved, the superficial radial nerve can be biopsied; however, this leads to numbness of the dorsum of the hand, which is problematic for most patients. Importantly, because of sampling error, the single small segment of distal sensory nerve may not be representative of focal disease processes elsewhere in the peripheral nervous system, especially in processes with predominant motor involvement. On rare occasions when a patient has a multifocal process and the lesion appears proximal (e.g., amyloidomas, inflammatory process, and tumors), a fascicular nerve biopsy of a lesion in the root, plexus, or proximal nerve may be required. This procedure should only be performed, however, by neurosurgeons experienced in the technique and where the tissue can be processed appropriately in the neuropathology laboratory.

Nerve biopsies are performed under local anesthesia in adults; general anesthesia is often required to obtain an adequate specimen from children or when a proximal nerve segment needs to be biopsied (e.g., root, plexus, or proximal nerve). Ideally, the pathology laboratory should be contacted in advance of the surgery so that the tissue can be picked up directly from the operating room and processed immediately. Local



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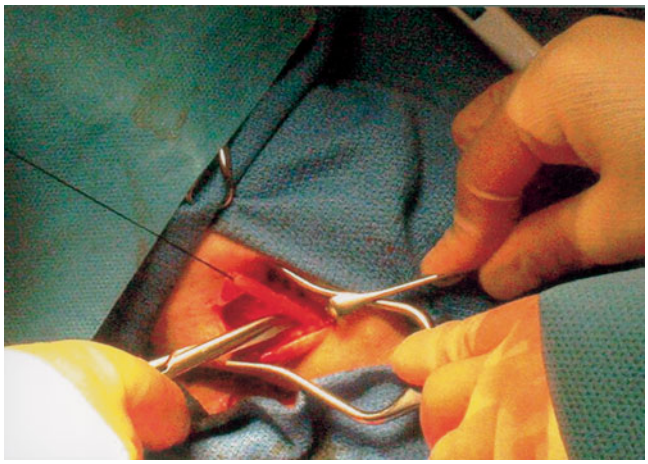

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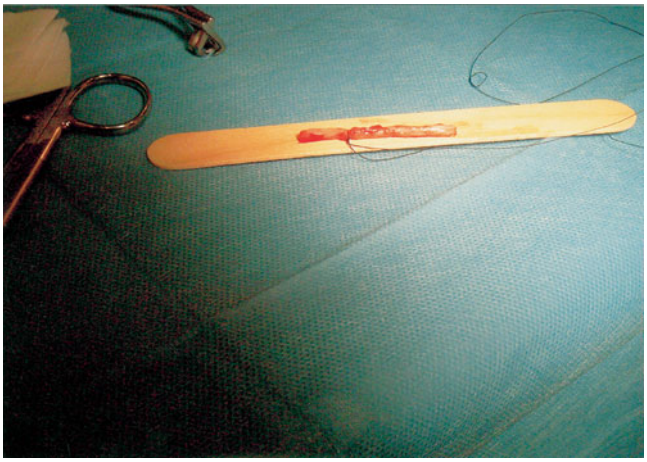


C

Figure 3–19. The sural nerve is usually biopsied approximately one-third up from the ankle just lateral to the midline in the grove made by the Achilles' tendon. It is important for the surgeon to isolate and distinguish the saphenous vein from the sural nerve as they lie next to each other. The saphenous vein can look nearly identical to the sural nerve, often leading to an erroneous "nerve biopsy" with a lumen if care is not taken. A silk suture is gently lifting the sural nerve away from the saphenous vein (A). The nerve is injected proximally with lidocaine, and then is dissected away from the surrounding tissue (B). A 4-cm segment is biopsied and divided into separate specimens for frozen section, paraffin embedding, semithin, EM, and teased fiber preparations (C).

anesthetic should be injected into the nerve just proximal to the site of transaction (Fig. 3–20). At least a cm-long section of nerve should be excised. The specimen can be wrapped in a saline-moistened gauze (not drenching wet).

The nerve biopsy is divided into several portions so that different types of studies can be performed. We generally take a small piece at the most proximal end for frozen section. This piece is rapidly frozen in mounting medium for immunofluorescence studies. These studies can reveal the deposition of immunoglobulins or other inflammatory markers such as complement or fibrinogen. Routine paraffin embedding (following fixation in formalin) is performed on a portion of tissue taken from the proximal and distal segments of the nerve biopsy (approximately 1 cm in length at both ends). The paraffin sections can be stained with hematoxylin and eosin, trichrome, Luxol fast blue (stains myelin blue), Bodian stain or neurofilament stains for axons, Congo red, Alcian blue, or cresyl violet for amyloid, and PAS (when polyglucosan body neuropathy is expected) (Fig. 3–21).[3,21,24–27] Immunohistochemistry studies can be done to better assess inflammatory cell infiltrates (Fig. 3–22) and other specific stains done to better evaluate Schwann cells and perineurial cells when indicated. For example, immunoreactivity against the Schwann cell marker S-100 is useful for Scwhannomas and neurofibromas (Fig. 3–23), while immunoreactivity to epithelial membrane antigen (EMA), which is present on perineurial cells, is helpful in diagnosing perineuriomas. The paraffin-embedded tissue is most useful for evaluating signs of vasculitis, other inflammatory cell infiltrates including granulomas and lymphoma, infection (e.g., leprosy), and amyloidosis. Because the pathology can be multifocal, we like to take sections for paraffin embedding at the proximal and distal ends of the biopsy segment. In addition, loss of myelinated nerve fibers can be appreciated with various stains of paraffin-embedded tissue.

The remainder of the tissue is stretched delicately on a tongue blade or kept isometric with sutures and fixed in glutaraldehyde or other fixatives (e.g., Karnovsky's fixative). Some of this tissue will then be embedded in plastic and processed for toluidine blue-stained

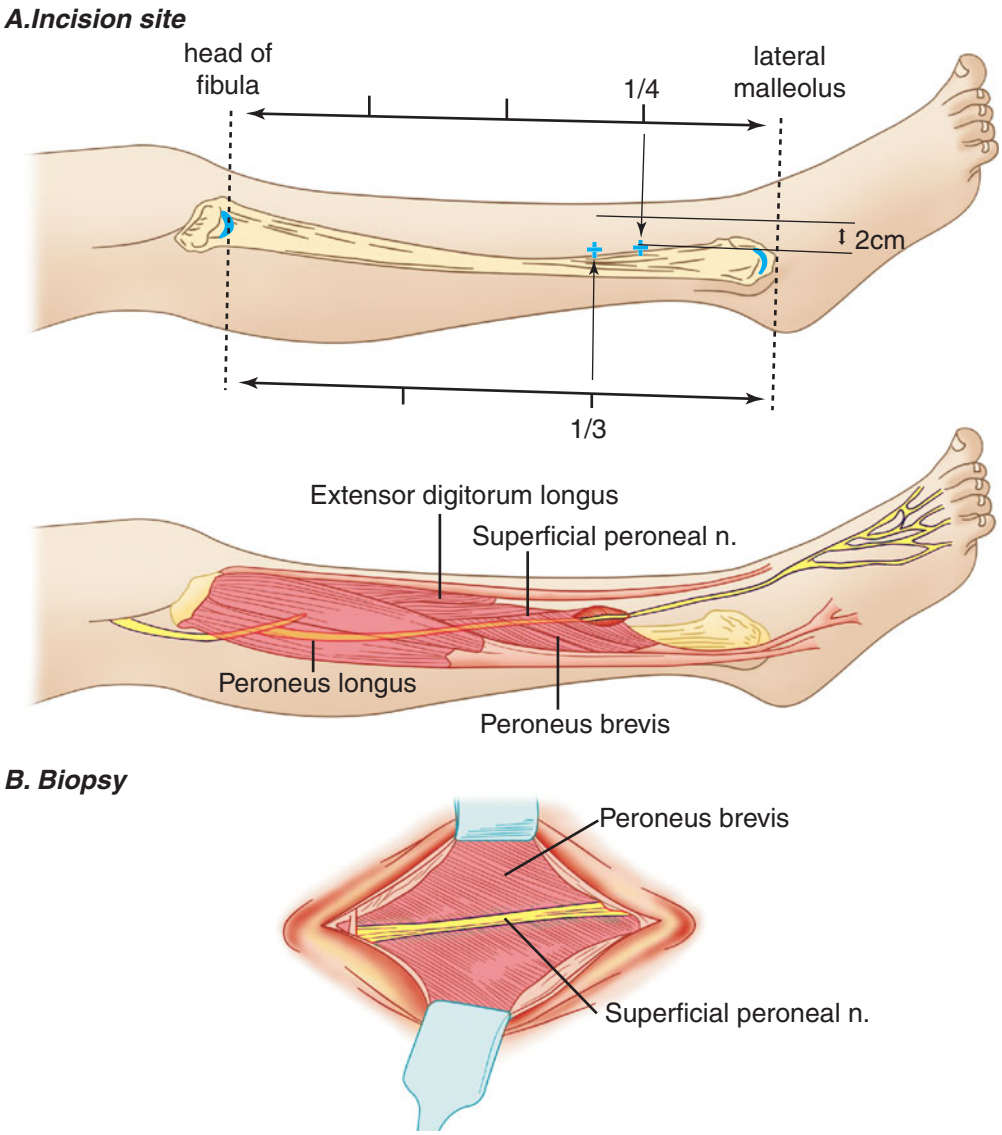
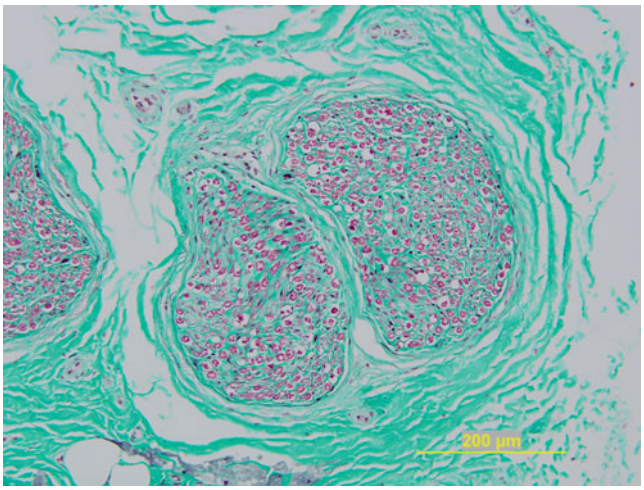


Figure 3–20. A combined superficial peroneal nerve and muscle biopsy is useful when looking for vasculitis. The nerve is typically found between one-third and one-fourth up from the lateral malleolus and approximately 1–1½ cm anterior to the fibula. The nerve in this position can lie above or beneath the fascia overlying the peroneus brevis muscle, so both can be taken from a single incision. (Modified with permission from Mendell JR, Erdem S, Agamonolis DR. Peripheral nerve and skin biopsies. In Mendell JR, Kissel JT, Cornblath DR (eds). Diagnosis and Management of Peripheral Nerve Disorders. Oxford Univ Press, 2001, p. 92, Fig. 7–2.)

semithin sections (10 μm) and thin sections (1 μm) for EM.[3,21,24–28] The semithin and EM analyses are most important in assessing the axons, Schwann cells, and myelin sheath of myelinated nerve fibers as well as in looking at abnormalities in small unmyelinated nerve fibers (Fig. 3–24). Quantitative morphometric methods can be employed to assess numbers of individual large or small myelinated and unmyelinated fibers in the biopsy, as certain neuropathies have a predilection for certain nerve fiber types. However, this is not routinely necessary. Other portions of this fixed material may be used for teased nerve fiber analysis (Fig. 3–25). With this method, individual myelinated fibers are separated from the nerve fascicles and lightly stained, allowing examination of the integrity and thickness of the myelin sheath as well as revealing alterations in internode length. Thus, one can better quantify the degree of demyelinated or thinly myelinated axon, axons with increased or redundant myelin, and axons undergoing active Wallerian degeneration. Teased fiber preparation, however, is very



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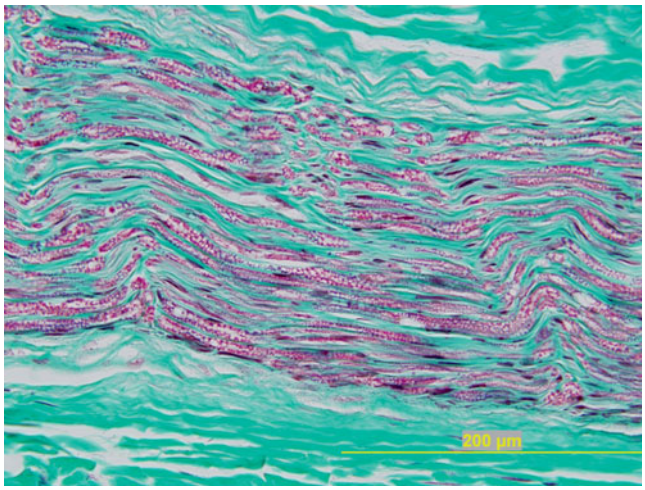

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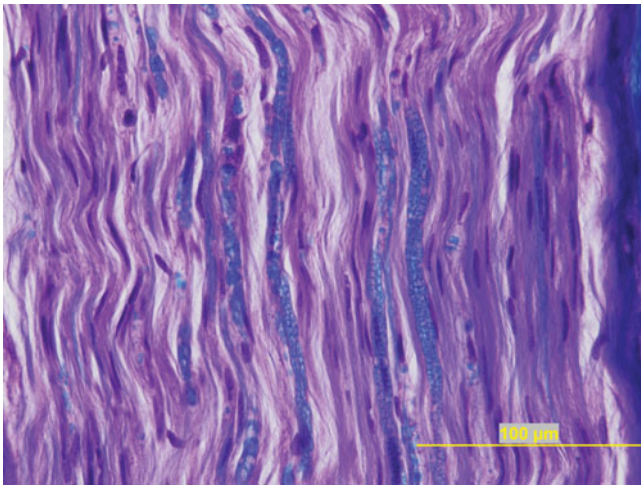

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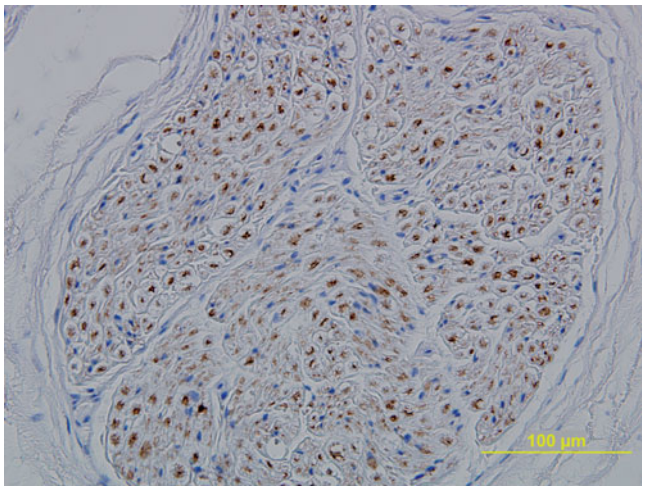

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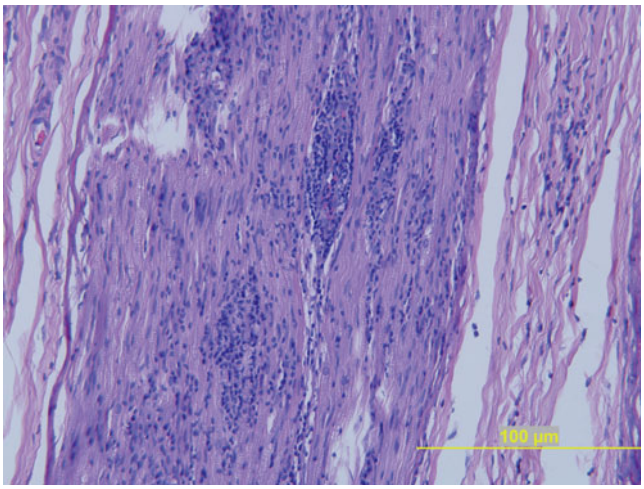


E

Figure 3–21. Paraffin sections of nerve biopsy. Myelin stains pink on modified Gomori trichrome in this normal nerve seen in cross section (A) and longitudinally (B). A reduction in blue staining myelinated nerve fibers can be seen here on this Luxal fast blue stain; however, it is not possible to tell if this is due to primary demyelinating neuropathy or secondary demyelination from a primary axonopathy (C). SMI-31 stains phosphorylated neurofilaments that are abundant in normal axons, as seen in this normal nerve (D). H&E stain does not distinguish very myelin axons well but is useful to look for vasculitis and other inflammatory cell infiltrates as seen in this biopsy of a patient with lymphoma. (E).

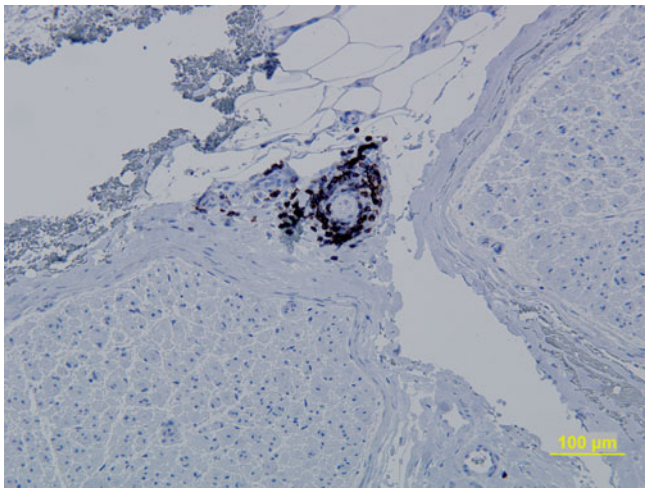


Figure 3–22. Immunoperoxidase stain reveals perivascular CD3+ T lymphocytes in a nerve biopsy in a patient with chronic inflammatory demyelinating polyneuropathy (CIDP).

labor intensive and often does not add much to what can be assessed from the semithin and EM sections; thus, it is reserved for more difficult cases (e.g., question of CIDP in biopsy with mild or nonspecific abnormalities on semithin or EM, the possibility of tomacula in patients with negative genetic testing for hereditary neuropathy with liability to pressure palsies).

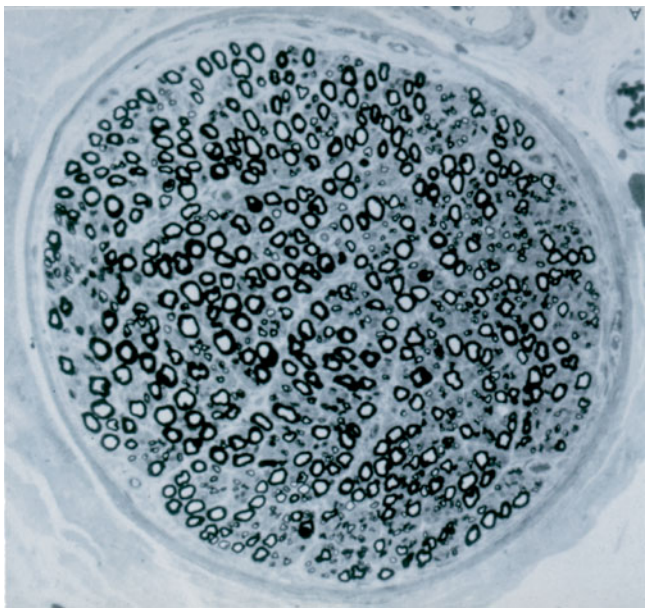
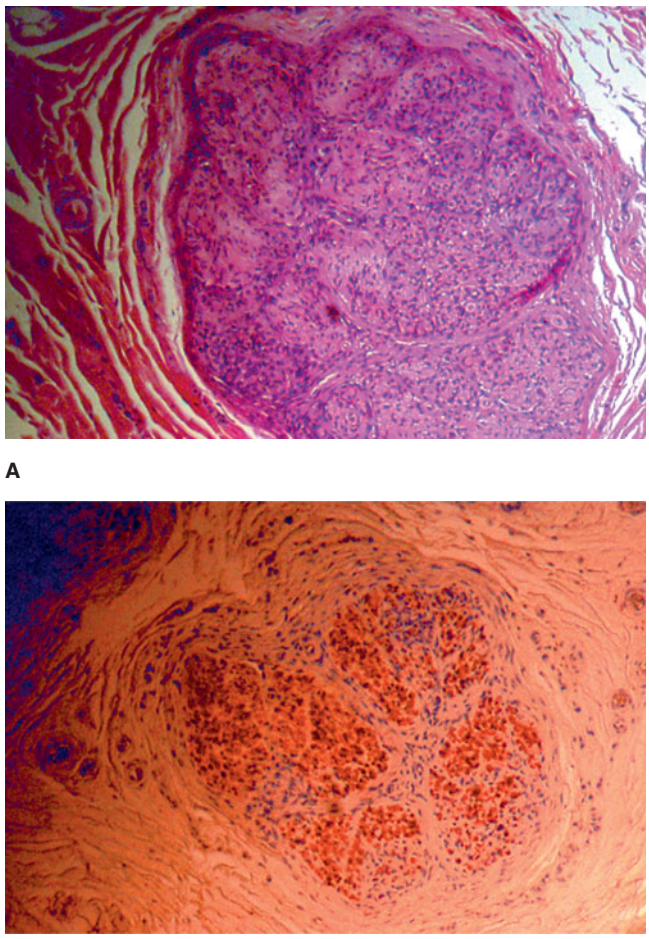


Figure 3–23. Semithin section reveals a normal nerve fascicle.



A

B

Figure 3–24. Neurofibroma. The nerve fascicle has a lobulated appearance, H&E Stain (A). The cells have a wavy, elongated nuclei and the background material is loosely arranged and myxoid. Bands of thick collagen are apparent in the center of the tumor. Some of the proliferating tumor cells are immunoreactive for S-100, suggesting Schwann cell origin (B).

STRUCTURE OF NORMAL NERVE

Peripheral nerves are composed of axons, Schwann cells, myelin sheaths, and supporting tissue. Individual nerve fibers are surrounded by endoneurial connective tissue and grouped into fascicles encased by perineurial sheaths. All the fascicles within a nerve in turn are surrounded by epineurial connective tissue. A blood–nerve barrier is regulated between the perineurial cells and endoneurial capillaries derived from the vasa nervorum, both of which form tight junctions. The blood–nerve barrier appears to be relatively less competent within nerve roots, dorsal root ganglia, autonomic ganglia, and terminal twigs. The nerve–CSF barrier is formed by the tight junctions between the cells that form the outer layer of the arachnoid membrane. These cells fuse with the

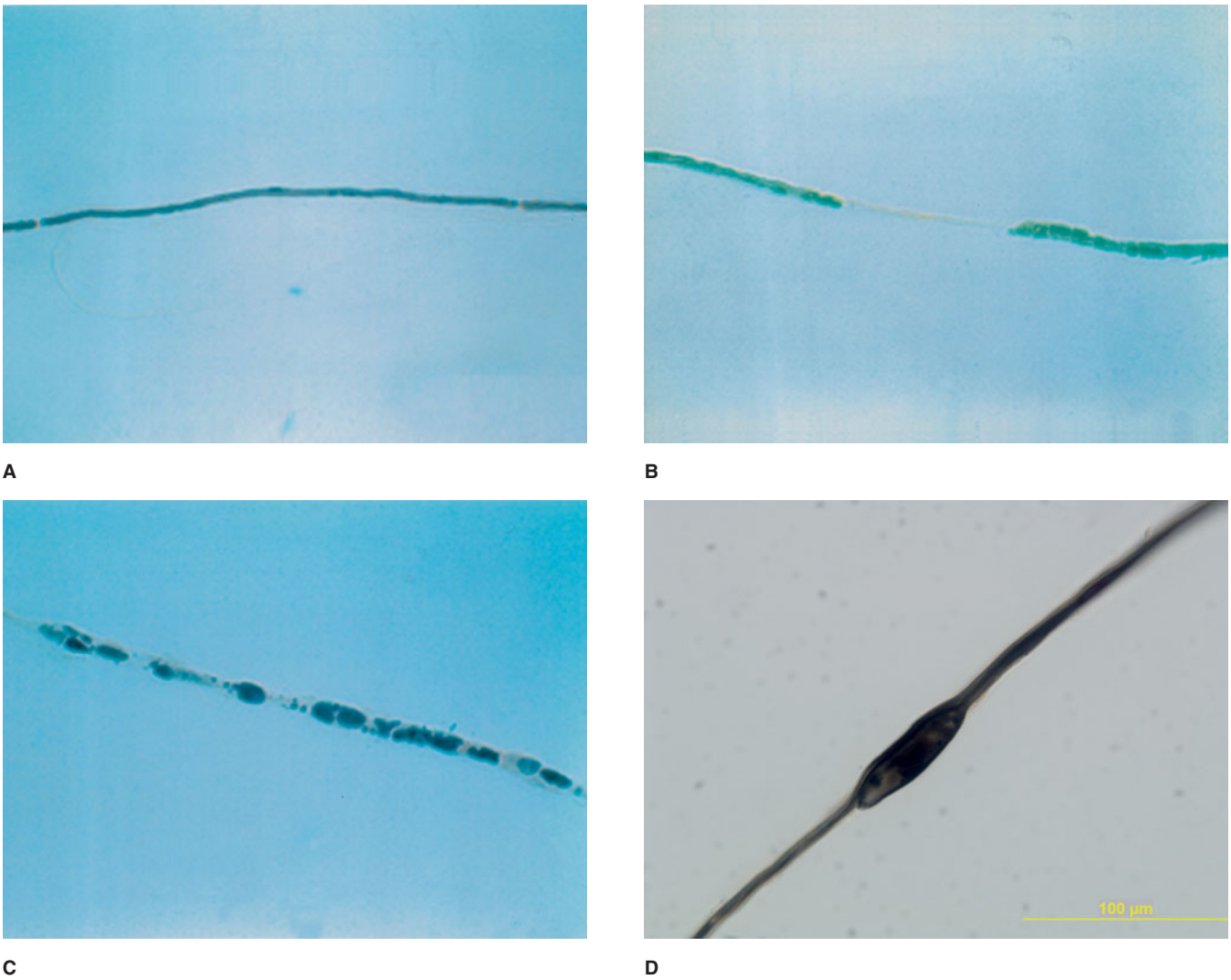


Figure 3–25. Teased nerve fibers. A normal teased fiber internode is seen (A) as well as a short, demyelinated internode (B). A teased nerve fiber segment undergoing Wallerian degeneration with myelin ovoids is appreciated in (C). Redundant folds of myelin lead to formation of tomacula (Latin for sausage) that are best appreciated on teased fiber preparations (D) and are commonly seen in hereditary neuropathy with liability to pressure palsies and occasionally in other forms of Charcot–Marie–Tooth disease.

perineurium of the roots and cranial nerves as these leave the subarachnoid space.

Myelinated and unmyelinated nerve fibers intermingle within each fascicle. Further, along the course of the entire nerve, individual nerve fibers course in and out of different fascicles. In the sural nerve, which is most commonly biopsied, myelinated fibers range between 2 and 15 µm in diameter and have a bimodal distribution. There are approximately twice as many small myelinated axons as there are large myelinated fibers. Segments of myelinated fibers (internodes) are separated by nodes of Ranvier. A single Schwann cell supplies the myelin sheath for each internode. The thickness of the myelin sheath is directly proportional to the diameter of the axon, and the larger the axon diameter, the longer the internodal distance. The ratio of the diameter of the axon to the diameter of the entire nerve fiber (axon plus its surrounding myelin) is approximately 0.6. A higher-than-normal diameter ratio implies that the axons are thinly myelinated. In contrast, lower G ratios are seen in axonopathies with axonal atrophy or rare conductions with redundant myelin (tomaculous neuropathy). Unmyelinated axons are more numerous than myelinated axons and range in size from 0.2 to 3 µm. Anywhere from five to 20 unmyelinated axons are enveloped by a single Schwann cell; there is no specialized differentiation to form myelin.

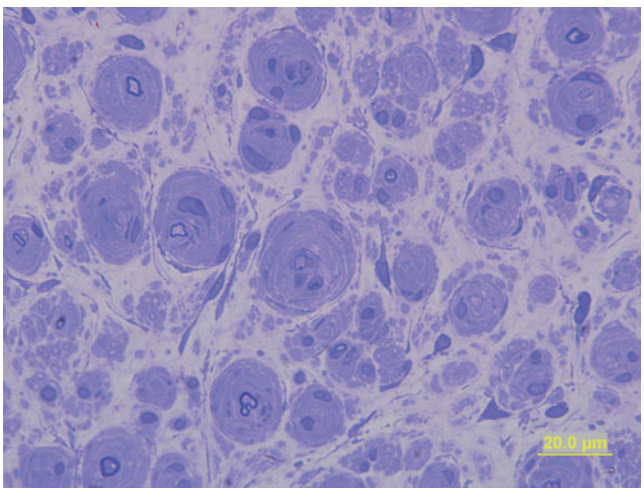
Schwann cells, regardless of their association with myelinated or unmyelinated fibers, have pale oval nuclei with an even chromatin distribution and an elongated

bipolar cell body. On EM, Schwann cells can be differentiated from fibroblasts because Schwann cells have a basement membrane. Within axons there are various organelles and cytoskeletal structures, including mitochondria, vesicles, smooth endoplasmic reticulum, lysosomes, neurofilaments, and microtubules. Because protein synthesis occurs in the cell body rather than the axon itself, essential proteins and other substances synthesized in the perikaryon are transported down the axon via axoplasmic flow. A retrograde transport system serves as a feedback to the cell body. These transport systems are dependent on the microtubules and neurofilaments as well as specific proteins such as dynein and dynactin within the axons. At the distal nerve terminal, dense-cored and coated vesicles are found.

REACTIONS TO INJURY

Although disease processes affecting nerves have different pathogenic mechanisms, these lead to two principal reactions to injury: demyelination or axonal degeneration.[3,21,24–28] Damage to Schwann cells or the myelin sheath itself can lead to demyelination. Because these diseases affect individual Schwann cells to varying degrees, the process is characteristically segmental along the length of the nerve. The disintegrating myelin is phagocytosed by Schwann cells and macrophages. Schwann cells are also stimulated to remyelinate the denuded axon. These newly remyelinated axons are thinner in total diameter and the internodes are shorter than normal—features that are best seen with teased nerve preparations. However, one can appreciate the thinly myelinated axons on semithin sections and on EM (diameter ratio greater than 0.6). With sequential episodes of demyelination and remyelination, concentric tiers of Schwann cell processes accumulate around the axons forming the so-called "onion bulbs" (Fig. 3–26). Some disease processes are associated with inclusions within Schwann cells (e.g., metachromatic leukodystrophy and certain toxic neuropathies). Other abnormalities in the myelin sheath include tomaculae (redundant folds of myelin characteristic of hereditary neuropathy with liability to pressure palsies) and widened periodicity of compacted myelin (seen in neuropathy associated with myelin-associated antibodies).

Primary damage to the axon may either be due to a discrete, localized event (trauma, ischemia, etc.) or be due to an underlying abnormality of the neuronal cell body or ganglion (neuronopathy) or its axon (axonopathy). These processes lead to axonal degeneration with secondary disintegration of its myelin sheath



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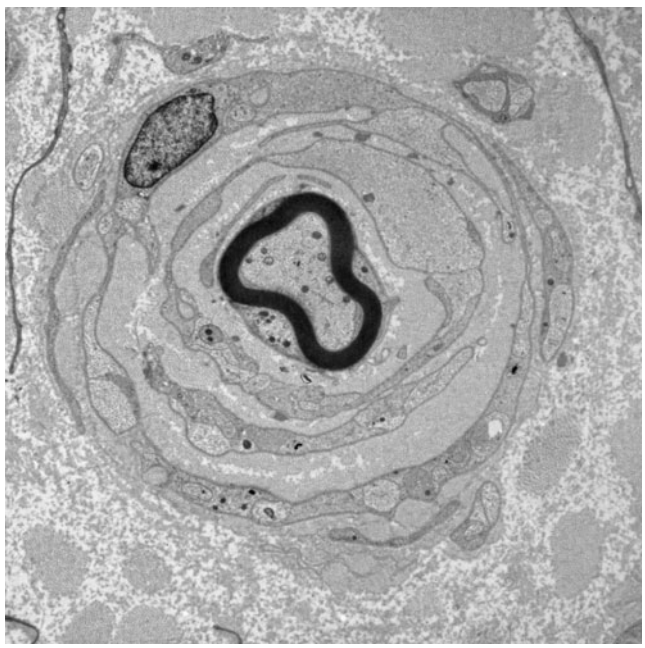
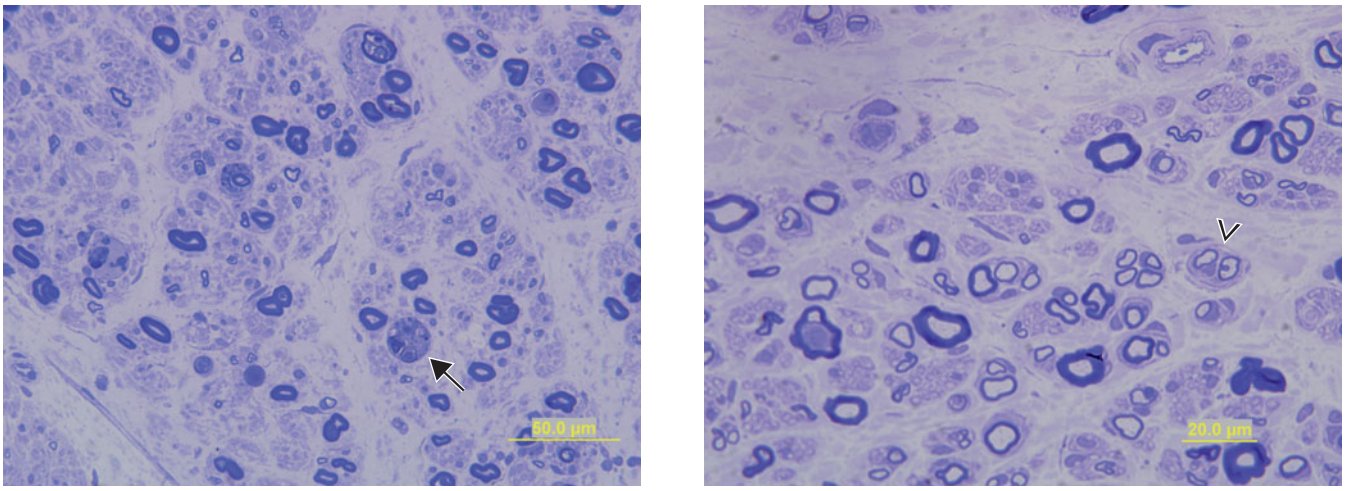


B

Figure 3–26. Onion bulb formation. With recurrent bouts of demyelination and remyelination, concentric layers of Schwann cell processes accumulate around the axons forming onion bulbs. Prominent onion bulbs can be seen in chronic inflammatory demyelinating neuropathy as in this case but are more typical of hereditary demyelinating neuropathies (i.e., Charcot–Marie–Tooth disease types 1, 3, and 4) on semithin section (A) and on EM (B).



A B

Figure 3–27. A semithin section reveals several fibers undergoing active axonal degeneration (Wallerian degeneration) is apparent (A). As nerve fibers attempt to regenerate these send out nerve sprouts. These can be appreciated and groups of thinly myelinated nerve fibers surrounded by the same basement membrane (B).

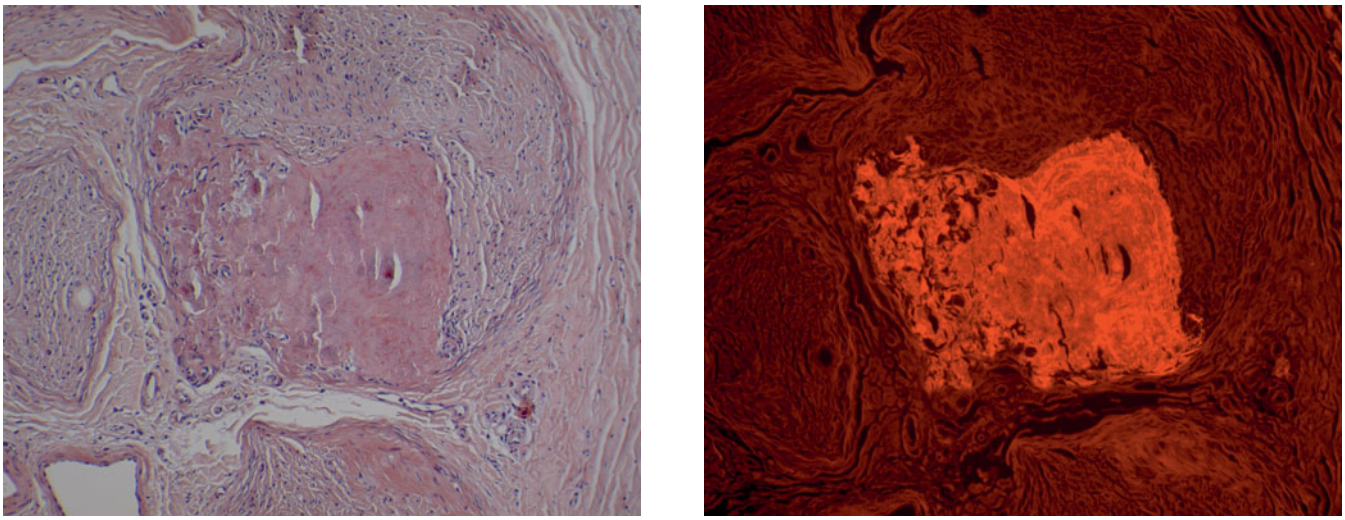
(Fig. 3–27A). If a nerve is transected, the distal portion of the nerve undergoes an acute disintegration (termed Wallerian degeneration) characterized by breakdown of the axon and its myelin sheath into fragments forming small oval compartments (i.e., myelin ovoids). These breakdown products undergo phagocytosis by macrophages and Schwann cells. Most neuronopathies or axonopathies evolve more slowly; therefore, evidence of active axon and myelin breakdown is scant because only a few fibers are degenerating at any given time. The proximal stumps of axons that have degenerated sprouts of new axons may attempt to grow along the course of the degenerated axon. Small clusters of these regenerated axons, which are small in diameter and thinly myelinated, can be recognized on cross section of semithin and EM sections (Fig. 3–27B). Also, as axonal transport of essential proteins and other substances synthesized in the perikaryon is often impaired in axonopathies, this leads to axonal atrophy that again is apparent on the semithin and EM sections (G ratio less than 0.6). In contrast, enlarged axons are seen in giant axonal neuropathy and hexacarbon toxicity.

In addition, nerve biopsies can reveal evidence of disease processes similar to those found in other organ systems. Amyloid deposition around blood vessels or within the endoneurium can be seen in systemic amyloidosis or in a familial amyloidotic polyneuropathy (Fig. 3–28). In systemic or isolated peripheral nerve vasculitis, there is transmural infiltration of vessel walls by inflammatory cells associated with fibrinoid necrosis of the vessel walls (Fig. 3–29). Because nerve fibers course between different fascicles along the length of the nerve and vasculitis can be patchy asymmetric loss of axons within and between fascicles is a characteristic finding of ischemic nerve injury. Infiltration of the nerve by neoplastic or inflammatory cells can also be recognized. Leprosy is one of the most common etiologies of polyneuropathy in the world. When granulomas or diffuse inflammation of the nerve are seen, a Fite stain can be done to look for the acid-fast bacilli (see Chapter 15) (Fig. 3–30).

SKIN BIOPSY

Skin biopsies are increasingly being performed to evaluate patients with peripheral neuropathy.[20,29–40] These are most useful in patients with small fiber neuropathies in which other testing modalities provide normal or inconclusive results. Because nerve conduction studies only assess the conduction of large myelinated nerve fibers, patients with pure small fiber neuropathies will have normal nerve conduction studies. In at least a third of people with painful sensory neuropathies, intraepidermal nerve fibers density on skin biopsies represent the only objective abnormality present following extensive evaluation.[35]

The rationale behind performing skin biopsies is to measure the density and assess the morphology of intraepidermal nerve fibers. These fibers represent the terminals of Aδ and C nociceptors, and these may be decreased in patients with small fiber neuropathies in whom nerve conduction studies and routine nerve biopsies are often normal. Skin biopsies are relatively easy to perform and are associated with a much lower risk than standard nerve biopsies. However, there are several



A B

Figure 3–28. (A and B) Familial amyloid polyneuropathy. Nerve biopsy demonstrates abnormal accumulation of amyloidogenic material in the endoneurium in the biopsy of a patient with a transthyretin mutation. The material stains faintly pink on Congo red under routine light microscopy but is intensely red when viewed under rhodamine optics.

drawbacks to skin biopsies. Importantly, these usually just confirm what you already know about the patient. That is, if a person complains of symmetric burning or tingling pain in the distal lower extremities, has normal strength and deep tendon reflexes, and has normal nerve conduction studies then he or she likely has a small fiber neuropathy. Skin biopsies are often not useful in identifying the etiology of the neuropathy. As stated in the previous section on nerve biopsies, we generally do not do a biopsy in order to prove that a patient has a neuropathy; rather we do so in order to identify the etiology, hopefully a treatable one. That said, assessing intraepidermal nerve fiber density and morphology may play a role in the future by defining the natural history of various neuropathies, monitoring response of the neuropathy to various therapies, and assessing for development of toxic neuropathies (e.g., during chemotherapy).[35]

Skin biopsies are usually done by performing a 3-mm punch biopsy of the skin under local anesthesia in the lower leg in an affected region. Other regions can be sampled to assess if there is a length-dependent loss of intraepidermal nerve fibers (e.g., in the dorsum of the

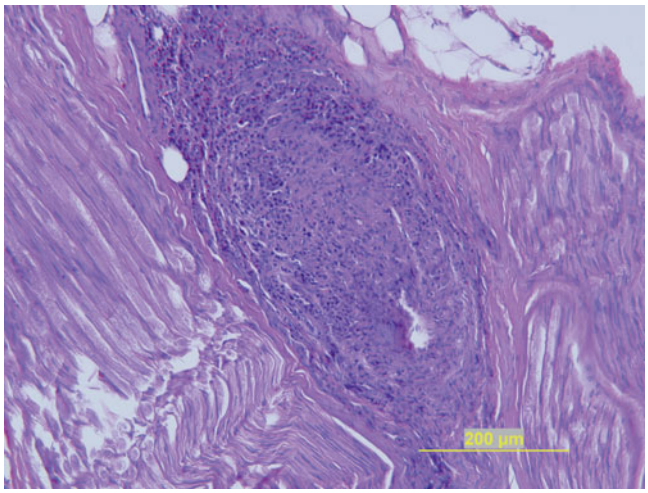


Figure 3–29. Nerve biopsy in a patient with Churg–Strauss syndrome reveals necrotizing vasculitis. Paraffin section, H&E stain.

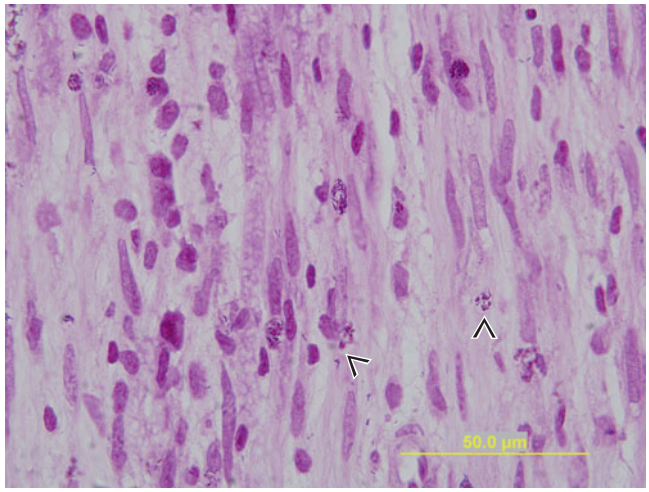


Figure 3–30. Borderline leprosy. Nerve biopsy in a patient with leprosy reveals red staining bacilli using the Fite stain on paraffin sections.

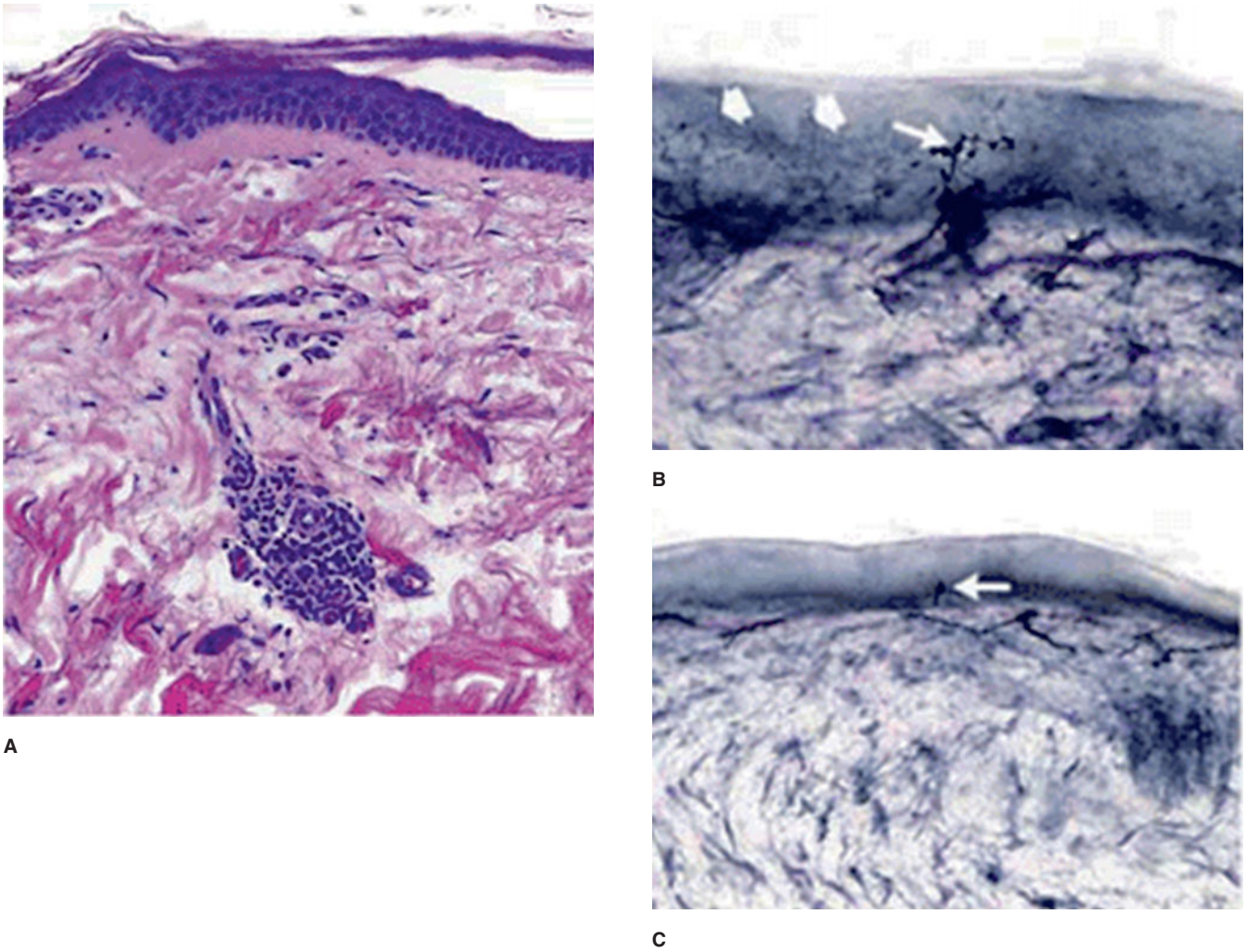


Figure 3–31. Skin biopsy in small fiber neuropathy. A specimen obtained at the time of the patient's first evaluation (A) shows a focal perivascular lymphocytic infiltrate (hematoxylin and eosin, ×125). A section immunolabeled against protein gene product 9.5 reveal neural processes or axons (thick arrows) (B) shows an epidermal neurite with axonal swellings, which are abnormal (thin arrow). The density of nerve fibers is greater than normal (immunoperoxidase, ×500). A specimen obtained 11 months later (C) shows marked reduction in neurite density and axonal swelling (arrow) in a remaining neurite (×300). (With permission of Drs. Thomas Smith and Lawrence Hayward, from Amato AA, Oaklander AL. Case 16-2004: A 76-year-old woman with numbness and pain in the feet and legs. N Engl J Med 2004;350:2181–2189, Fig. 2, 2187.)

foot, thigh, or forearm). The tissue is fixed in formalin, and then immunostaining protein gene product 9.5 (PGP 9.5) is applied to demonstrate the small intraepidermal fibers (Fig. 3–31). Morphometric methods are used to assess the number and complexity of these nerves, through parameters such as the linear density (number of fibers per millimeter of biopsy) or total length of intraepidermal nerve fibers. The morphology of the intraepidermal nerve fibers can also be assessed. Axonal swellings may be an early marker of small fiber neuropathy and may be appreciated before a reduction in density. However, axonal swellings can be seen in normal individuals. Immunostaining for vasoactive intestinal polypeptide, substance P, or calcitonin gene-related proteins can be used to measure the density of sudomotor axons innervating sweat glands, piloerector nerves to hair follicles, and nerves to small arterioles. Myelin can be immunolabeled with antibodies directed against peripheral myelin protein 22 and myelin-associated glycoprotein.

▶ SUMMARY

Muscle, nerve, and skin biopsies for epidermal nerve fiber analysis can be useful in diagnosis of the various neuromuscular conditions described in detail in the subsequent chapters. As with electrodiagnostic and other laboratory testing, these are only helpful in the

conjunction with a good clinical examination. Further, as it is imperative that neuromuscular clinicians neuromuscular disease be able to independently review and interpret results of electrodiagnostic testing, the same holds true for at least understanding biopsy reports. Whenever possible we would urge clinicians to review biopsy slides with their pathologists so that they can become more familiar with various disease processes and correlate the clinical and electrodiagnostic findings with the histopathology.

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SECTION II

Specific Disorders

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CHAPTER 4

Amyotrophic Lateral Sclerosis

▶ INTRODUCTION

The motor neuron diseases (MNDs) are categorized by their pathological affinity for the voluntary motor system including anterior horn cells, certain motor cranial nerve nuclei, and corticospinal/bulbar tracts. Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig' disease, is the most notorious of these disorders. As in other neurodegenerative conditions, the clinical course of ALS is one of inexorable progression. The cause is unknown except in the small proportion of individuals who have familial forms of the disease. Although recognized and characterized by the consequences of motor system degeneration, ALS is best conceptualized as a multisystem disorder in which the motor system is typically the first and most dramatically affected of the systems affected.[1] The recent recognition of the association between frontotemporal dementia and an otherwise typical ALS phenotype emphasizes this potential for multisystem involvement.

In 1849 and 1850, respectively, Duchenne and Aran described progressive muscular atrophy (PMA), a disorder they believed to be of muscular origin, now recognized as a disorder of anterior horn cell degeneration.[2] In 1860, Duchenne first described a syndrome of progressive dysphagia and dysarthria and coined the term progressive bulbar palsy (PBP).[2] In 1874, Charcot and Cuveilheir recognized that corticospinal tracts and anterior horn cells were often affected concomitantly and, by doing so, introduced the concept of ALS.[2] In the next year, Erb described primary lateral sclerosis (PLS), a progressive disorder of corticospinal tracts, without, at least initially, evidence of muscle atrophy, fasciculation, or weakness.[2]

Similar to any group of seemingly related disorders of unknown cause, a satisfactory classification system for the MNDs remains elusive. It has long been recognized that ALS, PMA, PBP, and PLS are interrelated entities. PMA, PBP, and PLS are clinical syndromes that usually but do not always evolve into ALS.[3] It is often impossible to determine the natural history of the disease in an individual patient at disease onset. The patient may rapidly evolve into ALS with its customary poor prognosis, regardless of initial phenotype. Conversely, it may remain as one of the limited forms of MND, potentially offering a more protracted and arguably a more favorable natural history.[4]

There are, however, conceptual and pragmatic limitations of this classification, which attempts to categorize patients based on an ALS, PLS, PBP, and PMA paradigm. Recognizing this, Lord Brain, in his text of 1962, proposed the term MND, used essentially as a synonym for ALS in the United Kingdom.[2] By doing so, Brain attempted to resolve the uncertainties provided by a sometimes ambiguous classification scheme, utilizing frequently overlapping phenotypes.

In 1990, the World Federation of Neurology met in El Escorial, Spain, and subsequently published criteria intended to solidify the diagnosis of ALS for research purposes (Table 4–1).[5] These El Escorial criteria (EEC) were further modified and relaxed following a meeting in Airlie House, Virginia, in 1998. This was, in part, an attempt to allow patients with ALS into clinical trials at an earlier stage of their disease, many having been precluded from participating due to the diagnostic stringency of the original criteria. The increased prevalence of clinical trials in that era represented a response to two other landmarks. In 1991, Siddique and colleagues identified that mutations of the superoxide dismutase gene (SOD1) on chromosome 21 caused ALS in some families.[6] This, in turn, led to the development of animal models of the disease, a better understanding of the pathophysiology of at least SOD-associated disease, and the ability to rationally develop and screen drugs for signs of efficacy. In 1994, Bensimon and colleagues reported that Riluzole altered the natural history of the disease, the first (and to this date only) drug treatment that has been shown to do so.[7]

There are pragmatic problems associated with the application of EEC to clinical situations.[8] These two statements emphasize this point:

1. Not all patients with MND who present with one of the restricted syndromes (PBP, PMA, or PLS) develop or follow the customary natural history of prototypic ALS.
2. Approximately 25% of patients who die from an idiopathic, rapidly progressive MND will never achieve a probable or definite diagnosis of ALS by EEC, despite postmortem confirmation of upper motor neuron (UMN) and lower motor neuron (LMN) degenerations.[9,10]

To further dilute the historical construct of ALS and the MNDs, ALS is a disorder that may affect nonmotor

▶ TABLE 4–1. EL ESCORIAL CRITERIA—MODIFIED[5]

Clinically definite ALS	Defined on clinical evidence alone by the presence of UMN, as well as LMN signs, in three regions.
Clinically probable ALS	Defined on clinical evidence alone by UMN and LMN signs in at least two regions, with some UMN signs necessarily rostral to (above) the LMN signs.
Clinically probable, laboratory-supported ALS	Defined when clinical signs of UMN and LMN dysfunction are in one region, or when clinical UMN signs alone are present in one region—coupled with LMN signs defined by EMG criteria in at least two limbs, with proper application of neuroimaging and clinical laboratory protocols to exclude other causes.
Clinically possible ALS	Defined when clinical signs of UMN and LMN dysfunction are found together in only one region or UMN signs are found alone in two or more regions, or LMN signs are found rostral to UMN signs (in absence of EMG evidence of more widespread LMN disease).
Clinically suspected ALS	Defined by a pure LMN syndrome in which other causes of LMN disease have been adequately considered and excluded by ancillary testing (this category has been deleted from the revised EEC).

ALS, amyotrophic lateral sclerosis; UMN, upper motor neuron; LMN, lower motor neuron; EEC, El Escorial criteria.
With permission from Brooks BR et al: El Escorial World Federation of Neurology criteria for the diagnosis of amyotrophic lateral sclerosis. J Neurol Sci. 1994; Jul; 124(Suppl.):96-107.

neurological systems. Thirty percent or more of an ALS population will have cognitive or behavioral abnormalities, implicating frontotemporal lobar dysfunction.[11,12] There are cultures where tracheostomy and long-term mechanical ventilation are frequently used, resulting in a larger percentage of long-term survivors.[13] Observations from this population suggest that involvement of other neurological systems may occur if patients are allowed to survive beyond the natural history of their illness.[14] Many authors have referred to ALS with other neurological system involvement as ALS plus.[5] ALS-like syndromes may rarely occur in association with, and perhaps as a result of, other degenerative or systemic illnesses. This might appropriately be referred to as secondary ALS.

Within the general population, MNDs are uncommon, although not rare. The incidence of ALS averages 1.8/100,000 across all studies. This incidence appears to be increasing both within and outside of the boundaries of an aging population.[1] The average age of onset is approximately 60 years. Both teenagers and elderly may be afflicted. The only risk factor appears to be gender, with men being affected half as often as women. There is a suggestion that this gender difference disappears in the postmenopausal age range and that there are an excess of women in the population that present with bulbar symptoms. There have been nests of apparent increased incidence. The ALS–Parkinsons–Dementia complex formerly endemic in Guam and other Western Pacific regions is the most notable example. Otherwise, neither ethnicity, geography nor occupation has been reproducibly demonstrated to provide either increased or decreased risk. The average life expectancy of a patient with ALS is approximately 3 years although varies considerably. Patient may succumb within 1 year or uncommonly survive more than 10 years without invasive mechanical ventilation. Progression seems to follow a linear course, although the abrupt loss of a critical function may provide the appearance of stepwise deterioration. Patients with PBP are said to have a shorter average life expectancy, although many lead protracted existences if aspiration risk is minimized. Young males seem to live longer on average. Rilutek, participation in a multidisciplinary clinic, noninvasive positive pressure breathing, and, possibly, percutaneous gastrostomy are interventions that have modest benefits in prolonging life expectancy.[15]

The majority of ALS is currently considered to occur on a sporadic basis (sALS). Familial ALS (fALS) has been recognized since 1850 (Aran) and is currently thought to constitute 5–10% of all cases (Table 4–2). As in sALS, fALS is heterogeneous in both phenotypic expression and rate of progression, both within and between different gene mutations (Table 4–3).[16] As in sALS, fALS preferentially affects LMNs, selected motor cranial nerves, and corticospinal/corticobulbar tracts in most cases. As in sALS, fALS may never fulfill EEC during the patient's lifetime.[17]

▶ CLINICAL FEATURES

The initial clinical features of ALS may be quite diverse. Typically, the patients seek medical care when they acknowledge their painless weakness and atrophy (Fig. 4–1). These signs are frequently asymmetric and sometimes monomelic at onset. The initial deficits may be restricted in distribution but involve more than a single nerve or nerve root. In instances where the patients do not seek early medical attention, or their physicians do not recognize the significance of the problem, the patients may not be seen until their disorder is fairly advanced. Less commonly, the initial symptoms may be impaired speech or swallowing, reduced head control, or disordered breathing. Fasciculations are usually first recognized by the examining physicians rather than by patients but may occasionally be the initial manifestation, particularly in those who have preexisting

TABLE 4–2. FAMILIAL ALS[24,39,40]

Inheritance	Name	Genetics	Phenotype
Dominant	ALS1	21q22.1 SOD1	Adult onset—multiple phenotypes (see Table 4–3)
	ALS3	18q21	Adult onset
	ALS4	9q34 Senataxin	Juvenile onset Slow progression with distal amyotrophy and UMN signs
	ALS6	16q12	Adult onset
	ALS7	20ptel-p13	Adult onset
	ALS8	20q13.33 vesicular-associated membrane protein	Adult onset
	ALS–FTD	9q21–22	Adult onset 3 chromatin modifying protein 2B under gene Usually FTD without ALS, rare ALS associations reported
	ALS with PD and dementia	17q21 microtubule-associated tau	Adult onset
	ALS	2p13 dynactin	Adult onset—progressive LMN disease with variable vocal cord and facial weakness
X-linked	ALSX	XLD-Xp11	Adult onset
Recessive	ALS2	2q Isin	Juvenile onset—pseudobulbar and UMN
	ALS5	15q	Juvenile onset—distal amyotrophy, minor spasticity, and long-term survival
	GM2 gangliosidosis	15q23–24 hexosaminidase A deficiency	Adult onset—primarily LMN disorder with variable UMN and spinocerebellar features—primarily Ashkenazi
	Brown–Vialetto–von Laere		Childhood onset, bulbar palsy, deafness, and UMN signs
Mitochondrial	Single case reports	Cytochrome c oxidase 1 Isoleucine t-RNA Synthetase 2	Predominantly UMN Predominantly LMN

ALS, amyotrophic lateral sclerosis; SOD, superoxide dismutase; UMN, upper motor neuron; LMN, lower motor neuron; FTD, frontotemporal lobar dementia; PD, Parkinson disease.

awareness of their significance. Fasciculations, in the presence of weakness, particularly if multifocal and continuous, strongly support a motor neuron disorder. Fasciculations in the absence of weakness and EMG abnormalities, particularly if restricted in their distribution,

TABLE 4–3. PHENOTYPIC VARIABILITY OF SOD MUTATIONS IN FALS[24]

Phenotype	SOD 1 Mutation
Lower motor neuron predominant	A4V, L84V, D101N
Upper motor neuron predominant	D90A
Slow progression	G37 R (18 yr), G41D (11 yr), G93C, L144S, L144F
Fast progression	A4T (1.5 yr), N86S (homozygous 5 months), L 106V (1.2 yr), V148G (2 yr)
Late onset	G85R, H46R
Early onset	G37R, L38V
Female predominant	G41D
Bulbar onset	V148I
Low penetrance	D90A, I113T
Posterior column involvement	E100G

SOD, superoxide dismutase.

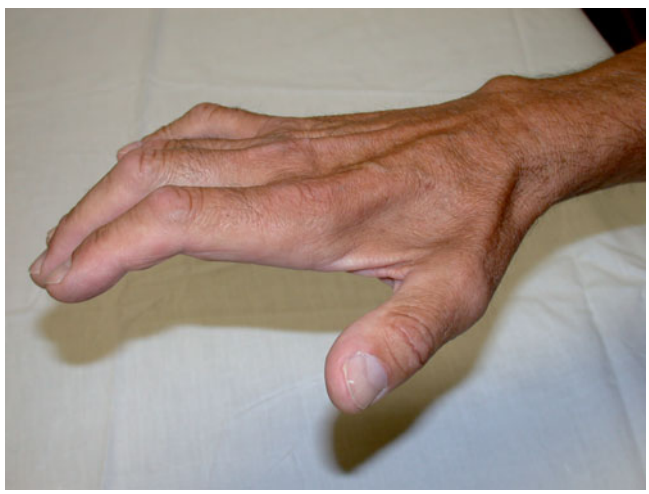

Figure 4–1. Hand atrophy in amyotrophic lateral sclerosis.

are typically benign.[18] Conversely, the absence of fasciculations in patients with painless weakness does not preclude the diagnosis, particularly in those with considerable subcutaneous tissue. An increased frequency of muscle cramping is common, which is often elicited during manual muscle testing.

The clinical diagnosis of ALS is dependent on the demonstration of LMN and UMN signs, which progress both within and between different body regions. As will be elaborated on subsequently, either may be absent, particularly early in the course. Signs of LMN involvement include muscle weakness, atrophy out of proportion to disuse, attenuation or loss of deep tendon reflexes, and fasciculations. Muscle weakness from pure LMN disease, which impairs coordination, does so proportionate to the degree of weakness. Conversely, with UMN disease, there is frequently a "stickiness" with attempted movements, resulting from disordered central nervous system control of activated muscle groups. Often, muscles not required for an attempted motion are inappropriately and synkinetically activated. UMN manifestations are more diverse and, at times, more subjective than their LMN counterparts. These may be fleeting, as these may develop and then disappear as LMN features develop and dominate in the same region of the body. For example, a Babinski sign may be lost as the extensor hallicus muscle atrophies and weakens. The elicitation of Babinski signs, sustained clonus, pathologically hyperactive deep tendon reflexes, and spasticity are universally accepted manifestations of UMN pathology. Unfortunately, these do not become clinically manifest in all ALS cases, thus confounding what is ultimately a clinical diagnosis. Other presumptive signs of corticospinal tract pathology include pathological spread of reflex (e.g., finger flexion with percussion of the brachioradialis tendon), emotional lability referred to as the pseudobulbar affect, an exaggerated gag or jaw reflex, Hoffman's signs, forced yawning, and preservation of reflexes in a wasted and weak extremity.

The most common ALS presentation is a patient with a combination of UMN and LMN features, limited initially in distribution, with the LMN findings typically dominating.[4,19] This syndrome could be referred to as a LMN-dominant form of the disease (LMN-D). The initial involvement is typically distally located in a hand or a foot. Initial weakness may occur in proximal muscles as well. A definite diagnosis cannot be made until these combined UMN and LMN signs spread over a period of months, both within and outside the initially affected body part. A diagnosis of definite ALS meeting EEC is uncommonly fulfilled at the time of the initial examination. Despite that, this combination is sinister, as there is little else other than ALS that produces both UMN and LMN signs in the same segments of even a single extremity, in the absence of pain or sensory symptoms.

Of the two-thirds of patients with ALS present with limb-onset disease,[3] at least a third will have the PMA phenotype initially with little or no suggestion of LMN-D involvement.[4] Seventy percent of these will develop UMN signs and evolve into ALS within a period of 6 years.[3] Even in the remaining PMA patients whose examination discloses only LMN features during life, degeneration of corticospinal tracts and ubiquinated inclusions (UIs) in motor neurons typical of ALS are frequently found post mortem.[10,20–22] As a result, there is strong justification to consider PMA as part of the continuum of ALS. At times, slowly progressive forms of PMA or LMN-D ALS may remain confined to both upper extremities, producing a flail arm syndrome.[23] A similar syndrome may affect both lower extremities, rendering the individual paraplegic for protracted periods before spreading to other regions.

PMA or LMN-D ALS may also occur on a familial basis. There are currently five of the >90 recognized SOD mutations known to have an LMN-D phenotype. The A4V SOD1 mutation represents the most common SOD mutation in North America and the most dramatic example of this phenomenon.

Approximately a third of individuals present with dysarthria or less commonly dysphagia.[3] A PBP presentation more commonly occurs in women than in men. Impairment of frontotemporal lobar function is more likely to occur in PBP than in limb onset phenotypes.[24] As in limb onset ALS, PBP may be dominated by UMN characteristics, LMN characteristics, or both. As in PMA and PLS, a PBP presentation may occur in fALS. In some individuals with sporadic PBP, signs and symptoms may remain confined to the "bulbar" musculature for considerable time, affecting the physicians' confidence in the accuracy of their diagnosis. Arguably, the most convincing indicator of LMN involvement of cranial nerves in ALS is tongue atrophy and fasciculations (Fig. 4–2). Weaknesses of tongue protrusion, neck flexion, and, with a lesser frequency, neck extension are common

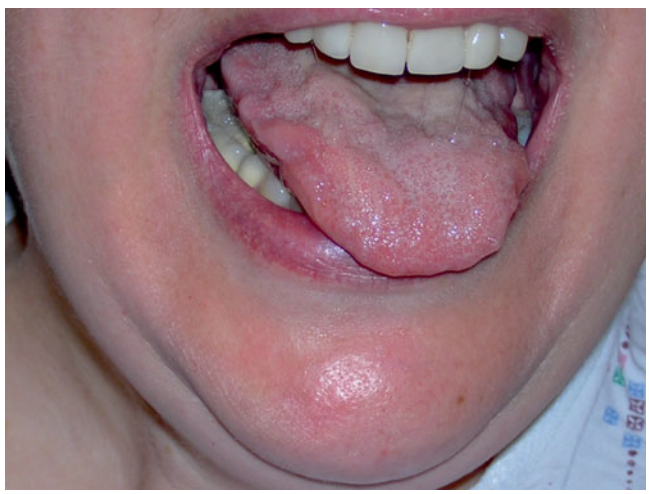

Figure 4–2. Tongue atrophy in amyotrophic lateral sclerosis.

LMN features. Facial and jaw weaknesses occur as well although tend to be more subtle. Ptosis and ophthalmoparesis do not occur in ALS as a general rule and should lead to another diagnostic consideration. Rarely, patients with ALS develop an apparent apraxia of eye opening or closing.

UMN involvement of cranial nerves is implicated by the presence of pseudobulbar affect (a tendency to laugh or cry with minimal provocation with lack of an associated emotional response), a heightened jaw, gag, or snout reflex. Slowing of attempted rapid blinking or tongue movements disproportionate to weakness in these muscles suggests a central nervous system problem although is not specific for corticobulbar tract pathology. Synkinesis of jaw movement with attempted side-to-side tongue movement may have a similar implication.

In a small percentage of cases, ALS begins and maintains itself as an UMN exclusive (PLS) or dominant (UMN-D) process, in which spasticity, not weakness, is the predominant source of functional impairment.[25–27] Approximately 2–5% of ALS cases begin with this PLS phenotype.[28] The average age of onset in virtually every series is about 50 years, approximately 10 years younger than typical ALS.[28] Three-quarters of PLS cases involve the legs, initially creating an inability to effectively run or hop. In most cases, onset is asymmetric.[28] In approximately 15% of cases, PLS affects the bulbar muscles initially. In 10% of cases, the upper extremities are the first region to become symptomatic.[29,30] It is commonly held that ALS spares the anterior horn of the sacral segments and, as a result, genitourinary symptoms do not occur in this disease. This is untrue in PLS where urinary urgency and urgency incontinence do occur, presumably on the basis of detrusor–sphincter dyssynergia from UMN involvement.

Authors have distinguished PLS from UMN-D ALS based on whether LMN signs are absent (PLS) or minimally present.[29] This distinction is somewhat artificial, as there is no consensus regarding what is a valid LMN sign and as a percentage of patients with PLS will evolve over time into ALS.[28] The life expectancy of PLS is considerably better than ALS. In nine reported series, the mean duration ranged between 7 and 14 years.[28] The large majority (80%) of individuals with PLS who evolve into ALS do so within the first 4 years of their disorder.[29] Conversely, development of LMN features, either clinically or electrodiagnostically, may not develop until 20 or more years after the initial symptoms. The natural history of patients who do not have clinical or electrodiagnostic evidence of LMN involvement during the first 4 years of their illness is statistically superior to those who have.

ALS is often not initially considered when the initial manifestations are dominated by UMN features, as there are many other far more common causes of progressive UMN disease. Typically, PLS is considered, and appropriately diagnosed, only after imaging and other investigations fail to provide an explanation for a patient's worsening spasticity.

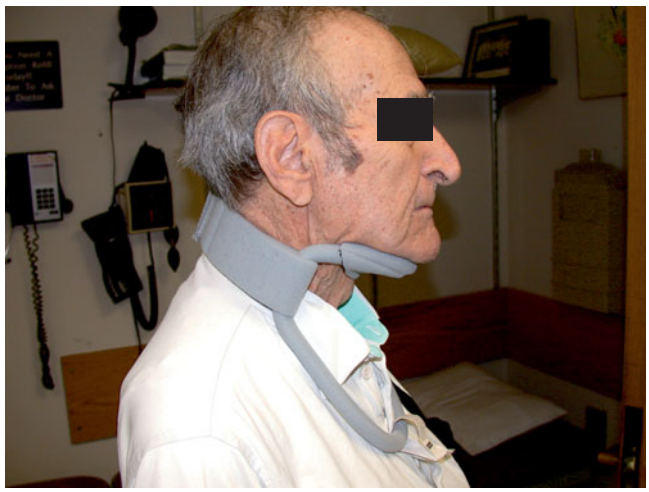

Figure 4–3. Head drop with cervical collar in amyotrophic lateral sclerosis.

In less than 1% of cases, ALS may initially present as ventilatory weakness[31] or with head drop from weakness of extensor muscles of the neck (Fig. 4–3). Ventilatory weakness may initially have protean clinical manifestations, including disordered sleep, early morning headache, fatigue, orthopnea, dyspnea on exertion, or perhaps even mental status change. On occasion, ALS may be first recognized in an individual who cannot be weaned from the ventilator following elective intubation. Paradoxical abdominal movements with ventilation should be sought as an indicator of diaphragmatic weakness in patients with suspected ALS or other causes of restrictive lung disease.

Behavioral and cognitive abnormalities in ALS have been recognized since the 19th century but, until recently, have been, in large part, overlooked as a significant part of the clinical spectrum.[11] These may exist in both familial and sporadic forms of the disease. Although the cognitive and behavioral abnormalities are frequently the initial symptoms, these are often overshadowed by the rapidly progressive MND. The existence and degree of cognitive and behavioral abnormalities may be obscured by numerous other factors. The severity of these frontotemporal features exists in an apparent continuum, and their manifestations may be quite subtle. Detection may further be thwarted by dysarthria and communication difficulties. Additionally, they may be blamed on comorbidities such as depression, pseudobulbar affect, and hypoxia.

The nomenclature may be confusing. Patients with frontotemporal lobar degeneration (FTLD) will have both cognitive and behavioral abnormalities. Criteria for this syndrome have been established.[32] Approximately 8% of patients will meet the criteria for frontotemporal lobar dementia (FTD).[33] The incidence of either cognitive or behavioral impairment in MND may be

much higher,[34] and each may exist without the other.[11] The cognitive changes are most prominent in the domain of executive dysfunction and language. Disorganization, impaired planning, mental inflexibility, nonfluent progressive aphasia (word finding), and fluent semantic dementia (word meaning) may dominate the clinical picture. Tests of verbal fluency provide a sensitive screening method.[33] Anti-saccade testing (the ability to look in the opposite direction in response to a lateralized visual stimulus) provides a screening method for those unable to verbally communicate.

Behavioral difficulties are typically displayed in social and interpersonal realms. Patients lose the ability to appreciate nonverbal clues and the insight to interpret them. Patients may become either withdrawn or disinhibited.[32]

There are at least four currently known genetic loci for hereditary FTLD, at least two and perhaps three of which may have an associated MND.[35] One of these results from mutations at 9p13.2–21.3, resulting in UMN and LMN degeneration, associated with behavioral, personality, and/or language change, and also in non-tau UIs in the anterior horn cells and the granular layer of the hippocampus. A second locus exists on the progranulin (GRN) gene on chromosome 17. It is distinct from another gene on chromosome 17 that encodes the microtubule-associated protein tau gene, which may also produce an FTD with or without Parkinsonism but typically without a motor neuron component.[12] This non-tau locus is also associated with UIs and a phenotype that may include an extrapyramidal as well as a behavioral and an amyotrophic component. A third, more tentative association exists with mutations of the chromatin modifying protein 2B gene (CHMP2B) on chromosome 3. This mutation is most closely linked to FTD without MND, but patients with ALS having this mutation have been reported. One had a bulbar-onset LMN-D form of ALS without dementia. The other had both FTLD and ALS, which began as a spastic bulbar palsy.[36]

▶ LABORATORY FEATURES

With the exception of DNA mutational analysis in a patient with a mutation of the SOD1 gene, there are no laboratory tests that currently confirm the diagnosis of sALS or the majority of fALS genotypes. ALS researchers are currently applying metabolomic methods in an attempt to identify one or more biomarkers of the disease.

Certain tests are done with the intent of identifying subclinical LMN involvement in UMN-predominant cases or, conversely, UMN involvement in individuals with LMN-predominant syndromes. Fortunately, there is an excellent surrogate marker of LMN degeneration, which can confirm the existence, distribution, and relative duration of LMN degeneration.[37] EMG and nerve studies are performed in virtually every patient suspected to have MND/ALS. The goals of the test are to

1. confirm a pattern of active denervation, chronic denervation, and fasciculation potentials in multiple muscles innervated by multiple segments in multiple regions, i.e., a pattern consistent with (although not diagnostic of) ALS;
2. exclude features that would suggest an alternative diagnosis that might phenotypically mimic ALS, e.g., abnormal sensory conductions in Kennedy syndrome, a large decremental response to repetitive stimulation more consistent with myasthenia, conduction block suggestive of multifocal motor neuropathy (MMN), or EMG findings more consistent with inclusion body myositis;
3. offer insight into the rate of progression, i.e., active denervation without chronic denervation and reinnervation, motor unit variability, and a rapid decline in motor unit estimation being electrodiagnostic indicators of a more rapidly progressive course.

Unfortunately, there is no widely available surrogate laboratory test capable of identifying subclinical UMN degeneration with adequate sensitivity and specificity. A test of this nature would be an invaluable tool in patients with a PMA presentation. Transcranial magnetic stimulation, magnetic resonance spectroscopy, and tractography performed with diffusion tensor imaging on high-field magnets are some of the laboratory methods that have been and continued to be developed with the hope of filling this diagnostic niche.

Imaging has also been used to demonstrate reduced blood flow or overt atrophy in a frontotemporal lobar pattern (Fig. 4–4). Single photon emission computerized tomography or positron emission tomography has been used, more for research than for clinical purposes.

The majority of laboratory tests are done to exclude other ALS differential diagnostic considerations. Elevations of serum creatine kinase levels are common in ALS, occurring in approximately two-thirds of patients.[38] Normal values are often obtained in patients with PLS and PBP, or in those who have lost large amounts of their muscle mass. Occasionally, an elevated CK value, in the appropriate context, can help neurologists with their confidence that ALS is or is not the correct diagnosis.

Antibodies directed at the GM1 ganglioside have been found in high titer in some patients with the MMN phenotype. They may occur in lower titers in other neuromuscular disorders, including ALS. They are most commonly ordered in individuals with LMN-D syndromes, in an attempt to identify potentially treatable MMN. They have been reported to occur in 30–80% of patients with MMN.

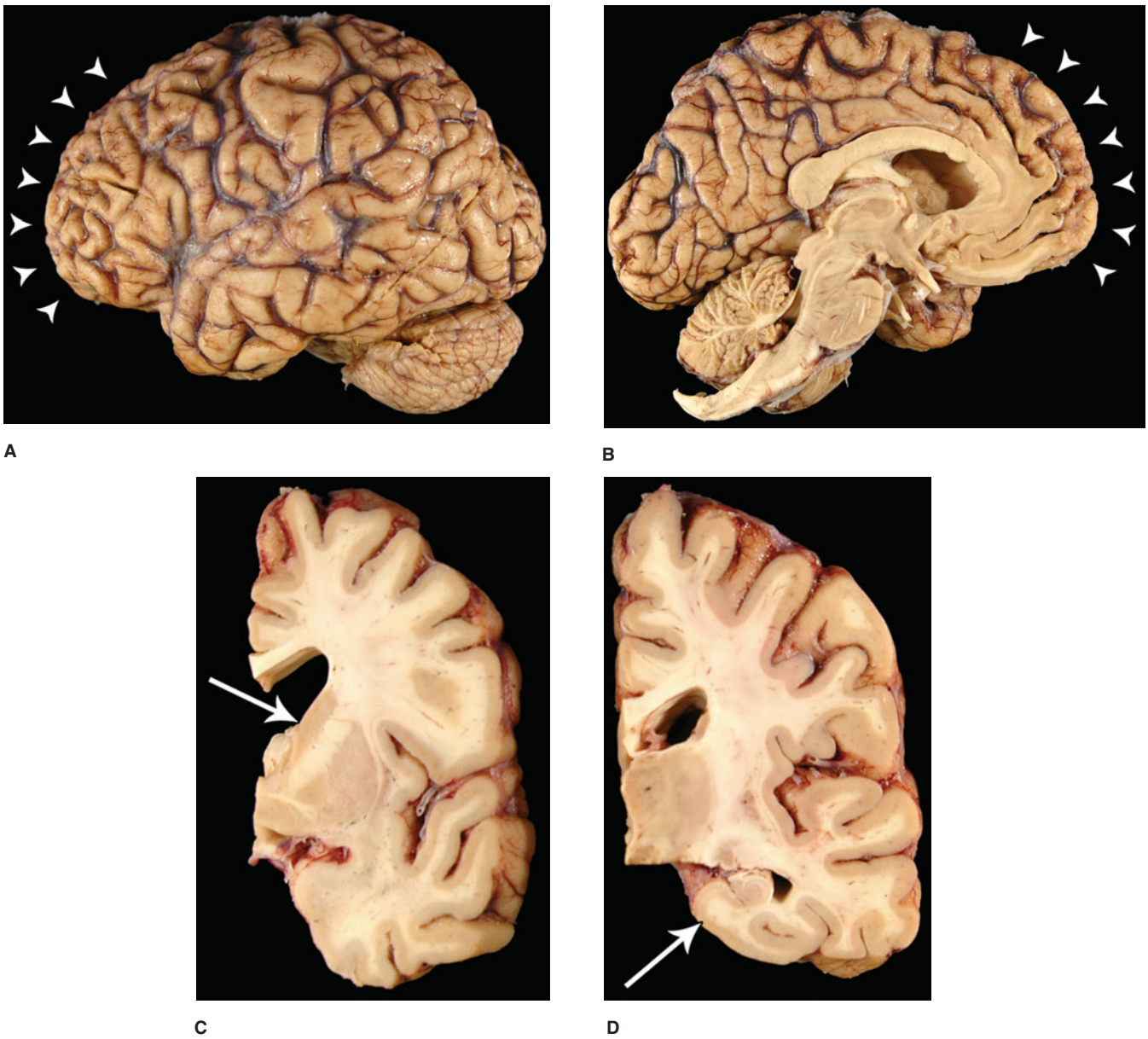

Figure 4–4. Preferential frontal atrophy in a patient with frontotemporal lobar degeneration and motor neuron disease.

Serological tests for myasthenia, typically antiacetylcholine receptor-binding and anti-muscle-specific kinase antibodies, are frequently obtained in ALS suspects who have neither atrophy nor UMN signs. This application is arguably most relevant to patients presenting with difficulty in speaking, swallowing, chewing, breathing, or holding their head up.

There are also laboratory tests that are used to monitor the course of the disease and to aid in management decisions. Tests of ventilatory function are the most common examples of these. Forced vital capacity and maximal expiratory and inspiratory pressure measurements are most commonly used. Although these may aid in the initial diagnosis, their primary purpose in ALS is to monitor progress, predict prognosis, and aid in medical decision making.

Currently, DNA mutational analysis for potential mutations within the SOD1 gene is the only commercially available test for fALS. Its application is least controversial in individuals who are symptomatic from ALS with a family history of other known or suspected members. Testing for this mutation is equally rational in symptomatic individuals with little or no knowledge of their family history. Testing in asymptomatic individuals from families with known affected family members should not proceed prior to genetic counseling and a clear

understanding by the subject, and arguably of family members at risk, of the implications of both a positive and a negative result. The expression of SOD1 mutations varies considerably. The A4V mutation is highly expressive, with 90% of individuals being clinically affected by the age of 70 years. Conversely, the I113T mutation appears to be expressed in less than 10% of patients harboring the mutation.[39,40] Further complicating this dilemma is the fact that the onset of symptoms in individuals with the same mutation may vary widely and that mutations in the same locus may behave differently in different populations. In the case of the D90A CuZn SOD homozygotes, onset may vary from 20 to 94 years of age.[16] That same locus acts as a recessive trait in Scandinavia where heterozygotes are asymptomatic. In North America, D90A heterozygotes develop ALS. Pragmatically, this means that some apparent sALS cases may, in fact, be hereditary. This promotes a moral dilemma that is not easily reconciled, i.e., should all patients suspected to have ALS undergo SOD1 mutational analysis regardless of family history? A dogmatic response to that rhetoric question cannot be confidently provided at this time.

▶ HISTOPATHOLOGY

There are two primary pathological features of ALS. Degeneration with the loss of myelinated fibers occurs in the corticospinal and corticobulbar pathways. Secondly, there is a loss of motor neurons within the anterior horns of the spinal cord and many motor cranial nerve nuclei. As a result, ventral roots become atrophic in comparison to sparing of their dorsal root counterparts (Fig. 4–5). There is a loss of anterior horn cells within virtually all levels of the spinal cord with cell preservation of the intermediolateral cell columns (Figs. 4–6 and 4–7). There is selective sparing of the third, fourth, and sixth cranial nerves, Onuf's nucleus, and the anterior horn of sacral segments 2–4.

Many patients with ALS will be found to have UIs within the central nervous system (Fig. 4–8). UIs are not unique to ALS, although their location and composition may be. TDP-43 is a DNA/RNA-binding protein, which is translated from a gene on chromosome 1. Little is known about its function. In sporadic ALS, TDP-43 (+) skeins are found in motor neurons, as well as the hippocampus, frontal, and temporal lobes. These UIs do not stain for either the tau or the α-synuclein proteins as UIs in other degenerative diseases are apt to do. To date, TDP-43 (+) skeins have been uncommonly demonstrated in disorders other than tau (−) FTLD and in sporadic ALS, further cementing the link between these two clinical syndromes. TDP-43 (+) skeins have not yet been demonstrated in other neurodegenerative diseases. Mutations of the TDP-43 gene in ALS or FTD have yet to be demonstrated.[41] Loss of function of the non-tau, neuronal growth factor progranulin, which has

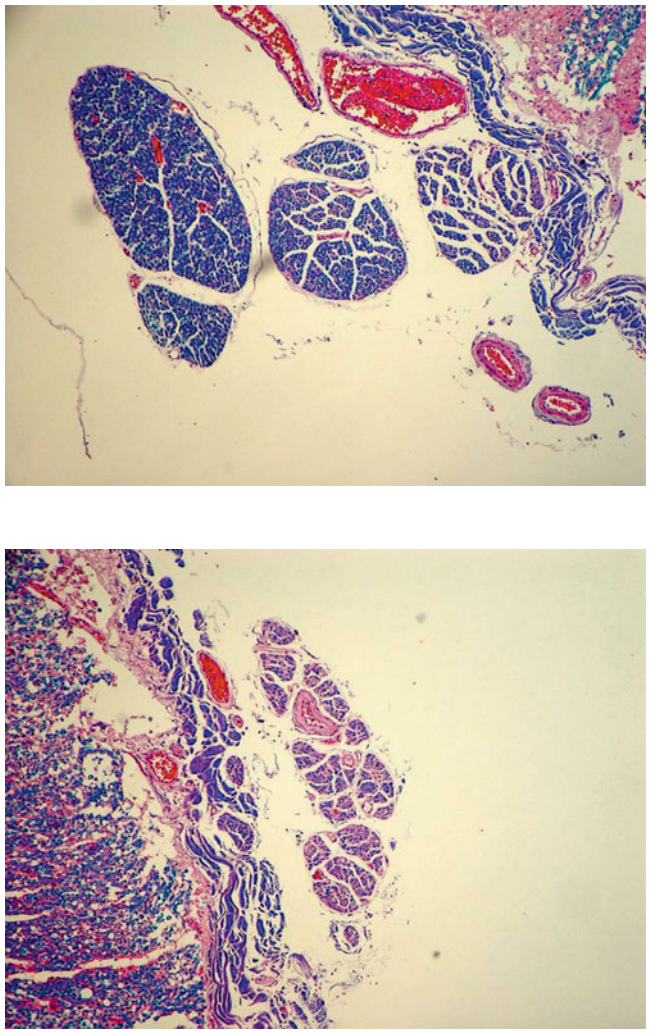

Figure 4–5. Dorsal root (upper) and ventral root (lower) of a patient with amyotrophic lateral sclerosis, demonstrating atrophy of the latter. (Luxol fast blue/hematoxylin and eosin) (Reproduced with courtesy permission of Lester Adelman, M.D.)

a chromosome 17 locus, has been reported to occur in some cases of FTLD. A link between progranulin deficiency and TDP-43 deposition is suspected but as of yet unproven.[42]

Additionally in ALS, spongioform changes of the first and second layers of the frontal cortex have been described. These are the most reliable pathological distinction between the cognitively impaired and unimpaired ALS patient population. There also appear to be seemingly unique intraneuronal and intraglial tau inclusions in the brains of patients with ALS, both with and without clinical evidence of cognitive impairment.[12] Bunina bodies, dense granular intracytoplasmic inclusions within motor neurons, are thought to be specific for ALS.

Pathological findings outside the motor system may be found in ALS plus syndromes, particularly those of a familial nature. Involvement of ascending sensory and descending spinocerebellar tracts has been

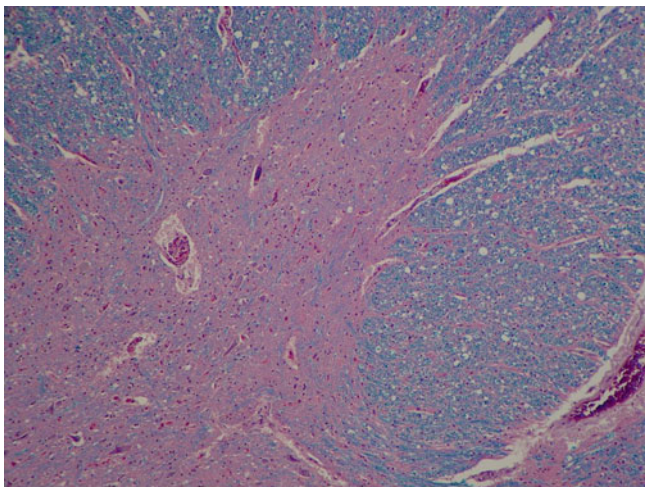

Figure 4–6. Ventral gray matter of lumbar spine in a patient with amyotrophic lateral sclerosis, showing rare, atrophic anterior horn cells. (Luxol fast blue/hematoxylin and eosin) (Reproduced with courtesy permission of Lester Adelman, M.D.)

pathologically demonstrated in specific superoxide dismutases (SOD1) mutations such as E100G.

Muscle biopsy is rarely done by most neurologists in most ALS suspects. It is primarily used if there is a clinical suspicion that the patient has a muscle disease. With ALS, the predominant findings are nonspecific and indicate only the presence of denervation (angulated fibers, target fibers, and group atrophy) and reinnervation (type grouping). The latter is uncommonly seen except in very slowly progressive cases.

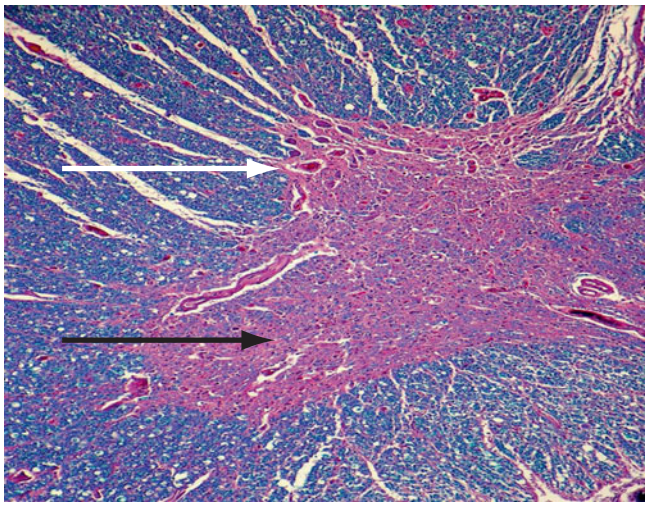

Figure 4–7. Thoracic spinal cord in a patient with amyotrophic lateral sclerosis, demonstrating normal complement of neurons in intermediolateral cell column (white arrow) and absence of neurons in ventral gray matter (black arrow). (Luxol fast blue/hematoxylin and eosin) (Reproduced with courtesy permission of Lester Adelman, M.D.)

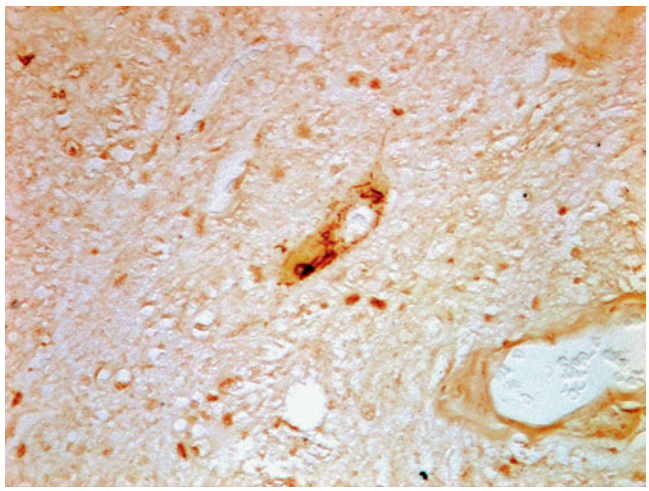

Figure 4–8. TDP-43 (+) skein in a motor neuron (lumbar) in a sporadic patient with amyotrophic lateral sclerosis (40× magnification—rabbit polyclonal antibody to human TDP-43, dilution 1:400). (Reproduced with courtesy permission of Michael Strong, M.D., and Robert Hammond, M.D.)

▶ PATHOGENESIS

The cause(s) of sporadic ALS remains unknown. Currently, we can only speculate as to whether ALS is a singular disorder producing multiple overlapping phenotypes or multiple disorders similar phenotypic expression. Our knowledge of disease pathogenesis has increased. Knowledge regarding which components of the pathophysiologic cascade defined to date are causative, or are reactive, and the means by which these components interact remains elusive. Currently, the most widely held hypothesis regarding the cause of sporadic MND/ALS proposes a combination of genetic susceptibility and environmental exposure. No susceptibility gene or environmental culprit has been conclusively identified to date. Recently, evidence supporting mutations of the paraoxonase gene cluster (PON 1, 2, and 3) on chromosome 7 has been promoted in this capacity.[40] Large-scale investigations in both the United States and Canada are attempting to identify this and other potential susceptibility gene(s) in sporadic ALS.

There is evidence to support a number of different mechanisms of motor neuron death, including oxidative stress, excitotoxicity, mitochondrial dysfunction, derangement of cytoskeletal elements and axonal transport, protein aggregation, formation of inflammatory cascades, and apoptosis.[1,43] Many of these mechanisms may interact and may not be mutually exclusive. Why motor neurons and corticospinal/bulbar tracts are vulnerable in a selective or semiselective manner remains unknown. Why the disease begins focally and seems to progress in a regional fashion in most patients remains enigmatic as well. Perhaps, misfolded and potentially toxic protein

TABLE 4–4. EVALUATION OF THE PATIENT WITH SUSPECTED LMN-D ALS

Tests That Should Be Considered in Every Patient	Tests That Should Be Considered in the Context of the Individual Patient
Electrodiagnostic studies (EMG and NCS) with multipoint stimulation for potential conduction block and repetitive stimulation	CSF evaluation
Anti-GM1 antibodies	Muscle biopsy
CK	Serum immunofixation
Serum immunofixation	ESR
Antiacetylcholine receptor-binding antibodies	Lyme serology—blood and CSF
Forced vital capacity	Paraneoplastic antibodies
	DNA mutational analysis for (androgen receptor gene) Kennedy's disease
	DNA mutational analysis for survival motor neuron gene (SMA I-III)
	Single fiber electromyography
	Antiacetylcholine receptor-binding antibodies
	Anti-voltage-gated calcium channel antibodies
	Anti-muscle-specific kinase antibodies (MuSK)

ALS, amyotrophic lateral sclerosis; LMN, lower motor neuron; CSF, cerebrospinal fluid; NCS, Nerve condition studies; ESR, erythrocytine sedimentation rate; CK, creatine kinase.

aggregates proselytize normal protein in adjacent neurons in a manner analogous to that proposed for the prion diseases.

Approximately 90% of ALS occurs on an apparent sporadic basis. There have been a number of different gene mutations identified, correlating with an MND phenotype, only some of which recapitulate the classic ALS clinical picture (Table 4–2). Mutations occurring within the gene for Cu^{2+}/Zn^{2+} superoxide dismutase 1 (ALS1) account for approximately 10–20% of all fALS cases, or 1–2% of all ALS. There are over a hundred known single base substitutions, insertions, deletions, missense, and nonsense point mutations of the SOD1 gene. This can result in an amazing array of phenotypes, which may essentially recapitulate the entire phenotypic spectrum of sALS (Table 4–3).[44] As the SOD1 protein is involved in free radical degradation, the mechanism of mutant SOD1-induced disease was initially attributed to decreased protein function, resulting in free radical toxicity. Subsequent research has indicated the opposite. It would appear that the mutated protein promotes motor neuron death through some "gain of function" or toxic effect, presumably through misfolding and deposition of the disfigured SOD1 structure.

DIFFERENTIAL DIAGNOSIS AND RECOMMENDED EVALUATION

Differential diagnostic considerations and evaluation varies with phenotype and the clinical context of the individual patient. Tables 4–4 to 4–7 offer guidelines in

TABLE 4–5. EVALUATION OF THE PATIENT WITH SUSPECTED UMN-D ALS

Tests That Should Be Considered in Any Patient	Tests That Should Be Considered in the Context of the Individual Patient
Electrodiagnostic studies (EMG and NCS)	CSF evaluation including IgG indexing and oligoclonal bands
MRI of brain	ACE level (serum and possibly CSF)
MRI of cervical and thoracic spine	Rapid plasmin reagin (RPR)
	C26–C22 long-chain fatty acid ratio
	Vitamin B12 level
CPK	HIV serology
Forced vital capacity	HTLV 1 serology
	Serum copper level
	DNA mutational analysis for HSP
	Lyme serology—blood and CSF
	Paraneoplastic antibodies
	Mammography
	ESR
	Antinuclear antibody (ANA)
	Lupus anticoagulant and anticardiolipin antibodies

CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; HSP, hereditary spastic paraparesis.

TABLE 4–6. EVALUATION OF THE PATIENT WITH SUSPECTED BULBAR ALS

Tests That Should Be Considered in Every Patient	Tests That Should Be Considered in the Context of the Individual Patient
Electrodiagnostic studies (EMG and NCS) with repetitive stimulation if LMN-D	CSF evaluation including cytology, acid-fast and fungal cultures, RPR, and ACE level
MRI of brain	Muscle biopsy
CK	ESR
Antiacetylcholine receptor-binding antibodies	Lyme serology—blood and CSF
Forced vital capacity	Single-fiber electromyography
	Anti-muscle-specific kinase antibodies (MUSK)
	DNA mutational analysis for poly A-binding protein 2 gene (oculopharyngeal dystrophy)

ALS, amyotrophic lateral sclerosis; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging.

this regard. For the patient with widespread UMN and LMN signs, there is an extremely limited differential diagnosis and limited ancillary testing may be required.

Secondary causes of ALS are rare and are often hereditary-degenerative disorders, many of which also affect other extrapyramidal and nonmotor neurological systems. Hereditary spastic paraparesis (HSP) is the disorder that may, most closely, approximate the ALS phenotype. ALS may present with a spastic paraparesis and approximate an HSP phenotype if slowly progressive. As with most heritable disorders, the absence of other obviously affected family member does not preclude an HSP diagnosis. To complicate matters further, some HSP genotypes such as SPG9, 10, 14, 15, 17, 20, 22, 26, and 30 may have a concomitant LMN component, making distinction from ALS particularly difficult.[45] Slow progression, cavus foot deformities, and the existence of lower extremity posterior column signs should increase the index of suspicion for HSP in what might otherwise be considered an ALS phenotype.[12] Significant involvement of the upper extremities or of bulbar musculature would be atypical for "pure" HSP but may occur in complicated phenotypes of the disease.[45,46]

Another hereditary disorder with a phenotype that has ALS-like features is one form of distal spinal muscular atrophy (hereditary motor neuropathy type V) associated with the S90L mutation of the BSCL2 gene. In this disorder, known as Silver syndrome, there is distal amyotrophy resembling Charcot–Marie–Tooth disease without sensory loss, associated with prominent spastic paraparesis.[47] This disorder is allelic if not identical to SPG17.[45]

Structural disorders of the spinal cord are usually dominated by UMN features (see below) but may at times have prominent LMN features as well, particularly in the case of dural vascular malformations. Imaging of the spinal cord should be included in any MND phenotype in which there are no compelling "bulbar" symptoms or signs.[48,49]

Recently, a report described three individuals with an ALS phenotype associated with copper deficiency.[50] These individuals had asymmetric foot drop as one of the initial manifestations of a progressive UMN and LMN disorder. Copper replacement stabilized but did not reverse their deficit. Retrospectively, there were clinical clues that would raise suspicion of copper deficiency in these and other patients with MND. These include prominent large fiber sensory loss, with or without symptoms in the setting of normal sensory conduction studies; prior history of disease of the stomach or duodenum that might interfere with copper absorption; chronic zinc ingestion; or concomitant anemia or other cytopenias as other manifestations of copper deficiency. Serum copper, ceruloplasmin, and zinc determinations, as well as

TABLE 4–7. EVALUATION OF THE PATIENT WITH SUSPECTED ALS WITH BOTH UMN AND LMN FEATURES

Tests That Should Be Considered in Every Patient	Tests That Should Be Considered in the Context of the Individual Patient
Electrodiagnostic studies (EMG and NCS)	CSF evaluation including cytology, acid-fast and fungal cultures, RPR, and ACE level
MRI of brain	Lyme serology in serum and CSR
CK	DNA mutational analysis for HSP
Serum copper, ceruloplasmin, zinc and, CBC	MRI of cervical and thoracic spinal cords

ALS, amyotrophic lateral sclerosis; UMN, upper motor neuron; LMN, lower motor neuron; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging.

complete blood counts should be considered in any ALS suspect, particularly if any of the aforementioned features is present.

Myasthenia is arguably the most important consideration in bulbar presentations of ALS, due to its prevalence and the opportunity for treatment that it provides. Involvement of extraocular muscles, significant fluctuation of weakness, absence of tongue atrophy, and absence of UMN signs all increase the probability of a diagnosis of myasthenia. Other disorders that should be considered, dependent on time course, include the inflammatory myopathies, oculopharyngeal muscular dystrophy, X-linked spinobulbar muscular atrophy, head and neck cancer, multiple cranial neuropathies resulting from inflammatory disorders such as sarcoidosis and Wegener's granulomatosis, from meningeal-based neoplasms, as well as structural disorders of the brainstem including neoplasms and syringobulbia.

There are rare bulbar syndromes that are rarely confused with PBP in view of their age of onset. Both are presumed to be hereditary in nature. Fazio–Londe syndrome is a syndrome that typically affects children in the first decade. Stridor, palatal weakness, dysphagia, and in some cases ventilatory failure occur. Unlike many MNDs, prominent facial weakness and occasional ophthalmoplegia may occur. There are no UMN features. The disorder is presumed to be inherited in a recessive fashion. Progression is rapid, and death typically occurs within a few years. The syndrome of Brown–Vialetto–Van Laere presents in the first or second decade. It is not purely an MND as sensorineural hearing loss accompanies a PBP. It may progress to involve the limbs as well, with suggested UMN involvement in the form of hyperactive deep tendon reflexes. The inheritance pattern and the clinical course are variable. Other neurological systems may be involved, including ataxia, retinal pigmentary degeneration, seizures, and dysautonomia.[51]

There are a number of seemingly pure LMN disorders affecting the limbs that may mimic PMA. Included among these are LMN syndromes that may defy current classification schemes.[51] MMN is a presumed immune-mediated disorder of motor nerve producing painless weakness, typically initially affecting a single, distal upper extremity. On average, it affects a younger population than ALS but there is a substantial overlap. Initially, the weakness may be evident in a nerve rather than in segmental distribution. This pattern of weakness, as well as weakness in the relative absence of atrophy, should raise consideration of this apparent demyelinating motor neuropathy. Unfortunately, with progression, these diagnostic clues may become obscured by disease progression. The presence of motor nerve conduction block on nerve conduction studies and anti-GM1 antibodies strongly implicates MMN as does a response to treatment. Neither test is sufficiently sensitive for a negative test result to exclude MMN from consideration. MR imaging of the brachial plexus may demonstrate swelling or increased signal of nerve elements in a third of MMN cases.[50] Although nonspecific, this finding may support what at times may be an elusive diagnosis.

Inclusion body myositis typically produces a distinctive pattern of weakness, i.e., preference for the wrist and finger flexors as well as knee extensors. It is not uncommon for it to be confused with ALS, both on clinical and on electrodiagnostic (EDX) grounds.[52] In younger men, Hirayama's disease or benign focal amyotrophy must be considered.[24,53] This is a presumed focal form of MND considered to be a sporadic form of spinal muscular atrophy. Weakness almost always begins in hand muscles unilaterally, progressing at times to affect the other hand in up to a third of cases. Proximal arm muscles may eventually be affected before the disorder seemingly arrests its progress. Most individuals with a rare lower extremity presentation of benign focal amyotrophy have been of Indian origin. In both Hirayama disease and MMN, reflexes may be preserved or even slightly exaggerated in an affected limb, leading to potential diagnostic confusion with ALS.[50]

Kennedy's disease is an X-linked, adult form of spinal muscular atrophy that results in prominent bulbar dysfunction and fasciculation as well as a slowly progressive, proximal, and symmetric pattern of MND.[54,55] Rarely, the disorder may be asymmetric or progress rapidly, both of which may increase the probability of an ALS misdiagnosis. Occasionally, an ulnar neuropathy at the wrist or palm producing atrophy of intrinsic hand muscles without sensory signs or symptoms will be initially confused with PMA.

Differential diagnostic considerations for predominantly UMN presentations of ALS include compressive, hereditary, inflammatory, infectious, and occasionally ischemic disorders of the spinal cord. Compressive myelopathies from spondylosis, tumor, or other mass lesions would rarely produce a pure motor syndrome mimicking PLS but need to be excluded early in their course because of the potential for intervention. Multiple sclerosis is rarely a serious differential diagnostic consideration other than for primary progressive motor syndrome, which can present as a progressive myelopathy in middle-aged individuals. Other inflammatory myelopathies such as neuromyelitis optica and paraneoplastic myelopathy associated commonly with breast cancer usually evolve too rapidly to offer serious consideration. Retroviral illnesses including HIV and particularly HTLV1 can produce a slowly progressive spinal cord syndrome. Rarely a female carrier of the X-linked disorder adrenoleukodystrophy will present as a slowly progressive paraparesis in young adulthood to middle age. Arguably, the most difficult differential diagnostic consideration is HSP, as described above. For a number of reasons including recessive inheritance patterns, adoption, early parental death, or false paternity, the

absence of a other affected family members does not exclude HSP from consideration. Both UMN-D ALS and HSP typically present with spasticity in the legs. Asymmetry at onset, the presence of early arm involvement, rapid progression, and absence of large fiber sensory loss would favor UMN-D ALS. In UMN-D ALS, the DNA mutation analysis for HSP is available but at considerable cost and for only a limited number of currently recognized genotypes. Lastly, pyramidal tract findings may occur in certain forms of distal spinal muscular atrophy and Charcot–Marie–Tooth disease. Neither would be commonly confused with ALS in view of the distal symmetric pattern of weakness, slow progression, and frequent cavus foot deformities.

ALS remains a clinical diagnosis supported by the results of both positive and negative ancillary testing. With the exception of DNA mutational analysis for SOD1 mutations causing fALS, there are no tests that confirm a diagnosis of ALS. At the time of initial evaluation, ALS may be suspected but the clinical features are not developed to the extent that the neurologists feel confident in sharing their concerns with their patients. The physician frequently feels conflicted as to when to have this conversation. To do so prematurely hazards the possibility of being wrong. Additionally, patients may lack confidence in someone who confronts them with a diagnosis of this magnitude without the appearance of careful consideration and testing. Balanced against this is the patients' need for answers. Perceived "foot dragging" and uncertainty may have equally deleterious effects on their trust in their physicians. Disclosing the suspected diagnosis as early in the course as possible, following exclusion of reasonable differential diagnostic considerations, with demonstration of unequivocal progression both within and outside of initially affected regions, would seem to be a reasonable approach.

Many neurologists will not wait for a patient to fulfill EEC for definite or probable ALS before disclosing their suspicions.[8] As mentioned, it is estimated that up to 25% of patients with ALS will die without having fulfilled the definite or probable EEC criteria.[9] Additionally, it has been recognized that the EEC criteria at diagnosis, e.g., definite, probable, possible, or suspected, do not correlate with clinical course and survival.[15] In view of the implications of an ALS diagnosis, and the lack of a confirmatory test in most cases, patients are frequently counseled to seek a second opinion from a knowledgeable source.

▶ TREATMENT

Currently, there are no effective treatments that can reverse or arrest disease progression in ALS. As a result, the major goals of MND/ALS management are to slow disease progression to the extent possible and maintain independent patient function, safety, and comfort. In 1999, an American Academy of Neurology Task Force constructed a Practice Parameter outlining the evidence basis for the care of patients with ALS.[56] Other comprehensive management reviews are available.[57]

In 1994, Rilutek was identified as the first and only disease-specific treatment to date that positively affected the natural history of the disease.[7] The dose is 50 mg twice a day. Its modest benefit results in an approximate 10% slowing of disease progression. Unfortunately, this benefit is imperceptible to the patient who neither feels nor functions better. It is an extremely expensive drug. Approximately a quarter of patients do not tolerate the drug due to upper gastrointestinal side effects. Reversible hepatotoxicity may occur with an associated requirement for monitoring of liver function tests. Whether the benefit of Rilutek exceeds its cost is a candid conversation that should take place with patients and their families.

The care of patients with ALS and their families involves education, counseling, and symptom management. Table 4–8 lists the most common problems that may afflict a patient with MND/ALS and some of the treatment options that are available. Two interventions that are often met with resistance by patients are percutaneous gastrostomy and noninvasive positive pressure support (NIPPV). In view of this, it may be prudent to introduce these concepts prior to the point in patient's illness when these are really needed. Both should be introduced with the idea that these improve quality of life rather than duration of life, even though the latter may be achieved to a certain extent as well. There are no absolute criteria that provide optimal percutaneous gastrostomy timing. Loss of weight of >10% of baseline weight, doubling of eating time, or recurrent coughing or choking during eating are the most common indicators that are used. Ideally, a percutaneous gastrostomy should be inserted before the forced vital capacity falls below 50% of predicted to limit risk associated with the procedure.[56]

NIPPV is typically recommended when the patient is symptomatic from shortness of breath, when disturbed sleep is attributed to hypoventilation, when symptoms attributable to hypercapnia such as morning headache occur, or when forced vital capacity decreases to less than 50% of predicted. Usually, initial use occurs at night when hypoventilation is most likely to occur. NIPPV appears to have the most dramatic effects on disease survival of any treatment options available. In the United States, most third party payers will not reimburse for NIPPV treatment in ALS unless the vital capacity has fallen to less than 50% of predicted or hypercapnia has been documented. This may be extremely problematic in patients who are symptomatic but who have yet to fulfill the aforementioned diagnostic criteria.

Optimal management of the patients with ALS and their families requires extensive effort and resources

TABLE 4–8. SYMPTOMATIC MANAGEMENT OF MND/ALS

Symptom, Management Issue	Potential Treatments	Symptom, Management Issue	Potential Treatments
Sialorrhea	Glycopyrolate	Tripping from foot drop	Ankle–foot orthoses
	Tricyclic antidepressants	Falling secondary to quadriceps weakness	Canes
	Robinul		Crutches
	Botulinum toxin		Walker
	Atropine		Wheelchair, manual or power
	Salivary gland radiation	Bed mobility	Hospital bed with side-rails and/or trapeze
	Scopolamine		
	Chorda tympani section	Bathroom safety and functionality	Stall shower
Secretion clearance	Tracheostomy		Shower chair
	Cough assist devices		Transfer bench
	Home suction		Toilet seat extension
	Expectorants (e.g., guaifenesin)		Shower and toilet bars
	Beta blockers	House accessibility	Stair lift
	Nebulized n-acetylcysteine and albuterol		Lift chair or chair lift
			Hoyer lift
Pseudobulbar affect	Dextromethorphan hydrobromide and quinidine sulfate		Elevators
			Ramps
	Tricyclic antidepressants	Improved ADLs	Velcro for buttons and shoelaces
	Selective serotonin reuptake inhibitors		Elastic shoelaces
			Long-handled grippers
Depression	Tricyclic antidepressants		Foam collars for pens and utensils
	Selective serotonin reuptake inhibitors	Dysphagia—malnutrition	Neck positioning
			Change in food consistency
	Stimulants		Percutaneous gastrostomy
Laryngospasm	Antihistamines	Constipation	Bulk
	H_2 receptor blockers		Fiber
	Antacids		Stool softeners/cathartics
	Proton pump inhibitors		Hydration
	Sublingual lorazepam drops	Urinary urgency	Tolterodine
Neck drop	Cervical collar	Cramps	Quinine sulfate
	Hi back wheelchair with supports		Gabapentin
Communication	Augmentative communication devices		Tizanidine
			Baclofen
	Pad and pencil or erasable slates		Benzodiazepines
Hypoventilation	Positive pressure ventilators, e.g., BiPAP		Phenytoin
			Carbamazepine
	Negative pressure ventilators, e.g., Cuirass		Mexilitene
			Primrose oil
	Tracheostomy and mechanical ventilation		Brewer's yeast
		Safety	Lifeline
	Morphine sulfate		Phone auto dialer
	Benzodiazepines		Home safety evaluation
Contractures	Night splints		
	Botulinum toxin		
	Range of motion exercises		

that undoubtedly surpass the capabilities of any single health-care worker. Although potentially emotionally and physically overwhelming to the patient, the multidisciplinary clinic is the currently preferred model in the provision of ALS care. Studies have demonstrated that participation in a multidisciplinary clinic improves both quality and duration of life.[15]

The role of exercise pertaining to its effect on both the disease progression and the preservation of function is a near universal inquiry by ALS patients. Although there are studies in progress to address this issue, there is currently limited information by which to form a factual response. Many ALS clinicians recommend low-level conditioning and nonfatiguing exercise that is safe, to their patients.

The majority of patients with ALS in this country choose not to accept tracheostomy and long-term mechanical ventilation as therapeutic options. Cultural

values regarding quality of life, the fear of being a burden, and the associated costs of long-term care, which are typically not covered by third party payers, represent the most likely causes of why patients decline this option.[58] Most patients choose to receive their terminal care at home. Hospice services provide an invaluable resource that allows most patients to die comfortably within the confines of their own home.

There are many counseling issues that occur in the course of illness of a patient with ALS. One significant issue concerns the timing and extent of discussion regarding emotionally charged subject matter relating to interventions, particularly at the end of life. Ideally, information should be delivered at a rate of the patient's choosing. The ideal and often elusive goal is to achieve a balance between honest disclosures of the realities of the disease, while maintaining a positive attitude that a reasonable quality of life still exists. At some point, the patients should be allowed to voice their opinion about what they do and do not want as their disease progresses and interventions are potentially required.

Many, if not all, patients fear that their death will involve physical suffering. Some may be intrepid enough to broach the subject, some may not. Providing patients with the reassurance that their death will not involve physical suffering is a difficult but important task for the ALS clinician to assume. A frank discussion about the logistics and limits of how this will be insured may be valued by the patient and the family as well. Typically, neurologists, through hospice nurses, provide analgesia and sedation, with the goal of relieving pain and dyspnea without significantly suppressing ventilation. As a result, most patients with ALS die peacefully and comfortably.

The last 12 years have seen an expansion in the number of clinical trials in ALS. Patients should be encouraged but not coerced to participate in these. Not all patients will be eligible. Patients with exclusively bulbar disease or vital capacities less than 60% of predicted are typically excluded from enrollment.

Many patients are concerned that their disease is contagious or hereditary. Fortunately, they can be assured that the former is not the case, and the latter is highly unlikely if there is no family history of the disorder, assuming that they are knowledgeable about their parents' identities, and that their parents lived to a reasonable age.

In part due to the paucity of effective treatments, many patients with ALS seek advice from their physicians regarding alternative, "natural treatments" for their disorder. There is no clear correct response. A dogmatic response on the part of a physician in opposition to this approach runs the risk of losing the patient. Conversely, the physician has a responsibility to dispel what seems to be a generally held perception that "natural" is synonymous with safe. Any substance that is biologically active enough to be beneficial is also biologically active enough to be harmful. "Natural" substances do not benefit from the same scrutiny and quality control as do pharmaceuticals and pose additional risk for that reason alone.

▶ SUMMARY

HIV and cancer are disorders that were uniformly fatal within many of our professional lifetimes. Now, in many instances, these are disorders that are controllable and at times curable. For patients with ALS, their families, and their physicians, it is important to realize that similar outcomes may be realized for ALS in the foreseeable future. Until that hope is realized, neurologists caring for patients with ALS are obligated to help maintain the quality of their patients' life to the extent possible. When that is no longer feasible, they have an obligation to support the quality and dignity of their patients' death as well.

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CHAPTER 5

Hereditary Spastic Paraparesis

▶ INTRODUCTION

Historically, hereditary spastic paraparesis (HSP) has been conceptually differentiated from amyotrophic lateral sclerosis (ALS) in four major domains. It is thought to be a universally hereditary disorder. Phenotypically, it is dominated by signs implicating upper motor neuron (UMN) pathology. It primarily affects lower extremity function, at least in the pure and uncomplicated cases. Finally, in contrast with the ALS prototype, HSP is considered a nonlethal disorder with an inexorably slow rate of progression.

The concept of a hereditary, progressive spastic disorder of the lower extremities was initially championed by Seeligmuller, Strumpell, and Lorrain in last quarter of the 19th century.[1] Historically, HSP was considered a singular entity with phenotypic variation. Subsequent to the observations and writings of Anita Harding, the nosology of HSP evolved. In 1981, she promoted a dichotomy of dominantly inherited HSP. Type I was considered to reflect an early-onset phenotype with predominant, if not exclusive, UMN features. Type II HSP referred to those with late onset in which weakness and presumed lower motor neuron (LMN) involvement overshadowed the UMN signs. In 1983, her clinically based classification system was expanded to encompass pure and complicated forms of the syndrome. Pure HSP refers to a disorder in which signs of corticospinal tract pathology are the sole or dominant feature of the disease. In complicated HSP, involvement of other neurological systems in addition to the corticospinal tract is apparent.[2,3]

In 1996, the nosology of HSP changed further from a primarily phenotypic to a primarily genotypic classification.[1] At the time of this writing, there are in excess of 30 different known genotypes that are associated with an HSP phenotype. The Harding terminology of uncomplicated (pure) or complicated phenotypes persists and is superimposed on the spastic gait locus (SPG) classification described below. In addition to UMN signs in the lower > upper extremities, the uncomplicated phenotype allows for the presence of urinary urgency or minor loss of vibratory sense in the toes. Complicated HSP may be phenotypically diverse, involving a wide array of other components of the nervous or other organ systems.

The HSPs are currently catalogued by a numerical system based on the order of individual gene discovery. Each number is prefaced by the acronym SPG (Table 5–1).

▶ CLINICAL FEATURES

In virtually every case, the presenting symptoms relate to lower extremity spasticity, which is symmetric or near symmetric in its distribution. Patients lose the ability to run or hop early in the course due to increased lower extremity extensor tone and the inability to flex the hip or knee in a facile manner. As a result, the stride is length reduced. The legs tend to scissor or cross over each other due to increased adductor tone (Fig. 5–1). Circumduction of the legs is common in an attempt to avoid tripping on a foot that may be tonically inverted and plantar flexed. High-arched feet and hammer toe deformity are common but not invariable features of the illness, more likely to occur with childhood onset when metatarsal shape and position can be easily altered (Fig. 5–2).

Morbidity from HSP arises in large part from increased tone and the associated loss of coordination of lower extremity muscles. Leg strength may be preserved or diminished. If affected, it typically occurs in a UMN pattern, with hip flexors, knee flexors, and foot dorsiflexors being affected to the greatest extent.

Hyperreflexia of the lower extremities is universal, almost always accompanied by extensor plantar responses. Hyperreflexia of the upper extremities with Hoffman's signs and reflex spread is common as well. Weakness, increased tone, impaired coordination, or loss of function of the upper extremities occurs infrequently and should lead to consideration of an alternative diagnosis.

There is typically evidence of posterior column involvement, with some degree of vibratory sense loss in the toes. Rarely is it severe enough to produce a sensory ataxia. A strikingly positive Romberg sign should once again lead to consideration of an alternative diagnosis. Urinary frequency, urgency, and urgency incontinence are common symptoms even within the "pure" forms of the disease. Rectal urgency and incontinence and sexual dysfunction are less common but do occur.

There is a wide range of associated neurological and non-neurological symptoms that can occur in complicated forms of the disease. Recognition may allow accurate prediction of a specific genotype (Table 5–1).

▶ TABLE 5–1. CLASSIFICATION OF THE HEREDITARY SPASTIC PARAPLEGIAS

Type	Phenotype	Genetics	Commercially Available DNA Mutational Analysis
SPG1	Complicated—II, hydrocephalus, aphasia, adducted thumbs	Xq28 LICAM	Research laboratories only
SPG2	Pure or complicated—white matter changes, PN allelic with Pelizaeus–Merzbacher	Xq28 Proteolipid protein	No
SPG3A (10% of all AD HSP[4])	Pure—typically childhood onset—slow progression	AD 14q11–q21 Atlastin	Yes
SPG4 (40% of all AD HSP[5])	Pure—variable onset—variable severity—possible late II	AD 2p22 Spastin	Yes
SPG5a	Pure	AR 8q11 Protein unknown	No
SPG6[6]	Pure—juvenile onset	AD 15q11.1 NIPA 1	Yes
SPG7 10% of all AR or sporadic[7]	Pure or complicated—dysarthria, PN, dysphagia, optic disc pallor, and cerebellar atrophy	AR 16q24 Paraplegin—mitochondrial abnormalities in muscle biopsy	Research laboratories only
SPG8	Pure	AD 8q23–q24 Protein unknown	No
SPG9	Complicated—cataracts, GERD, and LMNS	AD 10q23.3–q24.2 Unknown protein	No
SPG10[8]	Pure or complicated—distal LMNS	AD 12q13 Kinesin heavy chain KIF5A	Research laboratories only
SPG11 50% of AR HSP[9]	Pure or complicated—onset second decade—thin corpus callosum, II, UE LMNS, dysarthria, nystagmus, and extrapyramidal signs	AR 15q13 Protein unknown Estimated mutation in	No
SPG12	Pure	AD 19q13 Protein unknown	No
SPG13	Pure—adolescent or adult onset	AD 2q24–34 Heat shock protein 60	Research laboratories only
SPG14	Complicated—MR and distal LMNS	AR 3q27–28 Protein unknown	No
SPG15	Complicated—distal LMNS, RPD, dysarthria, II, and cognitive decline (Kjellin syndrome)	AR 14q22–q24 Protein unknown	No
SPG16	Pure or complicated—aphasia, visual loss, nystagmus, mild II, and UR dysfunction	Xq11.2–q23 Protein unknown	No
SPG17[10]	Complicated—UE LMNS (Silver syndrome)	AD 11q12–q14 BSCL2 selpin	Research laboratories only
SPG18		AD 6q22.33–24.1	No
SPG19	Pure	AD 9q33-q35 Protein unknown	No
SPG20[11]	Complicated—LMNS (Troyer syndrome)	AR 13q12.3 Spartin	Research laboratories only
SPG21[12]	Complicated—II, cerebellar, extrapyramidal, thin corpus callosum, and white matter changes (Mast syndrome)	AR 15q22.31 Maspardin	Research laboratories only
SPG22	Complicated—distal LMNS	AR 19q13.3 Neuropathy target esterase	Research laboratories only

▶ **TABLE 5–1. (CONTINUED) CLASSIFICATION OF THE HEREDITARY SPASTIC PARAPLEGIAS**

Type	Phenotype	Genetics	Commercially Available DNA Mutational Analysis
SPG23[13]	Complicated—pigmented skin abnormality	AR 1q24–q32 Protein unknown	No
SPG24	Complicated—childhood onset with spastic dysarthria and pseudobulbar signs	AR 13q14 Protein unknown	No
SPG25		AR6q23	No
SPG26[14]	Complicated—childhood onset—dysarthria, II, and distal LMNS	AR 12p11.1–12q14 Protein unknown	No
SPG27[15]		AR 10q22.1–q24.1 Protein unknown	No
SPG28[16]		AR 14q21.3–q22.3 Protein unknown	No
SPG29[17]	Complicated—hearing loss and intractable emesis uncomplicated	AD 1p31.1–21.1 Protein unknown AD 2p12 Protein unknown	No
SPG30[18]	Complicated—distal LMNS, saccadic ocular pursuit, PN, and cerebellar	AR 2q37.3 Protein unknown	No
SPG31[19]	Pure Onset typically third decade	AD 2p12 Receptor-enhancing expression protein 1	Yes
SPG33		AD 10q24 ZFYVE27	
SPOAN syndrome[20]	Complicated—optic atrophy, PN, dysarthria, contractures	AR 11q13 Protein unknown	

SPG, spastic gait locus; GERD, gastroesophageal reflux disease; II, intellectual impairment; LMNS, lower motor neuron syndrome; PN, peripheral neuropathy; RPD, retinal pigmentary degeneration; UE, upper extremity; UR, urorectal.
Modified with permission from Fink JK. Hereditary spastic paraplegia. Curr Neurol Neurosci Rep 2006;6:65–76 see www.genetests.org for up to date test availability.

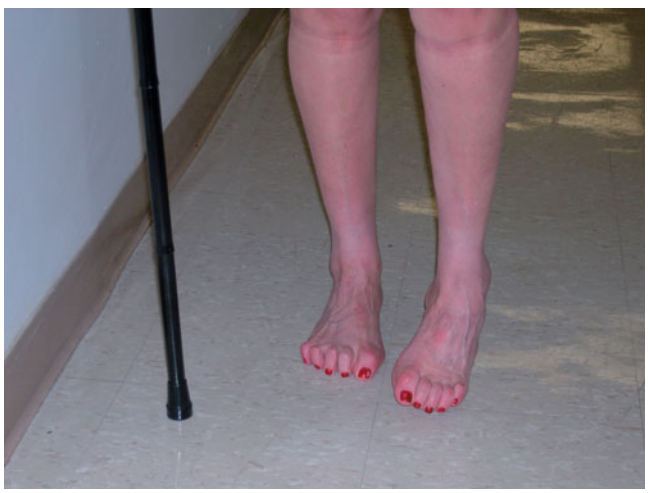

Figure 5–1. Circumducting leg with equinovarus foot posturing in HSP.

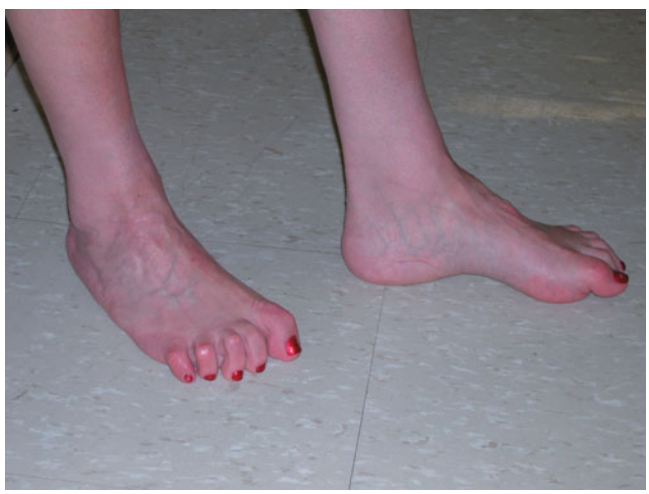

Figure 5–2. Hammer toes and cavus deformity in HSP.

Associated features may include signs of LMN dysfunction that typically begin distally. Either the hands or the feet may be initially affected. Ataxia, nystagmus, dysarthria, and other features of cerebellar dysfunction may occur. Extrapyramidal manifestations are most closely aligned with SPG11 and SPG21.[9,12] Certain genotypes may have associated mental retardation or include the development of dementia. Seizures, deafness, cataracts, icthyosis, and optic atrophy with visual loss are some of the other potential associated features.

Onset recognition and severity of HSP vary considerably both within and between families. Initial symptoms may be recognized in any decade of life. Although there is a tendency for an individual genotype to correlate with a relatively predictable age of onset, this is by no means a precise exercise. A homogeneous clinical course congruent within affected family members and slow disease progression are disease characteristics that correlate somewhat with pure HSP phenotypes and with an early age of onset. The reasons for variations of disease onset and severity of affliction, both within and between families of the same genotype, are not currently understood.[21] This variability does not appear to correlate directly with the mechanism of mutation, at least within the SPG4 genotype.[22] For the most part, individual families will remain segregated into either pure or complicated phenotypes. Occasionally families with apparent identical genotypes will have members manifesting both pure and complicated phenotypes.

▶ LABORATORY FEATURES

The diagnosis of HSP remains predominantly within the clinical domain.

Currently, commercially available DNA mutational analysis is available for four of the HSP genotypes; SPG3A, SPG4, SPG6, and SPG31.[23] In addition, a few research laboratories will provide clinical testing services for SPG2 and SPG20. The value of this testing is diminished by a number of considerations. Although these four disorders represent 60% of all autosomal-dominant HSP cases, these are of limited diagnostic value in the most difficult of clinical situations, i.e., the apparently sporadically affected individuals. Five to ten percent of these individuals will have unsuspected dominant inheritance for whom DNA mutational analysis may be diagnostic. In addition, the methodologies currently used do not assess for all mutational mechanisms of affected genes. For example, partial deletions of the *SPAST* gene (SPG4 locus), not detected by commercial laboratories at this time, will produce an HSP phenotype.[24] For that reason, approximately 10% of cases of SPG4 will have false-negative testing. Lastly, cost represents a pragmatic consideration. Many third party payers will only reimburse a portion of the four-digit cost of DNA mutational analysis. This places a substantial financial burden on patients or institutions with the real possibility that the diagnosis will remain unconfirmed.

▶ HISTOPATHOLOGY

HSP appears to be a "dying back myelopathy." Individuals who are affected will have degeneration of the corticospinal tracts that is most marked in the lumbosacral and thoracic segments of the spinal cord, becoming less apparent in the more proximal cervical regions. Conversely, degeneration of the posterior columns is most evident in their most centrifugal locations, at the cervical–medullary junction.[1] Decreased numbers of anterior horn cells or cortical motor neurons have been reported.

▶ PATHOGENESIS

The multiple genotypes underlying HSP suggest that there is a common mechanism by which mutations of different proteins translate into an identical or near-identical phenotype. A uniform final common pathway, however, is yet to be defined. Proposed mechanisms including disturbances in axon transport, impaired Golgi function, mitochondrial dysfunction, disordered myelin synthesis, and maturational disturbances of the corticospinal tracts.[1] Some of these hypotheses are based on the normal intracellular location of the affected proteins.

▶ DIFFERENTIAL DIAGNOSIS AND RECOMMENDED EVALUATION

The differential diagnosis of HSP includes any disorder capable of producing bilateral pyramidal tract disease (Table 5–2).

MR imaging of the brain and spine is obtained in the majority of patients with HSP. The primary role of imaging in patients suspected to have HSP is to exclude other differential diagnostic considerations associated with imaging abnormalities. These would include spinal cord compression of any cause, or inflammatory disorders such as multiple sclerosis or neuromyelitis optica (NMO), or chronic ischemic myelopathy from dural vascular malformations. Imaging in HSP is typically normal in pure cases, although atrophy of the thoracic spinal cord has been reported.[1] It may identify some of the features associated with complicated forms of HSP, including atrophy of the corpus callosum, hydrocephalus, or white matter changes. This would be of more value in identifying the type of HSP rather than establishing the initial diagnosis. Serological testing for the IgG NMO antibodies may be helpful in solidifying the diagnosis of

▶ **TABLE 5-2. DIFFERENTIAL DIAGNOSIS OF HSP**

Disorder	Features That May Distinguish from HSP	Diagnosis
Compressive myelopathy	Typically more rapid course—asymmetry—spine or radicular pain—sensory level	Imaging of spinal cord
MS	Relapsing course—prominence of sensory symptoms	MR imaging of brain and spine—↑ CSF IgG index and oligoclonal bands
Neuromyelitis optica	Typically more fulminant course—optic neuropathy—prominence of sensory loss	Longitudinally extensive increased cord signal on T2 cord images—serum IgG NMO antibodies
Primary lateral sclerosis	Asymmetry—more rapid course—bulbar and upper extremity involvement	By exclusion—supported by clinical and EMG evidence of LMN involvement
Adrenoleukodystrophy	Adrenal or cognitive involvement—associated neuropathy	C26–C22 long chain fatty acid ratio
HTLV1	Associated myopathy—burning back and leg pain—urinary retention	HTLV1 serum serology
Vitamin B12 deficiency	Prominent proprioceptive loss—absent ankle DTRs	Serum B12 level—methylmalonic acid–homocysteine
Copper deficiency	Same as vitamin B12	Serum copper–ceruloplasmin
Freidreich's ataxia	Nystagmus—dysarthria—limb ataxia—prominence of sensory loss	DNA mutational analysis for frataxin gene—hypertrophic cardiomyopathy
Distal spinal muscular atrophy	Phenotype dominated by LMN rather than UMN features	Clinical features-EDX
Cerebral palsy	Failure of disease progression—speech, upper extremity, or extrapyramidal involvement	MR of brain may identify suggestion of perinatal injury
Dopa-responsive dystonia	Diurnal variation of dystonic posturing—other extrapyramidal features—kyphoscoliosis	Response to dopamine—increased CSF protein
Refsum disease	Nerve deafness—retinal pigmentary degeneration—icthyosis—anosmia, demyelinating sensory motor polyneuropathy—cerebellar features	Elevated serum phytanic acid level

HSP, hereditary spastic paraparesis, MS, mutiple sclerosis; CSF, cerebrospinal fluid; DTRs, deep tendon reflexes; NMO, neuromyelitis optica; LMN, lower motor neuron; UMN, upper motor neuron; EDX, electrodiagnosis.

NMO. Identification of an elevated IgG index or the presence of oligoclonal banding in the CSF would be supportive of multiple sclerosis. In general, lumbar puncture is a test of limited utility in the patient suspected to have HSP.

Primary lateral sclerosis is a major differential diagnostic consideration in HSP.[25,26] Significant asymmetry of leg involvement or symptomatic involvement of the upper extremities or bulbar muscles would favor a diagnosis of primary lateral sclerosis in a sporadic case of spastic paraparesis. In these individuals, abnormalities of somatosensory-evoked potentials done in the legs would favor a diagnosis of HSP, whereas evidence of active denervation or significant chronic partial denervation on EMG would implicate primary lateral sclerosis as a more likely consideration.

Adrenoleukodystrophy or adrenomyeloneuropathy are x-linked disorders. Most affected individuals are young males with a regressive illness producing varying combinations of adrenal insufficiency, myelopathy, neuropathy, and cognitive decline. Arguably, it is the symptomatic female carrier presenting with a slowly progressive spastic paraparesis during middle age that is most readily confused with HSP. Serum testing for the C22–C26 long chain fatty acid ratio should be considered in many HSP suspects.

Certain retroviral infections may produce a chronic myelopathy. Of these, HTLV1 (tropical spastic paraparesis) is most likely to enter into the differential diagnosis of HSP. Serological testing for this virus is readily available on a commercial basis.

Vitamin B12 and copper deficiency affect pyramidal tracts. Typically, posterior column deficits are more pronounced than UMN features although spasticity may be pronounced in some patients. Blood testing for vitamin B12, methylmalonic acid, homocysteine, copper, and ceruloplasmin should be strongly considered in any undiagnosed spastic patient.

Friedreich's ataxia (FA) is another heritable disorder whose age of onset is similar to HSP. Pyramidal features are typically mild, and the disorder is usually dominated by an ataxia attributable to posterior column and spinocerebellar tract degeneration. Although nystagmus and dysarthria may occur in complicated forms of HSP, these are more common and severe manifestations of FA. An occult or symptomatic cardiomyopathy would support the diagnosis of FA in this context. DNA mutational analysis for the frataxin gene is commercially available.

Molecular genetics has blurred the interface between certain complicated forms of HSP and specific distal forms of spinal muscular atrophy (dSMA). Although, the latter are theoretically dominated by distal LMN features, dSMA V and VII, in particular, may have prominent UMN features just as certain forms of HSP may have distal LMN manifestations. There may be no easy way to provide diagnostic resolution for this dilemma. In fact, the distinction may be artificial, as SPG17 and dSMA V represent allelic disorders of the same BSCL2 selpin gene on chromosome 11.

Many childhood-onset cases of HSP may be minimally progressive, particularly during the first two decades of life. For that reason, cerebral palsy may provide a relevant differential diagnostic consideration. Delayed motor milestones during the first 2 years of life or involvement of the nervous system in locations other than the legs would favor a cerebral palsy diagnosis.

Dopa-responsive dystonia may manifest itself as a progressive, spastic gait disorder of childhood. Low-dose therapy with levodopa would serve both a diagnostic and a therapeutic purpose.

Refsum disease is a heritable disorder of phytanic acid metabolism, which can cause anosmia, ataxia, retinal pigmentary degeneration, deafness, icthyosis, and neuropathy. The latter four features may occur in HSP. EMG evidence of a demyelinating polyneuropathy and elevated serum phytanic acid levels would favor a diagnosis of Refsum's.

▶ TREATMENT

Treatment for HSP is supportive. There are a number of different options to reduce spasticity including oral tizanidine, lioresal, dantrolene, or benzodiazepines, intrathecal baclofen, or botulinum toxin injections directly into spastic muscles (Table 5–3). In extreme cases, surgical release of tendons may be considered in nonambulatory patients to facilitate hygiene or suppress discomfort. The treatment of spasticity requires considerable clinical judgment. The goal of treatment is to improve mobility, augment range of motion, and relieve the discomfort associated with spastic muscles, without the promotion of unwanted side effects. Although spasticity hinders gait, it may also aid it. In an individual who also has considerable underlying weakness, the

▶ TABLE 5–3. TREATMENT OPTIONS FOR SPASTICITY (LISTED IN APPROXIMATE ORDER OF USE)

Drug	Initial Dose	Maximal Dose	Common or Significant Side Effects
Baclofen	5 mg po tid	20 mg po QID	Constipation, nausea, emesis, ↓ muscle tone, dizziness, headache, somnolence, coma, seizure, and abrupt withdrawal syndrome
Tizanidine	4 mg po daily	12 mg po TID	Hypotension, xerostomia, asthenia, dizziness, and sedation
Botulinum toxin type A	Varies with product—1 unit/kg	Total dose per treatment averages 250–400 units	↓muscle tone and allergy
Benzodiazepines (e.g., diazepam)	2 mg po, IM or IV daily	15 mg po QID	Sedation, ataxia, hypotension, fatigue, respiratory depression, and withdrawal symptoms
Dantrolene	25 mg po daily	100 mg po QID	Lightheadedness, constipation, diarrhea, asthenia, headache, sedation, diplopia, visual, CHF and arrhythmia, myelosuppression, and hepatotoxicity
Intrathecal baclofen	50 μg test dose adults, 25 μg children, increase dose by 10–30%/day in adults, 5–15 micrograms in children titrated to response	2000 μg/day	Pump failure, catheter fracture, CNS infection, CSF leak with intracranial hypotension, and complications of baclofen
Rhizotomy	NA	NA	CSF leak with intracranial hypotension, excessive

CHF, congestive heart failure; CSF, cerebrospinal fluid; NA, not applicable; CNS, central nervous system.

increased tone of extensor muscles may represent the major source of antigravity resistance. Suppression of this tone may deprive individuals of their ability to stand.

To improve tolerance, oral antispasticity drugs are typically initiated at very low doses and then titrated upward. The goal is to gain optimal mobility without producing unwanted side effects. The most frequent of these is sedation, which often precludes obtaining an adequate antispasticity effect. Baclofen and tizanidine are preferred as first-line agents by most. Rapid withdrawal of these agents may lead to unwanted CNS side effects, including confusion and psychosis. Dantrolene is used less frequently because of risks associated with hepatotoxicity. Benzodiazepines have less well developed antispasticity properties and are frequently used as an adjunct rather than as a primary antispasticity treatment.

Intrathecal baclofen delivered by a programmable pump is an option if oral drugs do not provide the desired effect. The theoretical benefit is to deliver the drug directly to the afflicted end organ in small titratable doses in order to avoid the side effects commonly associated with the larger oral doses required. Intrathecal baclofen may allow certain patients who are spastic to remain ambulatory longer than their natural history would otherwise allow. A more realistic goal is to diminish refractory painful spasms or to diminish lower tone to facilitate personal hygiene.

Injection of botulinum toxin into spastic muscles provides an alternative means to diminish muscle tone.[27] Although attractive in concept because of the ability to affect only selected muscles, identification of the best dose and the number of muscles that may require injection remain significant obstacles. The effect is greatest when the toxin is delivered in proximity to the motor point. Identification of the most severely affected muscles and delivery of the lowest effective doses are the two major principles used. Repeat injections are typically required at 3-month intervals. As spasticity typically produces the most morbidity in the legs, large doses are often required to achieve the desired effect. Third party payers may not view this option favorably due to the cost and need for recurrent treatment. Many limit reimbursement to 400 units per session, which may be inadequate to achieve the desired goals.

Ankle–foot orthoses are of great benefit to individual patients. Ideally, they should be custom fitted to improve comfort and, as a result, compliance. Their primary purpose is to prevent tripping by maintaining the foot in a partially dorsiflexed position by overcoming equinovarus posturing.

There are a number of types of durable medical equipment that may benefit a patient with HSP. Many patients resent the symbolism of durable medical equipment, viewing it as a "setback" and a constant reminder of their impaired condition. It may be effective to promote durable medical equipment to them as an opportunity. Specifically, it may allow them to maintain their independent mobility while minimizing the risk of falls and the potential of severe injury. A skilled physical therapist is an invaluable tool to decide whether a cane, Lofstran crutches, a walker, or a wheelchair is the best solution for an individual patient. Power chairs or scooters are rarely necessary due to preservation of upper extremity function and the patients' maintained ability to propel themselves in a manual chair. In patients who live in multiple-story dwellings who require access to more than one floor, stair lifts provide a safe and energy-sparing option. Patients motivated to perform daily stretching exercises claim to enjoy considerable benefit from doing so.

Organizations serving as resources for patients and other individuals seeking information about the disease include the following:

- National Institute of Neurological Disorders and Stroke
- Hereditary Spastic Paraplegia
- Foundation, Inc., 209 Park Rd., Chelmsford MA 01824. (Phone: 703–495-9261; e-mail: community@sp-foundation.org; sp-foundation.org.)
- National Ataxia Foundation, 2600 Fernbrook Lane Suite 119, Minneapolis MN 55447. (Phone: 763–553-0020; fax: 763–553-0167, e-mail: naf@ataxia.org; www.ataxia.org.)

Genetic counseling in HSP is complex. Prenatal testing is available for those forms of HSP for which DNA mutational analysis exists. HSP does not reduce life expectancy, and the penetrance of many HSP genotypes is quite variable. For those reasons, it is difficult to understand the benefits of prenatal testing or to justify the fetal risk involvement with amniocentesis or chorionic villous sampling.

▶ SUMMARY

HSP is a heritable disorder in which over 30 different mutations correlate with a fairly homogeneous phenotypic syndrome dominated by spastic paraparesis. It is a disorder that offers the opportunity to understand how semiselective vulnerability of a single component of the nervous system can occur as a result of seemingly disparate pathophysiologies. Like other heritable disorders in which the molecular biology is providing new insights into disease mechanisms, the nosology of the HSP will undoubtedly be revised as the overlapping genetics of different heritable disorders is increasingly clarified.

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CHAPTER 6

Spinal Muscular Atrophies

▶ INTRODUCTION

The spinal muscular atrophies (SMAs) may be conceptualized as progressive, hereditary diseases of anterior horn cells and selective motor cranial nerve nuclei.[1] As a group, they are phenotypically heterogeneous (Table 6–1). The nosology of the SMAs is confusing for a number of reasons. Familial amyotrophic lateral sclerosis (ALS) is also a hereditary progressive disorder of anterior horn cells but is not typically considered an SMA. Most familial ALS phenotypes have clinical and pathological features of corticospinal/bulbar tract involvement, the major distinguishing feature from SMA. ALS is also typically a rapidly progressive disease in contrast with most SMA phenotypes. There are exceptions to both rules, however, confounding diagnosis in individual patients and families.

To confuse matters further, nearly identical terms, progressive SMA and progressive muscular atrophy have been frequently used on what would seem to be an interchangeable basis. As a result, there is an implied link between what are generally considered to be two different conditions. Progressive muscular atrophy is typically used in the context of a lower motor neuron exclusive or predominant form of ALS, which is primarily sporadic, degenerative, and progressive. Conversely, the progressive SMAs, or SMAs as these are referred to in this chapter, are hereditary disorders, primarily of childhood, which often have protracted natural histories. The use of the adjective progressive prior to SMA serves only to perpetuate the confusion between these two categories of disease (SMA, ALS) and provides more confusion than clarity.

The history of SMA dates to the writings of Werdnig and Hoffman who independently described an infantile disorder of progressive muscular weakness in 1891 and 1892.[2,3] This disorder still bears their eponym. Historically, the SMAs were classified based on age of onset and clinical phenotype. These classification schemes remain useful despite significant advances in the molecular genetics of these disorders.

The molecular genetic era in SMA began in earnest in 1990 when the gene responsible for the majority of cases of SMA I, II, and III was located on the long arm of chromosome 5.[4] In 1995, this gene was identified as the survival motor neuron (SMN) gene.[5] In 1968, Kennedy and colleagues defined a unique x-linked form of bulbospinal muscular atrophy affecting middle-aged men.[6] In 2001, LaSpada and colleagues identified that Kennedy's disease resulted from mutations of the androgen receptor gene.[5]

▶ CLINICAL FEATURES

SMA types I–III have been historically distinguished from each other by phenotypic considerations. These include patient age at symptom onset, life expectancy, and primarily the milestones the individuals achieve. These disorders are recessively inherited, allelic in genotype and differ only by the degree, not by type of mutation. As a result, these are best considered as a continuum of a single disorder rather than as three separate disorders.[7] Clinically, they share more similarities than differences. Progression and life expectancy correlate with age of onset. Age of onset and clinical course tend to be similar in siblings.[7]

SMA I (INFANTILE) WERDNIG–HOFFMAN DISEASE

Werdnig–Hoffman disease is the most severe form of SMA and the most common form of motor neuron disease. Its incidence is estimated to be between four and 10 per 100,000 live births, depending on the geographic cohort studied.[8] Its clinical manifestations are evident within the first 6 months of life. In some cases, recognition of reduced movement occurs prenatally or in the first few days of life. Affected infants are hypotonic with a symmetric, generalized, or proximally predominant pattern of weakness (Fig. 6–1). As in ALS, facial weakness is mild and extraocular muscles spared. Fasciculations are seen in the tongue but rarely in limb muscles, presumably due to the ample subcutaneous tissue of neonates. Manual tremor, so characteristic of SMA types II and III, is rarely present. Deep tendon reflexes are typically absent. Abdominal breathing, a weak cry, and a poor suck are commonplace. Ventilatory difficulties stem primarily from intercostal rather than diaphragmatic weakness. Pectus excavatum and a diminished anterior–posterior diameter of the chest are commonplace. Mild contractures may occur, but arthyrogryposis is not part of the classic phenotype. There is no intellectual impairment. Children with SMA I are distinguished from

▶ **TABLE 6–1. THE SPINAL MUSCULAR ATROPHIES—HISTORICAL CLASSIFICATION**

Name	Phenotype	Genetics	Natural History	Associated Clinical Features
SMA Ia Severe neonatal SMA	Hypotonia at birth	AR homozygous SMN1 deletion	Life expectancy very short	Arthrogryposis Tongue fasciculations
SMA I (Werdnig Hoffman)	Hypotonia and ventilatory-bulbar weakness	AR homozygous SMN1 deletion with <3 SMN2 copies	Onset <6 months—never sit—life expectancy	Tongue fasciculations
SMA II (intermediate)	Hypotonia and ventilatory-bulbar weakness	AR homozygous SMN1 deletion with three SMN2 copies	Onset 6–18 months—sit but never stand—two-thirds survive until 25	Tongue fasciculations Tremor
SMA III (Kugelberg–Welander)	Proximal symmetric weakness	AR homozygous SMN1 deletion with four SMN2 copies	Onset >18 months—with onset <3 yr—20% walking at 40 yr, with onset >3 yrs—60% walking at 40 yr	Limb and tongue fasciculation Tremor
SMA IV (adult onset)	Proximal symmetric weakness	30% AD AR—may be SMN related, X linked	Normal life expectancy	Limb and tongue fasciculations tremor
X-linked bulbospinal SMA (Kennedy disease)	Bulbar and proximal symmetric weakness	X-linked androgen receptor gene	Onset of fatigue, cramps, and gynecomastia as early as teens—weakness typically mid-late adulthood	Mild sensory neuropathy—tremor Signs of androgen insensitivity including gynecomastia, hypogonadism, and impotence—tremor
Distal SMA	Multiple (see Table 6–2)	Multiple (see Table 6–2)	Variable—typical is onset in first three decades with slow progression	May be restricted to distal weakness—complicated forms
Juvenile segmental SMA (Hirayama)	Asymmetric weakness and atrophy of unilateral or bilateral hand and forearm muscles	Primarily a sporadic disorder	Progression for 2–6 years, then plateau	May be positional cervical cord compression from posterior longitudinal ligaments
Childhood bulbar SMA (Fazio–Londe and Brown–Vialetto–von Laere)	Bulbar palsy with other features	Unknown	Onset in first two decades—variable rate of progression	B–V–VL associated with sensorineural hearing loss and other neurological system involvement Fazio–Londe may have prominent facial weakness and ophthalmoplegia
Scapuloperoneal SMA (Davidenkow)	Asymmetric weakness of shoulder girdle and peroneal muscles	AD or sporadic—single case with 17p11.2 deletion	May progress to more generalized weakness over years	Frequent foot deformities—may be allelic to HNPP

SMA, spinal muscular atrophy; B–V–VL, Brown–Vialetto–von Laere; SMN, survival motor neuron; HNPP, hereditary liability to pressure palsy.

SMA II and III by motor milestones, i.e., they never develop the capability of sitting independently. Without mechanical ventilation, death almost always occurs within a year or 2. Eight percent of individuals will survive to 10 years of age. A 20-year lifespan is unexpected.[9]

SMA type 1a is used to refer to a severe form of neonatal SMA associated with arthrogryposis multiplex congenita and a paucity of movement. Prognosis is very poor, with ventilatory support often being required at birth.[10]

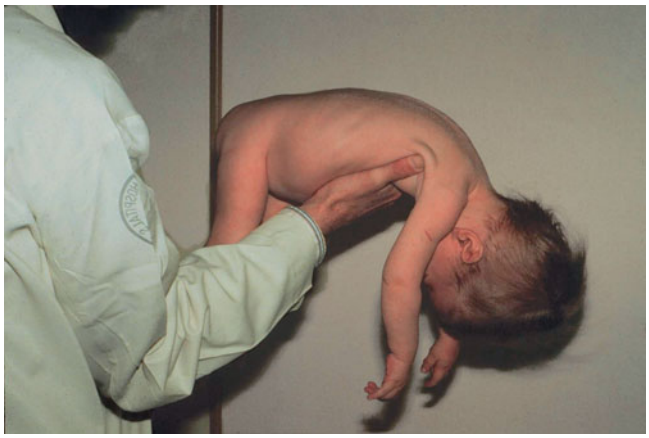

Figure 6–1. Hypotonic SMA I patient. (Figure courtesy of Dr. Basil Darras at Boston's Children's Hospital.)

SMA II (INTERMEDIATE FORM)

The intermediate form of childhood SMA typically begins between 6 and 18 months of age. The disorder is clinically defined by a child who sits independently but never walks. Postural hand tremor is the only significant phenotypic variance from Werdnig–Hoffman disease. Tongue fasciculations, areflexia, and a generalized to proximally predominant and symmetric pattern of weakness mimic the SMA I phenotype. Approximately 98% of these individuals survive to the age of 5 years and two-thirds to the age of 25 years. In view of the more protracted course and the ability to sit, patients with SMA II and III commonly acquire kyphoscoliosis and joint contractures.

SMA III (JUVENILE FORM) KUGELBERG–WELANDER DISEASE

The Kugelberg–Welander phenotype differs from the intermediate form only in the age of onset, life duration, and milestones achieved. Individuals who are affected develop the ability to stand and walk. Onset age is typically after 18 months. Certain authors have attempted to divide SMA III into types a and b, based on age at onset of symptoms, with the intention of better defining the natural history in individual patients.[10] In SMA type IIIa, defined as symptom onset before 3 years, 70% were still walking 10 years after symptom onset and 20% at 40 years. In SMA type 3b, defined as symptom onset after 3 years, almost all were still walking at 10 years and 60% at 40 years. Life expectancy extends into the sixth decade and may be normal in many individuals. Initial symptoms are typically related to proximal weakness. Hand tremor, areflexia, and tongue fasciculations, like SMA II, are commonplace. Presumably related to the older age of these patients, and the diminished proportion of subcutaneous tissue, limb fasciculations are more evident than SMA types I and II.

SMN GENE MUTATIONS NOT ASSOCIATED WITH TYPICAL SMA I–III PHENOTYPES

In 95% of cases, SMA I–III are associated with complex genetic alterations of the SMN types I and II genes located on chromosome 5.[11] Conversely, penetrant mutations of these genes are almost associated with an SMA I–III phenotype characterized by generalized limb, trunk, and bulbar weakness. On occasion, other phenotypes including a congenital axonal neuropathy and an SMA phenotype with prominent facial weakness have been described.[12–14]

SMA IV (ADULT ONSET)

Adult-onset SMA is a rare, genotypically heterogeneous disorder. Children achieve motor milestones at normal ages. Onset of weakness is typically in the third or fourth decade in the recessively inherited cases.[10] Initial symptoms are typically referable to proximal weakness of the lower extremities, particularly the hip flexors, extensors, and knee extensors. The shoulder abductors and elbow extensors are the most affected muscles of the arms. Tongue fasciculations, hand tremor, and, in some cases, calf hypertrophy occur.[15] The latter can be confounding, particularly in males, as myopathies are a more common cause of proximal weakness in this age group. Life expectancy is normal.[16]

X-LINKED BULBOSPINAL MUSCULAR ATROPHY (KENNEDY DISEASE)

Kennedy's disease, or bulbospinal muscular atrophy, is an X-linked, adult-onset form of SMA.[6,17] Males identify symptoms of bulbar or proximal weakness at a median onset of 44 years.[7] Its initial symptoms often begin in younger males and are usually nonspecific. These include muscle cramping associated with elevated serum creatine kinase (CK) levels, tremor, gynecomastia, and/or fatigue.[7,18] The diagnosis is commonly overlooked in younger males in the absence of other affected family members.

As the name implies, the clinical manifestations are largely referable to the lower cranial nerve motor nuclei and anterior horn cells of the spinal cord. The weakness usually progresses insidiously and is proximally predominant symmetric and symmetricin pattern.

Typically, symptoms referable to the lower extremities have the greatest initial impact. Clinical heterogeneity exists. Asymmetry of muscle weakness at onset has been emphasized by some authors.[19] Approximately 10% of the time, the initial symptoms pertain to difficulty in swallowing, chewing, or speaking.[7] Facial weakness is common. A dropped jaw due to weakness of muscles innervated by cranial nerve V may occur as well.[18] Perioral and tongue fasciculations are common and represent helpful clinical clues. Unlike most other SMAs, there is often an associated, but frequently asymptomatic, sensory neuropathy detected during the performance of nerve conduction studies. Occasionally, rapidly progressive weakness occurs.[20] The median age of wheelchair dependency is 61 years or approximately 15 years after onset of weakness.

Symptomatic women who are heterozygous for the Kennedy's disease mutation may rarely be identified. Usually, the phenotype is similar to young men with cramps, tremor, elevations in serum CK, and perioral fasciculations.[21]

The effects of Kennedy disease are not restricted to the neuromuscular system. It is a disorder that results from mutations of the androgen receptor gene on the X chromosome (see below).[22] As a result, affected males suffer the consequences of androgen insensitivity, including gynecomastia, impotence, testicular atrophy, and potential infertility. There is an increased incidence of diabetes mellitus.

JUVENILE SEGMENTAL SMA, BENIGN FOCAL AMYOTROPHY (HIRAYAMA DISEASE)

In 1963, Hirayama described a slowly progressive, focal motor neuron disease affecting the upper extremities.[23] In this and subsequent descriptions, males were affected in 60% or more of cases. Most cases occur on a sporadic basis. There have been occasional reports of more than one first-degree family member involved. The onset of this syndrome is typically between ages 15 and 25 years, with a range of 2–30 years.[24]

Hirayama disease has been referred to by a plethora of names. It is perhaps best considered as a segmental or regional form of SMA. Atrophy and weakness develop insidiously in C8–T1 hand and forearm muscles unilaterally, typically the dominant extremity. Over the course of months to years, the weakness may spread gradually to more proximal arm muscles. In a third of cases, there is clinical weakness of the opposite limb, with an even higher percentage having electrodiagnostic evidence of bilateral involvement (Fig. 6–2).[24] Unlike most non-ALS anterior horn cell diseases, reflexes in the involved limb may be spared although neither overt pyramidal nor bulbar involvement occurs.[24] This may represent a reflection of the restricted segmental involvement in which no deep tendon reflex is readily available for testing. As in many other SMAs, tremor may occur. In most cases, after 6 years or less, progression plateaus. Although a significant decline in affected limb function in the cold is common with all motor neuron diseases, "cold paresis" is particularly emphasized in this population.[24] Hyperhidrosis of the involved limb(s) has been described.

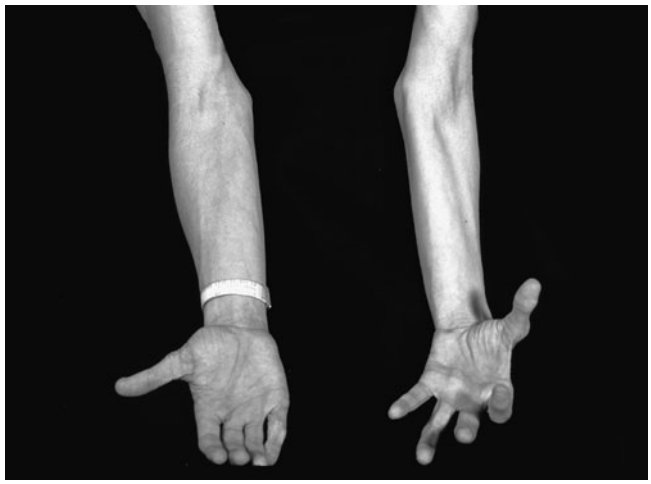

Figure 6–2. Asymmetric forearm and hand atrophy in Hirayama disease.

Hirayama disease has been described less frequently in Western and nonoriental populations. An apparently rare lower extremity analog has been described in India. In most of these individuals, the weakness is distributed throughout the affected limb but in some patients, preferential involvement of the quadriceps occurs.[16,25]

SCAPULOPERONEAL FORM OF SMA (DAVIDENKOW SYNDROME)

A neuropathic form of the scapuloperoneal syndrome has been described and referred to as Davidenkow syndrome. Recognition typically occurs by late childhood. Asymmetric weakness of the shoulder girdles and foot dorsiflexors are the usual initial manifestations. Weakness may progress to a more generalized pattern over a period of years.

Twelve of Davidenkow's original 13 patients had a familial disorder with apparent dominant inheritance.[26] Sporadic cases have been described as well. Neurogenic scapuloperoneal syndrome has been classified as an SMA even though distal sensory loss was common in Davidenkow's original series. Despite the frequent occurrence of foot deformities, he eschewed any relationship to Charcot–Marie–Tooth (CMT) disease. This belief has not been universally held.[45]

DISTAL SMA (HEREDITARY MOTOR NEUROPATHY)

The concept of a distal form of spinal muscular atrophy (dSMA) was introduced by Harding and Thomas in 1980.[27] The dSMAs have been historically perceived as progressive, hereditary disorders, producing distal symmetric weakness in the absence of clinical and electrodiagnostic sensory loss. The dSMAs have also been referred to as hereditary motor neuropathies but are considered to be anterior horn cell disorders in view of their pure motor manifestations. Approximately a third of cases are inherited in a dominant fashion. The remainder is recessive, sporadic, or rarely X linked in nature.[16,28]

As in CMT disease, which distal SMA phenotypically resembles, weakness in distal SMA typically predominates in ankle dorsiflexors and evertors and toe extensors. Foot deformities characteristic of CMT disease are also common. Hand muscles may eventually become involved. dSMA V in the Harding classification is a phenotype in which weakness and atrophy begins in the hands. There are two associated genotypes, including those associated with mutations of the glycyl t-RNA synthetase gene on chromosome 7p15 and the BSCL2 gene on chromosome 11q12–q14.[11,29] At least four genotypes of dSMA may have concomitant pyramidal features, including mutations of the senataxin gene, both forms of dSMA V mentioned above, and the kindred reported in the Jerash region of Jordan.[29–33] This provides for considerable clinical overlap with some phenotypes of HSP, CMT disease, and even ALS. The dSMAs may have other complicated phenotypes, which may include diaphragmatic paralysis, vocal cord paralysis, and arthrogryposis (Table 6–2).[35]

▶ **TABLE 6–2. DISTAL SPINAL MUSCULAR ATROPHIES (DUBOURG, HANEMANN, IROBI, TAKATA)**

Type	Phenotype	Genotype	Notes
dSMA I	Juvenile onset—CMT phenotype	AD Locus unknown	
dSMA II	Onset 15–25 yr—rapid progression—CMT phenotype	AD 12q24.3 Heat shock protein 22 AD 7q11–q21 Heat shock protein 27	Allelic to CMT2F
dSMA III	Early adult onset—slow progression—CMT phenotype	AR Locus unknown	
dSMA IV	Juvenile onset—severe	AR Locus unknown	Diaphragmatic paralysis
dSMA V	Onset in hands—occasional spastic paraparesis	AD 7p15 glycl t-RNA synthetase	Allelic to CMT2D
	Prominent hand wasting and weakness—associated paraparesis	AD 11q12–q14 BSCL2	Allelic to Silver syndrome (SPG17)—allelic to Bernardinelli–Seip congenital lipodystrophy
dSMA VI	Infantile-onset severe diaphragmatic paralysis	AR 11q13–q21 Immunoglobulin-binding protein 2	
dSMA VII	Adult-onset-associated vocal cord paralysis	AD 2q14	
	Adult-onset-associated vocal cord paralysis and facial weakness	AD 2p13 DCTN1 (dynactin) X linked Xq13.1–q21	No UMN or sensory involvement Brazilian[34]
	Congenital, nonprogressive dSMA with arthrogryposis	AD 12q23	
	Onset 6–12 yr, pyramidal and sural involvement	AR 9p21.1–p12	Jerash type—Jordanian children
	Onset in arms with pyramidal tract involvement		Austrian kinship
	Juvenile onset CMT phenotype occurs in some with this mutation, with varying degrees of UMN findings	AD 9q34 senataxin	Allelic to ALS4

CMT, Charcot–Marie–Tooth; UMN, upper motor neuron; AR, autosomal ressive.

CHILDHOOD BULBAR SMA (FAZIO–LONDE AND BROWN–VIALETTO–VAN LAERE SYNDROMES)

Fazio–Londe disease is a progressive bulbar palsy that begins in the first two decades of life. Both the inheritance pattern and the rate of disease progression are variable. With early-onset presentations, the initial manifestation is vocal cord paralysis resulting in stridor. Unlike other motor neuron diseases, ophthalmoparesis is common. Bifacial weakness may be severe. Weakness of jaw, tongue, throat, and neck muscles are common. Some patients develop "cerebellar" features, including intention tremor, ataxia, and titubation. Individuals who are affected rarely survive past early adulthood. The genetics of the disorder are unknown.[16]

The syndrome of Brown–Vialetto–Von Laere is another childhood bulbar syndrome that occurs predominantly in males with multiple modes of inheritance. Again, the onset is typically within the first two decades. In addition to bulbar palsy, sensorineural hearing loss occurs. It is a complex, often multisystem, disorder in which lower motor neuron weakness of the limbs, upper motor neuron signs, ventilatory impairment, ataxia, optic atrophy, retinal pigmentary degeneration, seizures, and dysautonomia may occur. The course is quite variable with either rapid or slow progression.

▶ LABORATORY FEATURES

Elevations in serum CK levels are modestly elevated in most patients with motor neuron disease. In Werdnig–Hoffman disease, it is elevated to less than 5× the upper limits of normal. In Kennedy's disease CK levels may be normal or as high as 8000 IU/L.[20]

Historically, electrodiagnosis was a major diagnostic tool applied to childhood SMA suspects. With the development of commercially available mutational analysis of the SMN gene, EMG has limited utility. It is primarily used in individuals with an SMA phenotype and negative DNA testing. In this circumstance, the electromyographer would anticipate low-amplitude compound muscle action potentials, normal sensory nerve action potential (SNAP) amplitudes, and widespread evidence of both ongoing denervation (fibrillation potentials and positive waves) and chronic partial denervation and reinnervation (reduced numbers of motor unit potentials of increased amplitude and duration). Fasciculation potentials may or may not be identified.

In Kennedy disease, electrodiagnosis plays a more active contemporary role. In the SMN-related SMAs, the clinical diagnosis is usually strongly suspected before ancillary diagnostic testing is considered. DNA mutational analysis is often the first test considered and provides the most painless, accurate, and perhaps expeditious means by which to confirm the clinical suspicion. Conversely, Kennedy disease is less frequently entertained at initial presentation. Understandably, EMG is done in an attempt to provide diagnostic insight and may well provide the first clues to the diagnosis. The electrodiagnostic findings in Kennedy's disease are similar to any other motor neuron disease. The compound muscle action potential amplitudes are reduced or normal. The needle examination demonstrates features of widespread denervation, although the features of chronic denervation and reinnervation typically dominate. Unlike most motor neuron diseases, there is involvement of the sensory system manifested by absent or low-amplitude SNAPs and H reflexes.[19]

Electrodiagnosis may have a small role to play in the determination of SMA prognosis. The density and geographic distribution of fibrillation potentials in comparison to changes of chronic partial denervation and reinnervation is related to the rapidity with which these disorders progress. Motor unit instability and the rate of decline of motor unit number estimation may also provide prognostic insight.[30,36,37]

The distal forms of SMA are distinguished from CMT disease by the presence or absence of normal SNAPs. Normal SNAPs would negate consideration of CMT disease and more correctly categorize the disorder as a distal SMA. Hirayama disease could be readily misconstrued as a disorder of the cervical spinal cord, brachial plexus, or motor nerve. Demonstrating electrodiagnostic features indicative of a segmental motor neuron disease without demyelinating features would strongly favor juvenile segmental SMA as the correct diagnosis. Electrodiagnosis in scapuloperoneal syndromes may identify neurogenic features consistent with SMA rather than features suggestive of the more common "myopathic" forms of this phenotype.

Both SMA I–III and Kennedy disease can be diagnosed by commercially available DNA mutational analysis. Approximately 95% of patients with the SMA I–III phenotypes will have chromosome V mutations.[38] Rarely, an adult-onset AR case of SMA will have an SMN mutation.[15] The DNA mutational analysis for Kennedy disease is highly sensitive, but penetrance of gene expression may be variable.[20] Carrier detection and prenatal testing for SMA I–III are available. Ninety-eight percent of parents of children with SMN mutations are heterozygotes for the mutation. Two percent of patients with SMA I–III represent spontaneous mutations. An SMA child born of only one heterozygote parent can result from either a spontaneous mutation on the child's second allele or a germline mosaicism in the seemingly normal parent. In this situation, there is the potential risk of a couple consisting of an identified heterozygote and an apparent normal partner (but actual heterozygote) being erroneously counseled that their risk of an

affected child is zero. Interpretation of carrier testing is also complicated by consideration that both SMN copies may exist on a single chromosome in 4% of individuals. Unknowingly, the presumed normal parent may transmit his or her deficient allele rather than the one carrying two SMN1 copies, resulting in a 25% risk of an affected child.[39]

The role of imaging in the SMAs is limited. In Hirayama's disease, imaging of the cervical spinal cord may reveal atrophy. In keeping with the hypothesis mentioned below, magnetic resonance or CT myelographic imaging of the cervical spine done in a flexed position has been reported to demonstrate forward displacement of the cervical spinal cord, and flattening of its posterior surface as an apparent consequence of buckling of the posterior longitudinal ligament.[40] Oligo- or azospermia, elevated gonadotrophin levels, and glucose intolerance may all occur in patients with Kennedy disease.

▶ HISTOPATHOLOGY

As in electrodiagnosis, the role of muscle biopsy in SMA has greatly diminished. Even in cases of SMA I–III or Kennedy disease in which the diagnosis has not been made through DNA mutational analysis, EMG will provide information analogous to what a muscle biopsy will provide, i.e., denervation and reinnervation. EMG has the additional advantage of more readily demonstrating the geographic distribution of these findings. In SMA I, the biopsy will demonstrate sheets of rounded, atrophic fibers of both fiber types. Hypertrophic fibers are intermixed and are exclusively type I (Fig. 6–3). Type grouping is uncommon. In SMA type II, the biopsy may be similar to type I disease or may differ because of hypertrophic type II fibers and/or the presence of type grouping. In SMA type III, type grouping and group atrophy of both fiber types are common. In addition, the so-called "pseudomyopathic" features may be seen including fiber splitting, increased endomysial connective tissue, and an increased number of internal nuclei.

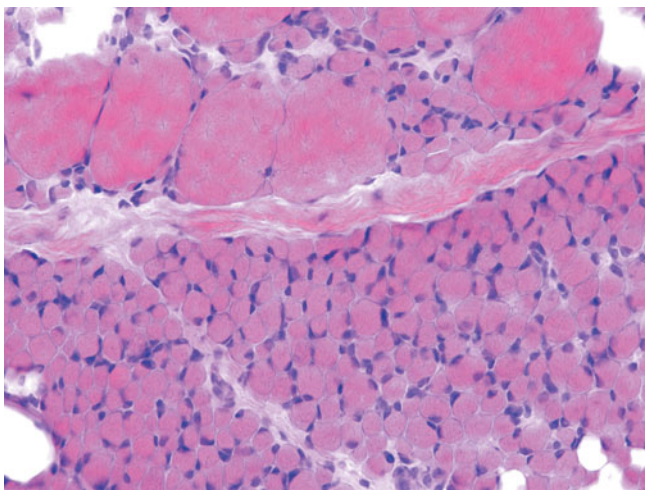

Figure 6–3. Muscle biopsy of SMA patient demonstrating complete fascicles of sheets of round, atrophic muscle fibers and a few preserved normal sized myofibers. (hematoxylin and eosin) (Figure courtesy of Dr. Umberto DiGirolami of Brigham and Women's Hospital, Boston, MA.)

In Kennedy's disease, similar changes of neurogenic atrophy have been reported, including angulated fibers of both types, pyknotic nuclear clumps, and fiber-type grouping. In addition, like many chronic neurogenic disorders, "pseudomyopathic" features including increased numbers of central nuclei, and necrotic fibers with occasional invasion with inflammatory cells may be seen. Sural nerve biopsy predictably identifies loss of myelinated fibers.[20]

Muscle biopsy in Hirayama's disease demonstrates the anticipated findings of a chronic denervating disorder, fiber-type grouping, and grouped atrophy.[24] One autopsy case of Hirayama's disease demonstrated ischemic changes in the cervical spinal cord.[40]

In Fazio–Londe disease, there is neuronal loss in all cranial nerve motor nuclei and in the ventral horns of the upper half of the spinal cord. In addition, there is cell loss within the cerebellar cortex and dentate nuclei of the cerebellum.

▶ PATHOGENESIS

The SMAs are, for the most part, either known or presumed to be genetic disorders. The genetics of SMA types I–III are complex. Initially, abnormalities both within the SMN and the neuronal apoptosis neuronal inhibitory protein genes were suggested. To date, no apparent pathogenetic role for the latter has been found. In normal individuals, there are two copies each of the SMN1 and SMN2 genes. Both genes produce similar proteins. The SMN2 gene, however, lacks exon 7 and, as a result, appears to produce an unstable and rapidly degrading protein. There are no known clinical consequences from mutations of the SMN2 gene alone.

In SMA I–III, the SMN1 gene is homozygously deleted or point mutated. The severity of the phenotype appears to be related to the number of SMN2 copies available, to make an imperfect but partially effective SMN protein to compensate for the lack of normal SMN1 protein. Two copies of SMN2 correlate with an SMA I phenotype, three copies with SMN II, and four copies with SMA III. Individuals homozygous for the SMN1 mutation with five copies of the SMN 2 gene have been reported to be asymptomatic.[10,41]

Wild-type SMN protein appears to have an integral role in messenger RNA synthesis. It appears to interact with a number of cytoplasmic proteins to facilitate the formation, nuclear importation, and regeneration of

nuclear spliceosomal RNA.[42] The SMN protein is found in many different types of cells. Why motor neurons remain selectively vulnerable to SMN deficiency remains unknown.

Autosomal-dominant inheritance is estimated to occur in approximately 30% of patients with SMA IV. The gene for this uncommon disorder has not been identified. Patients with recessively inherited SMA IV are associated with homozygous SMN I deletions buffered by multiple SMN II copies at least in some cases.[15,43,44] Asymptomatic adults with identical genotypes have been described.[39] Autosomal-recessive and X-linked patterns of inheritance produce the majority of individuals who are affected.

Kennedy's disease was the first trinucleotide repeat disorder described.[22] It results from a mutation of the androgen receptor gene on the X chromosome producing an abnormal number of cylosine-adenine-guanine (CAG) repeats. Normal males will have 21–37 repeats whereas affected males will have 40–62. The number of repeats correlates with disease onset but not with rate of progression.[7] Current theory suggests that CAG expansion, in a manner similar to SOD mutations in familial ALS, results in a toxic gain of function rather than loss of function pathogenesis. There is evidence of nuclear inclusions in Kennedy's disease that are ubiquinated aggregates of abnormal protein.[16]

Hirayama's disease may be the least likely of the SMAs to have a genetic mechanism. Ischemic changes in the cervical spinal cord of a single autopsied case of Hirayama's disease led to the hypothesis of a compressive mechanism. In 2000, Hirayama reported the results of dynamic imaging in 73 patients and 20 controls. Ninety-four percent of patients had significant forward displacement and flattening of the posterior surface of the cervical cord during neck flexion. Presumptively this compromises the cord blood supply, with preferential susceptibility of the anterior horn to ischemia. Other observations from this study that were consistent with clinical observations were the frequent asymmetric flattening of the cord, and the lesser degrees of cord distortion in older patients in whom progression had stopped.[40]

Recently, an 11-year-old girl with a scapuloperoneal phenotype was reported with a deletion of the PMP 22 gene at the chromosome 17p11.2 locus.[45] This mutation is identical to the most common mutation associated with hereditary liability to pressure palsy and allelic to the CMT1a duplication. It would appear that at least some neurogenic scapuloperoneal syndromes would be more correctly classified as hereditary peripheral neuropathies. Genetic heterogeneity in neurogenic scapuloperoneal syndrome exists. The disorder has also been linked to chromosome 12q24.1–q24.31.[46]

Distal SMA may be inherited in a dominant, a recessive or an X-linked manner. Mutations of numerous genes on multiple chromosomes may be related to this phenotype, which, like hereditary spastic paraparesis, can be either "pure" or "complicated," based on involvement of other neurological systems (Table 6–2). Impaired axonal transport has become an increasingly attractive model to explain the pathogenesis of a number of different neurological disorders. Although there is currently no unifying hypothesis for the pathogenesis of the dSMAs, impaired axonal transport is the apparent mechanism for a least one form of this syndrome.[47] Dynactin, the protein product of the mutated gene in dSMA VII, is a microtubular motor protein responsible for retrograde axonal transport.

▶ DIFFERENTIAL DIAGNOSIS AND RECOMMENDED EVALUATION

The differential diagnosis of SMA I is the differential diagnosis of the floppy infant (Table 6–3).[48] The majority of hypotonic neonates will be afflicted with a central nervous system disorder. An alert and cognitively appropriate child with diminished or absent deep tendon reflexes would suggest a less common infantile neuromuscular disorder. Neonatal or congenital myasthenia, neonatal myotonic dystrophy, the myopathy of Pompe's disease, severe nemaline, myotubular or other congenital myopathies, infantile botulism, and rare hypomyelinating neuropathies are the major neuromuscular considerations in a hypotonic infant. Fasciculations of the tongue in an alert child would favor a diagnosis of Werdnig–Hoffman disease. The evaluation of such a child would depend on index of suspicion. In a suspected CNS disorder, magnetic resonance imaging and, if appropriate, testing for chromosomal abnormalities and inborn errors of metabolism would be appropriate. DNA mutational analysis for the SMN mutation would be the first and possibly only diagnostic test in a Werdnig–Hoffman suspect.[49] In other contexts, or with a negative chromosome 5 test, EMG and nerve conduction studies, serum CK level, antiacetylcholine receptor antibodies, stool assays for botulinum toxin, and muscle biopsy may be considered.

SMA II, III, and IV need to be primarily separated from a wide variety of myopathic disorders, including the dystrophopathies, congenital, limbgirdle, myotonic, and Emery–Dreifuss muscular dystrophies; congenital myopathies; mitochondrial disorders; and lipid and glycogen storage disorders. Chronic inflammatory demyelinating polyradiculoneuropathy would be the primary neuropathic consideration. The presence of limb or tongue fasciculations and tremor would favor an SMA diagnosis. Again DNA mutational analysis for SMA or a dystrophinopathy would be the initial step dependent on the clinical index of suspicion. Otherwise, the evaluation would proceed in a similar direction to the neuromuscular differential diagnosis of SMA I.

TABLE 6–3. DIFFERENTIAL DIAGNOSIS OF THE SPINAL MUSCULAR ATROPHIES

Phenotype	Differential Diagnostic Considerations	Recommended Testing
Hypotonic infant	CNS disorders (two-thirds)	Brain imaging
	Congenital myopathies	Muscle biopsy
	Congenital myasthenia	Electrodiagnosis
	Congenital myotonic dystrophy	DNA mutational analysis
		Maternal examination
	Congenital hypomyelinating neuropathy	Electrodiagnosis
	Acid maltase deficiency	Muscle biopsy
	Mitochondrial myopathy	Diagnosis made clinically in appropriate context
	Neonatal tetanus	
Proximal symmetric weakness of childhood or early adulthood	Dystrophinopathy	DNA mutational analysis
	Limb girdle muscular dystrophy	Muscle biopsy
		DNA mutational analysis
	Congenital myopathies	Muscle biopsy
	Glycogen or lipid storage myopathy	Electrodiagnosis
	CIDP	Electrodiagnosis and bioassay
	Infantile botulism	
Kennedy's syndrome	ALS	EMG and DNA analysis
	Inclusion body myositis	Muscle biopsy
	Myasthenia gravis	Electrodiagnosis with RS
		ACHR antibodies
		MuSK antibodies
	Lambert–Eaton syndrome	Electrodiagnosis with RS
	Oculopharyngeal dystrophy	Anti-VGCC antibodies
		DNA mutational analysis
Hirayama's disease	Multifocal motor neuropathy	Electrodiagnosis
		Anti-GM1 antibodies
	ALS	Electrodiagnosis
	Syringomyelia	Cervical cord imaging
	Cervical cord pathology	Cervical cord imaging
Scapuloperoneal syndrome	FSH dystrophy	DNA mutational analysis
	Other myopathies	Muscle biopsy
Distal SMA	Charcot–Marie–Tooth disease	Electrodiagnosis
		DNA mutational analysis
	Distal myopathy	Muscle biopsy

RS, repetitive stimulation; ACR, acetylcholine receptor; CIDP, chronic inflammatory demyelinating polyneuropathy; FSH, facioscapulohumeral; VGCC, voltage-gated calcium channel; MuSK, muscle-specific kinase.

Kennedy's disease may be misdiagnosed as ALS.[17] DNA mutational analysis for X-linked bulbospinal muscular atrophy should be at least considered in any male with suspected ALS with only lower motor neuron manifestations. In view of its predilection to produce a limb-girdle pattern of weakness and bulbar symptoms, the Lambert–Eaton myasthenic syndrome,[54] myasthenia, as well as any myopathy with a similar potential pattern of weakness should be considered in the Kennedy's differential. In view of its propensity to affect older males and cause symptomatic dysphagia as well as limb weakness, inclusion body myositis is a primary myopathic consideration. The presence of significant wrist and finger flexion weakness would be typical of inclusion body myositis and very unusual in Kennedy's. If bulbar symptoms predominate early in the course, the progressive bulbar palsy phenotype of ALS, myasthenia, and oculopharyngeal dystrophy are the major differential diagnostic considerations. Tongue and chin fasciculations, tremor, clinical or electrodiagnostic evidence of a sensory neuropathy, and signs of androgen insensitivity would favor a Kennedy's diagnosis. Antiacetylcholine receptor binding and modulating antibodies, muscle-specific kinase antibodies (myasthenia), anti-voltage-gated calcium channel antibodies (Lambert–Eaton myasthenic syndrome), DNA mutational analysis for the polyadenylate-binding protein type 1 (oculopharyngeal dystrophy), EMG and nerve conduction studies potentially including repetitive stimulation and single fiber electromyography, serum CK determination, and muscle biopsy are all tests that may be used in a Kennedy's suspect in whom mutational analysis is negative.

Focal limb-onset presentations of motor neuron disease are commonly mistaken as mononeuropathies, monoradiculopathies, plexopathies, or an intramedullary myelopathy such as syringomyelia. Many

patients with motor neuron disease may actually undergo unnecessary surgical procedures for this reason.[55] The absence of pain or sensory symptoms should make any of these localizations suspect. A more accurate differential diagnosis for a focal motor neuron disorder such as Hirayama's disease would include the progressive muscular atrophy variant of ALS and multifocal motor neuropathy. In the latter disorder, weakness without atrophy, weakness in nerve rather than segmental distributions, demyelinating features on nerve conduction studies, and the presence of high titers of antibodies directed against the GM1 ganglioside would provide diagnostic support.

The distal SMAs are frequently misdiagnosed as the far more common CMT disease. Other than for the presence or absence of sensory involvement, the disorders may be phenotypically identical. Molecular genetics have, however, cast doubt on whether distal SMA and axonal forms of CMT disease will be considered different disorders in the future. Individuals with both mutation of the KIFBβ gene, heat shock protein gene 27 located on chromosome 7q11–q21, and a separate mutation on chromosome 7B may associate with CMT 2A, 2F, and 2D or with a distal SMA phenotype.[32,53] The distal SMAs may be readily confused with a number of the distal myopathy genotypes. Slowly progressive, symmetric weakness of foot dorsiflexion is a common feature of both disorders. Either may associate with other features including vocal cord paralysis. Muscle biopsy may be required for distinction.

The bulbar motor neuron disorders of childhood (Fazio–Londe and Brown–Vialetto–von Laere diseases) are rare and have a limited differential diagnosis. The primary consideration would be an infiltrative disorder of the brainstem or lower cranial nerves requiring magnetic resonance imaging of the brainstem and potentially cerebrospinal fluid examination for exclusionary purposes.

▶ TREATMENT

Unfortunately, there are currently no treatments that effectively alter the natural history of any of the disorders described in this chapter.

In a manner similar to ALS, ventilatory failure in SMA I and II is inevitable. Tracheostomy, long-term mechanical ventilation, and insertion of a percutaneous feeding tube are decisions with enormous emotional and financial consequences to the parents of an affected child. Noninvasive positive pressure ventilation may provide an improved quality and duration of life until a decision regarding tracheostomy is required.

Clinical trials utilizing gabapentin, riluzole, acetylcarnitine, and phenylbutyrate have been or are being performed on patients affected with SMA I–III. The results of these studies are negative, inconclusive, or incomplete to date.[10] Valproic acid has been shown to increase the rate of SMN2 transcription.[51] Recently, an observational study demonstrated that valproate appeared to increase strength by a mean of 16% in patients with SMA types III and IV.[52] Valproate therapy is not without risk, including liver toxicity and carnitine deficiency. Its use in patients with SMA outside of a currently active clinical trial is not recommended.

The development of kyphoscoliosis is a common problem in children who can sit and who become wheelchair bound. Spine stabilization is commonly recommended in individuals whose curves exceed 50° and whose vital capacities exceed 40% of predicted. The goals of this intervention are patient comfort, ease of patient management, and potentially stabilization of restrictive pulmonary deficits.[50]

With Hirayama's disease, decompression of the cervical spinal cord has been attempted. It is unclear whether this meaningfully affects the natural history of the disease.

▶ SUMMARY

The SMAs are phenotypically heterogeneous disorders that share common features of motor neuron degeneration. In most cases, these are heritable conditions. Knowledge provided by molecular genetic investigations has provided insight that the SMAs are genetically heterogeneous as well. In some cases, diseases historically classified elsewhere have been found to be allelic to certain SMA phenotypes. It is safe to predict that future classifications of what are currently considered SMAs will be revised considerably.

More importantly, molecular biology has provided significant insights into disease pathogenesis, offering optimism that rational and effective treatments for these disorders will occur in the foreseeable future. Until such time, supportive care by committed clinicians remains of paramount importance.

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CHAPTER 7

Poliomyelitis

▶ INTRODUCTION

The polio virus remains the most notorious of all of the neurotropic enteroviruses. Although new cases have been virtually eradicated in the United States, many survivors of the paralytic polio epidemics of the late 1940s and early 1950s continue to populate neurology clinics today.[1] Many of these individuals, having experienced decades of a nonprogressive neurologic deficit, have experienced new symptoms including increasing weakness. Late effects of polio, the postpolio syndrome (PPS) and postpolio muscular atrophy (PPMA) are terms that have been coined to address this issue.

Poliomyelitis is a term that has been used synonymously with paralytic polio caused by the polio virus. Strictly speaking, it is a syndrome caused by any number of virions with a particular affinity for the ventral horns of the spinal cord and their analogous motor cranial nerve nuclei (Table 7–1). Although poliomyelitis is a disease of largely historical interest, it continues to have some contemporary relevance. Patients who have been raised in countries where childhood vaccination has not been provided, those who have refused vaccination for religious or cultural reasons, patients who are immunosuppressed, and the rare individual who contracts the disease from exposure to the attenuated live virus vaccine remain as populations at risk. Additionally, there are other viral pathogens that apparently share polio's tropism for anterior horn cells, essentially reproducing the poliomyelitis syndrome (Table 7–2). The virulence of most of these agents remains unchecked by available vaccines or effective treatments. The West Nile virus (WNV) is the most recent, notable example of this.

This chapter not only will discuss infections with the polio virus and the delayed consequences of paralytic polio but will also address other neurotropic viruses with an affinity for anterior horn cells and the poliomyelitis that may result.

▶ CLINICAL FEATURES

POLIOMYELITIS

Poliomyelitis may be either a monophasic or a biphasic disease. The initial symptoms or "minor" illness are nonspecific, lasting 1–2 days. Symptoms are predominantly constitutional or gastrointestinal in nature. They consist of some combination of fever, malaise, pharyngitis, headache, nausea, vomiting, and/or abdominal cramping. In the majority of individuals who are infected, the illness is self-limited and ends at this point. In individuals who fall victim to the "major" illness, initial symptoms subside for 3–10 days before recurring. The major illness is defined by CNS involvement with meningoencephalitis, with or without an associated paralytic component. Stiff neck, back pain, and fever are prominent. In less than 5% of cases, encephalitis with altered mental status occurs as a nonparalytic component of the "major" illness.[2]

In individuals destined to develop paralytic disease, prominent myalgias and cramping rapidly develop into paralysis, which peaks in its severity within 48 hours of onset. The paralysis is typically asymmetric and is confined to the limbs and trunk in half of the cases (Fig. 7–1). There is a certain predilection for lumbosacral segments and proximal more than distal muscles but these tendencies have little value in the evaluation of an individual case. Ten percent to 15% of cases have bulbar weakness only. The majority of these are children. The seventh, ninth, and 10th cranial nerves seem to be the most susceptible.[2] A similar number will have a more severe combination of spinal and bulbar weakness. Ventilatory failure is more common in this latter group. Affected limbs are flaccid and areflexic in the vast majority. As in virtually all disorders with a predilection for anterior horn cells and motor cranial nerves, the third, fourth, and sixth cranial nerves are inexplicably spared. Sensory signs and symptoms are atypical. In keeping with the known pathological involvement of the brainstem tegmentum and hypothalamus in cases with encephalitic components, clinical dysautonomia including fluctuating blood pressure, cardiac arrhythmia, and hyperhydrosis may occur.[2] In these same individuals, clinical features suggesting pyramidal tract pathology may provide confounding diagnostic distraction.

The natural history of paralytic polio is variable, dependent in large part on the severity and extent of the initial illness. As in Guillain–Barré syndrome (GBS), less than 10% of individuals will die from the acute illness, typically due to the complications of ventilatory failure or immobility. Those who survive typically regain strength inversely proportionate to the severity of the initial illness. The majority of this recovery takes place over the

▶ TABLE 7–1. DIFFERENTIAL DIAGNOSIS OF POLIO VIRUS INFECTIONS

Disorder	Clinical Features	Diagnosis
Other viral causes of poliomyelitis	May be indistinguishable from polio with viral prodrome, followed by aseptic meningitis and acute, asymmetric limb and bulbar paralysis	Cultures of throat, stool, or CSF CSF serology for viruses in Table 7–2 Acute and convalescent serum antibody titers to specific viruses in Table 7–2
Guillain–Barre syndrome	Acute onset of motor > sensory signs and symptoms affecting limbs and cranial nerves—dysautonomia	Elevated CSF protein without pleocytosis Demyelinating sensory motor neuropathy on electrodiagnostic examination
Transverse myelitis	Acute-onset paraparesis or quadriparesis with sensory level—back pain	↑signal, swelling on spinal cord MR imaging
Botulism	Cranial nerve including extraocular muscle weakness, generalized weakness, and symptoms of cholinergic dysautonomia	Electrodiagnostic findings of a presynaptic disorder of neuromuscular transmission Toxin isolation or organism culture from wound, stool, or ingested food History of appropriate exposure
Rabies	Pain, weakness, and sensory symptoms in the bitten limb in 20% of individuals who are affected	Clinical diagnosis in context of appropriate exposure
Porphyria	Prodrome of abdominal pain, encephalopathy including psychosis, followed by acute, proximally predominant motor > sensory neuropathy	Family history (variable) Increased products of heme synthesis in urine
Spinal epidural abscess	Back pain Rapidly progressive paraparesis/quadriparesis with sensory level	Imaging of spine Blood cultures
Hypokalemia and hypophosphatemia	Rapidly progressive, symmetric, and generalized weakness	Potassium <2 meq/L Phosphorus <1 mg/dL

course of weeks to months, presumably due to reinnervation occurring from neighboring motor units not affected by the disease.

The concept of a PPS was first addressed by Cornil and Lépine in 1875. They described the clinical and postmortem features of an individual who developed progressive weakness following a remote episode of poliomyelitis.[3] This concept received no more than cursory attention until 1981 when an international

▶ TABLE 7–2. OTHER VIRAL AGENTS CAUSING POLIOMYELITIS

Coxsackie virus group A type 7
Echovirus 6
Enterovirus 70
Enterovirus 71
Japanese encephalitis virus
Poliovirus types 1, 2, and 3
Rabies virus
West Nile virus

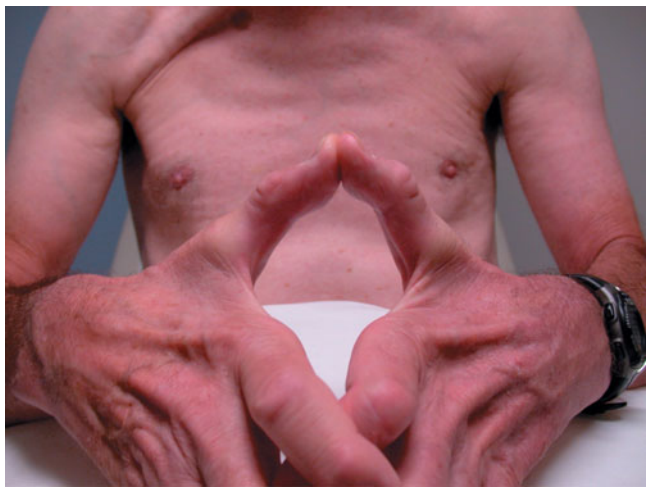

Figure 7–1. Asymmetric pectoralis and severe intrinsic hand muscle wasting in a 67-year-old who contracted polio in 1955 affecting only cervical segments.

symposium of experts was convened in Chicago, representing a response to the large numbers of people affected by the epidemics of the early 1940s and early 1950s. There is convincing evidence that some individuals with prior polio may develop slowly progressive weakness (average decline 1%/yr) after a protracted period of stability (PPMA).[4] How frequently PPMA occurs as a manifestation of PPS is a matter of some controversy. In one study, 50 patients with prior polio were selected from a cohort of 300 patients and followed for 5 years.[5] Sixty percent of this group developed symptoms. Of this symptomatic group, only a third had symptoms attributed to musculoskeletal complaints and none of them had measurable evidence of progressive atrophy and weakness.

When it occurs, PPMA typically manifests in the spinal segments or bulbar regions most severely afflicted by the initial illness. Ventilatory function may decline, with one study suggesting approximately 2% loss of vital capacity a year, in keeping with the slowly progressive nature of the illness.[6] Criteria have been established to solidify this diagnosis. These include increasing weakness, atrophy, or fatigue in a person previously afflicted with a documented polio-like illness. This must occur subsequent to a protracted period of stability, absent an alternative explanation.

Other than for sequential quantitative measures of strength, there is no "gold standard" to determine which polio victims have developed PPMA. Consequently, estimates of the prevalence of PPS have ranged from 22% to 85%. Signs and symptoms of PPS have been reported to begin as early as 8 years after the initial illness or as late as 71 years, with an average of 35 years. The likelihood of developing PPS seems to correlate with both the age of the patient at the time of the initial illness and its severity.[7]

The limits of what are or are not legitimate components of the PPS remain controversial as well. Reactivation of the initial symptoms of infection, including increasing weakness, cramping, and fatigue, are understandable. So too are problems readily attributable to the indirect effects of worsening muscle weakness. Myalgias may result from what would be otherwise considered routine muscle use, which, in a sense, has now become overused due to weakened state of the involved musculature. Orthopedic problems such as adhesive capsulitis are a frequent sequelae of immobilized joints. Premature degeneration of joints is commonplace in the postpolio population. Presumably, this occurs as a result of compensatory overuse of unaffected limbs, in an attempt to avoid use of their more affected and less reliable counterparts. Alternatively, excessive laxity of joints and excessive wear applied to articular and periarticular anatomy may result from lack of muscular support to those joints. Additionally, there may be unbalanced vectors of force brought to bear on individual joints, produced by disproportionate weakness of the muscle groups supporting them.

Sleep-disordered breathing is another syndrome that is easy to understand as a potential manifestation of late polio. Hypopharyngeal muscles, normally relaxed during rapid eye movement (REM) sleep, may further weaken as a consequence of the late effects of polio and contribute to airway obstruction and the symptomatology of disordered sleep. Sleep-disordered breathing may also be the result of adverse late effects on the breathing centers in the brainstem reticular formation.

More difficult to comprehend are other symptoms that have been ascribed to the late effects of polio. Many of these symptoms cannot be readily explained by the known pathology of the initial illness or by the indirect effects of the more readily understandable delayed progressive weakness.[5] Impaired concentration and the ability to process information with the usual speed are complaints sometimes voiced by postpolio patients. This may result as an indirect effect of impaired sleep patterns. Alternatively, physicians should be cognizant that adverse psychological effects can result from late polio. Patients' sense of well-being can be seriously undermined by their realization that their muscles are weakening and that they may be losing control of a disease with which they had formerly believed that they had achieved an equilibrium.

WEST NILE VIRUS

WNV is a mosquito-borne viral pathogen belonging to the Flavivirus family of more contemporary interest.[8] As in polio, most individuals who are infected develop a minor, nonspecific illness, which often includes fever, gastrointestinal complaints, back pain, and rash, in addition to potential neurological manifestations.[9] A number of reports have linked WNV to a poliomyelitis-like phenotype that may affect facial as well as limb muscles with or without an associated meningitic or encephalitic component.[9–14] Approximately half of recognized patients will develop flaccid weakness over a 3—8-day period, which tends to be proximal and asymmetric in distribution.[9] Electrophysiological and pathological observations have suggested that this weakness originates from anterior horn cell injury in most cases. Confounding these observations are indicators that the WNV may produce similar but distinct Guillain–Barré and transverse myelitis phenotypes. As in the polio virus, the outcome may be favorable although irreversible paralysis may result.

OTHER POLIOTROPIC VIRUSES

Poliomyelitis is reported with other viral pathogens. Enterovirus 71 is phenotypically heterogeneous, producing

hand–foot–mouth disease, aseptic meningitis, rash, and an acute respiratory syndrome or myocarditis. It has been reported to produce a virtually identical illness to poliomyelitis in Bulgaria, affecting predominantly children less than 5 years of age in the summer months.[15] Acute hemorrhagic conjunctivitis may associate with a poliomyelitis syndrome[16] as well as with enterovirus 71 infection.[17,18] Paralytic poliomyelitis has also been described with Coxsackie virus group A type 7, echovirus type 6, and the Japanese encephalitis virus (Flavivirus).[19–21] Rabies may present as a paralytic illness (see differential diagnosis).

▶ LABORATORY FEATURES

Examination of the cerebrospinal fluid (CSF) may be initially negative in 10% of cases of polio. Within 2 weeks of onset, however, a pleocytosis develops. Initially, there may be a neutrophilic predominance, but 50–200 lymphocytes/mm^3 represent the typical pattern. These cells typically dissipate within 2 weeks. There is a gradual increase in the CSF protein level to a peak of 150 mg% or less, which then resolves within 2 months. This pattern is similar with all of the viral agents that may produce a poliomyelitis syndrome. A firm diagnosis of polio can be made with a fourfold increase in serum antibody titers over time or by viral culture obtained from stool or throat. Viral capture of the polio virus in the CSF is rare.

Confirmation of WNV infection can be made by detection of IgM-WNV antibodies or WNV RNA in the spinal fluid, by a fourfold increase in IgG-WNV antibodies detected in the serum 4 weeks apart, or ultimately through detection of the virus in the brain or spinal cord.[8]

Electrodiagnosis in poliomyelitis will serve to confirm a disorder affecting anterior horn cell, ventral root, or motor nerve in a polysegmental pattern. Sensory nerve conductions will be spared. Amplitudes of compound motor action potentials will be reduced in involved limbs. Conduction velocities will be spared unless compound motor action potential amplitudes are severely reduced, e.g. <1 mV, at which time these will be slowed proportionate to the degree of axon loss. Typically, this is no slower than 70% of the lower limits of normal. Motor unit recruitment will be reduced as soon as weakness is apparent. Within 3 weeks of onset, the markers of recent denervation, fibrillation potentials and positive waves, will be found in affected muscles including corresponding paraspinal musculature. Within months, motor unit potentials will increase in both amplitude and duration in keeping with the initial denervating and subsequent reinnervating processes.

In the PPMA, in keeping with its presumed pathogenesis, fibrillation potentials and positive waves are far less prevalent. Electrodiagnosis is dominated by features of chronic denervation and reinnervation. Motor unit potentials with amplitudes in the 15–20 mV range (normally 2 mV or less) are not uncommon.

Imaging has a supportive role. Leptomeningeal and cauda equina enhancement, and increased signal in the basal ganglia and thalami, have been described with MRI imaging in patients with WNV infection.[8]

Mild elevations of serum creatine kinase are common in poliomyelitis. These may occur in PPS as well and seem to correlate to patients with new complaints.[22] High-resolution MR imaging of the spine may demonstrate increased signal in the ventral horns in West Nile poliomyelitic illness.[12] Viral cultures of the CSF are far more likely to recover Echo and Coxsackie virus than polio when these agents produce a paralytic illness.

▶ HISTOPATHOLOGY

The initial pathology consists of pial inflammation, vascular dilatation, and petechial hemorrhages, which are confined to or at least most severe in the ventral horns. Perivascular and parenchymal inflammatory infiltrates occur as well. Degeneration of the posterior columns or loss of neurons in the dorsal root ganglia is uncommon. The nonextraocular muscle motor nuclei, the vestibular nuclei, and the reticular formation of the brainstem may be afflicted in a manner similar to their spinal counterparts. Above the tentorium, encephalitic symptoms, if present, would appear to correlate with changes in the thalamus and hyperthalamus. The cortex, with the occasional exception of the precentral gyrus, is usually spared.[2]

The histopathology of the WNV poliomyelitis syndrome also includes perivascular mononuclear cell infiltrates in brain and ventral horns of the spinal cord.[8,23]

The relevant pathology in the paralytic form of rabies seems concentrated on the ventral nerve roots and motor axons of peripheral nerves, although rabies virus RNA may be found in anterior horn cells.[8]

▶ PATHOGENESIS

The polio virus is a small RNA enterovirus of the *Picornaviridae* family. There are three known serotypes. Type 1 is most frequently associated with paralytic disease. The incubation period is commonly 6–20 days, with epidemics occurring in the summer and fall of the years. Polio is an enteric virus contracted primarily through the oral route, with occasional nasopharyngeal introduction with subsequent viremia. Amplification of the viral load in non-neural tissues precedes the development of the major illness in most cases. The mode of CNS viral ingress is uncertain, although retrograde neural

transport is thought to play a role. The majority of individuals who are infected will develop only the minor illness and go unrecognized. Of the small percentage of individuals who develop the major illness, the majority will develop aseptic meningoencephalitis without paralysis. Paralytic polio develops in no more than 2% of individuals who are infected.[24,25]

Individuals infected with the polio virus is shed orally for a period of several weeks and remains in the stool for months. In tropical areas or areas where sanitation is suboptimal, the disease is typically endemic in nature. Paralytic polio may be less common in these situations, as children may be infected at an earlier age, which in turn leads to a higher likelihood that they will suffer only the minor form of the disease. In temperate climates or in areas where sanitation is improved, the disease is more likely to be epidemic in nature. Children are less likely to be exposed until late in life, thus increasing the likelihood that they will develop the more severe, major form of the illness.[26] As in other illnesses where different individuals respond to similar insults in varying degrees, a genetic predisposition for development of the paralytic form of the disease has been suspected.[2]

Poliomyelitis can be contracted paradoxically from the administration of the attenuated live virus vaccine.[27] Between 1969 and 1980, 290 million doses of this vaccine were administered, with 92 reported cases of vaccine-initiated disease. These latter individuals were either recipients or nonvaccinated contacts of recipients.[28] Unlike naturally acquired paralytic polio, vaccine-initiated disease is most commonly associated with type 2 and type 3 serotypes. Since 2000, only inactivated polio vaccine has been used in the United States, eliminating vaccine-induced poliomyelitis in this country.

The pathogenesis of the late effects of polio are not completely understood. Many theories have been espoused. The extent to which an acutely weak muscle in polio recovers its strength is due, in large part, to the number of remaining motor units innervating that muscle, and the ability of those motor units to reinnervate denervated and orphaned muscle fibers by the development of collateral sprouting. As a result, muscles denervated by polio will have reduced numbers of enlarged motor units, i.e., motor units whose innervation ratios are greater than they were premorbidly.

One theory proposed to explain the late development of new muscle weakness is that these enlarged motor units are not as durable as their normal counterparts. There are a number of lines of evidence that the largest motor units in muscles previously denervated by polio become unstable first, presumably on the basis of their increased metabolic demands.[7]

Another theory, not necessarily mutually exclusive from the first, is that the effects of polio are simply an acceleration of the normal aging process. Loss of anterior horn cells and motor units is a known, normal consequence of aging, clinically obscured by a reserve of motor unit capability in excess of what is required for activities of daily living. Acute polio understandably erodes if not eradicates this reserve. Theoretically, when loss of anterior horn cells occurs as a result of aging in a patient with prior polio, the consequences are far more clinically evident. Not only is there no reserve to fall back on, but a larger number of muscle fibers become inactivated than would be the case with the loss of a normal-sized muscle unit.

As attractive as this hypothesis is to explain the delayed and slowly progressive weakness that may occur in late polio, it has a potential flaw. PPMA appears to be more closely linked to the interval after the acute illness than to the age of the patient. This is relevant as the loss of motor units with aging is not apparent in normal individuals until after the age of 60 years. It would be hard, therefore, to ascribe the late development of weakness in a 50-year-old to this mechanism alone. If both of the aforementioned theories are combined, the apparent flaw in the second proposed mechanism becomes less damaging.

The varicella zoster virus is the most notable example of viral dormancy with delayed reactivation. Persistent poliovirus infection has been proposed as an alternative explanation for the late effects of polio. Evidence in support of this theory exists but is inconclusive. Equally uncertain is the role of a delayed, immune-mediated mechanism for PPS. Again, evidence to support this theory exists but is indirect and inconclusive. At one time, it was suggested that PPMA was actually a forme fruste of amyotrophic lateral sclerosis (ALS) to which patients with poliomyelitis might be predisposed as a result of their prior illness.[29] There is little or no current support for this hypothesis.

▶ DIFFERENTIAL DIAGNOSIS AND RECOMMENDED EVALUATION

The differential diagnosis of paralytic polio includes any illness capable of producing acute paralysis. A poliomyelitic illness may occur with a number of other neurotropic viruses. As mentioned above, certain strains of echovirsus, Coxsackie virus, enterovirus, Japanese encephalitis, and WNV may produce an identical range of symptoms, although both the severity and the residual effects of some of these are typically milder. Viral cultures of CSF, stool, and throat should be obtained in any individual with an aseptic meningitis and suggestion of lower motor neuron involvement including myalgias, cramps, fasciculations, or paralysis.

Subsequent to the development of effective polio vaccines, the GBS has become the most common cause of acute areflexic paralysis in developed countries. In

most cases, the paralysis of GBS is generalized and symmetric in pattern. Initial paresthesias and loss of "large fiber" sensory modalities such as vibratory and position sense are the rule. These sensory signs and symptoms on examination are typically overshadowed by the morbidity of weakness, and in some cases do not occur. This may render the differential diagnosis from polio challenging. Electrodiagnosis is predictably quite helpful, as GBS is associated with features of demyelination and abnormalities of sensory nerve action potentials in many although not all cases. The CSF examination in GBS unassociated with HIV infection typically demonstrates elevated protein levels without the associated pleocytosis that is typical of polio and other enteroviral infections.

Transverse myelitis is a myelopathic syndrome with multiple causes. Most cases are thought to be infectious or postinfectious in nature, associated with a wide range of viral and nonviral agents. Transverse myelitis may also occur in the setting of inflammatory diseases either confined to the central nervous system (e.g., multiple sclerosis and neuromyelitis optica) or systemic (e.g., paraneoplasia and connective tissue disease) in nature. Clinically, transverse myelitis affects most, if not all, descending and ascending pathways in the spinal cord at the involved level(s), producing a sensory level in addition to an acute para- or quadriparesis. MR imaging in transverse myelitis would be expected to acutely demonstrate a swollen and expanded spinal cord with increased T2 signal in the involved segments.

Botulism is a presynaptic disorder of neuromuscular transmission causing weakness of limb and bulbar muscles. It can adversely affect both nicotinic and muscarinic cholinergic receptors. As a result, patients not only experience somatic weakness but often develop symptoms of cholinergic dysautonomia as well. These may include nonreactive pupils with associated visual blurring or photophobia, constipation, urinary retention, or sicca symptoms of the mouth and eyes. Weakness is typically areflexic, generalized, and symmetric, with a strong predilection for cranial-innervated musculature. Dysarthria, dysphonia, dysphagia, and facial weakness are often prominent. Unlike polio, diplopia and ophthalmoparesis occur frequently. Another clue that might prompt consideration of botulism is the context in which it occurs. Infantile botulism typically occurs between 3 and 6 months of age. Wound botulism may be traced to a dirty puncture wound or associated with subcutaneous injection of recreational drugs. Adult food-borne botulism typically occurs in the setting of improperly canned foods.

Botulism has a fairly characteristic electrodiagnostic signature, which is a pattern that correlates with presynaptic disorders of neuromuscular transmission. This would include normal sensory nerve action potentials and diffusely low-amplitude compound muscle action potentials that increment (increase in amplitude) in response to brief (10 seconds) periods of exercise or fast (5–50 Hz) repetitive stimulation. Definitive diagnosis is based on isolation of the toxin from stool, serum, or ingested food or culture from patient wound, stool, or food ingested by the patient. None of these assays has 100% sensitivity.

Rabies victims may present with a paralytic rather than encephalopathic illness and do so in approximately 20% of cases.[30] Prodromal symptoms are nonspecific and include fever, chills, fatigue, malaise, anorexia, irritability, and insomnia. The paralysis typically begins in the bitten extremity. Pain, sensory symptoms, genitourinary, and bulbar involvement may occur. Hydrophobia, the classical feature of "furious" rabies, is uncommon in the this form of the disease. The diagnosis is clinical and is based on a history of animal bite, typically within 1–3 months of symptom onset, in an endemic area. Paralytic rabies may be confused with axonal forms of GBS.[31]

An acute–subacute motor predominant polyneuropathy is a common manifestation of certain forms of porphyria. Proximal muscles may be preferentially weakened. Although usually symmetric in distribution, the weakness may rarely be asymmetric or focal, making the distinction from polio more challenging. Cranial muscles, even extraocular muscles, may be affected. The initial symptoms are often that of abdominal pain, presumably due to an associated autonomic neuropathy. The latter may be a prominent or even lethal (cardiac arrhythmia) feature of the illness. An encephalopathic and/or psychotic component may be the prominent feature. Despite the motor predominance of the phenotype, the electrodiagnostic examination demonstrates an axonal neuropathy pattern that affects sensory as well as motor fibers. Definitive diagnosis is dependent on elevation of one or more byproducts of heme metabolism detected in urine specimens. Despite autosomal-dominant inheritance, variable penetrance may obscure the familial nature of the illness.

Fever, back pain, and an acute flaccid paraparesis or quadriparesis are signs and symptoms that polio and spinal epidural abscess may share in common. Sensory involvement, particularly a sensory level, would be a characteristic and distinguishing feature of an epidural abscess. As a result of its relatively acute nature, the paralysis is initially flaccid rather than spastic, as might be anticipated from the usual myelopathic location of the disease. The diagnosis is based on imaging, supported by documentation of bacteremia.

Hypokalemia and hypophosphatemia are two electrolyte disturbances that are capable of producing acute, generalized weakness. An infectious prodrome would not be expected. Paralysis induced by hypokalemia is usually generalized or proximally predominant and typically spares cranial musculature with the potential exception of neck flexors and extensors. There are no

sensory symptoms. The serum potassium level is typically less than 2 meq/L when weakness develops. Hypophosphatemic paralysis typically occurs when the serum level is less than 1 mmol/L. The pattern is strikingly similar to GBS with a motor predominant neuropathy, which may be severe enough to produce ventilatory failure. Diagnosis is based on demonstration of serum levels and response to treatment. Electrocardiographic features of hypokalemia are supportive of this disorder.

The differential diagnosis of PPS includes any disorder that can produce slowly progressive weakness, fatigue, or myalgia in an older population. As emphasized by many authors,[5,32,33] the development of these symptoms in a postpolio population is more likely related to an unrelated illness than to the polio itself. Sleep disorders, spondylosis, malignancy, and endocrine disorders such as hypothyroidism and cardiopulmonary disease represent just a few of these considerations.

▶ TREATMENT

In 1954, a parenterally delivered, inactivated polio vaccine was introduced. Although effective, the immunity it confers extends to no more than 10 years with a single injection. In 1961, the orally delivered attenuated live virus vaccine was introduced and initially became the vaccine of choice in most situations. It confers lifetime immunity. Since 2000, there has been a return to the use of inactivated vaccine, due to the small but significant risk of vaccine-initiated disease. Currently, CDC recommendations call for four doses of the inactivated vaccine.

The efficacy of the vaccine is unquestioned with an approximated 95% efficacy rate against the paralytic form of the disease, when administered in full dose. In 1952, the incidence of paralytic disease was 13.7 cases per 100,000. In 1981, this number was reduced to 0.003. There have been no cases of vaccine-induced disease in the United States since 2000 when the current center for disease control (CDC) recommendations were initiated.

Symptomatic treatment of polio and PPS primarily addresses the direct and indirect consequences of muscle weakness. The goals should be to maximize a patient's safe and independent function and mobility and to minimize risk of future orthopedic injury. During the peak of the polio epidemics of the mid-twentieth century, surgical procedures such as tendon transfers and joint fusions were used in an attempt to restore function (e.g., posterior tibial tendon transfer to improve foot dorsiflexion) or to provide joint stability.

Ankle–foot orthoses are commonly used in individuals with foot dorsiflexor weakness, to diminish the risk of tripping and unwanted falls. Long-leg braces or knee–ankle–foot orthoses are more problematic. These are most readily applicable to patients having polio and others whose weakness is chronic and stable. These are used for patients with significant quadriceps weakness in an attempt to provide knee stability. Their drawback is that these add weight to an already weak extremity. These also impair patients' ability to control their falls, thereby adding to the risk of injury.

Patients may also benefit from canes, walkers, manual wheelchairs, motorized wheelchairs, and scooters. The appropriate choice is determined by a number of factors. Canes are most appropriate in an individual whose weakness is primarily in one leg. Walkers or crutches may be more appropriate for individuals with bilateral leg weakness who can still support their weight and who have normal or near-normal arm strength. Manual wheelchairs are best suited for those individuals who can no longer weight bear but who have the arm strength to self-propel a wheelchair. Motorized scooters require adequate strength of trunk muscles for the patient to support themselves in an upright position as well as adequate upper extremity function to allow operation of the controls. Motorized chairs offer more trunk support and require less upper extremity function to operate a typical joystick control.

Ventilatory support in the form of the "iron lung" and other negative pressure devices was used on a widespread basis during the polio epidemics. Ventilatory muscle function, like limb muscle strength, typically improves in the months after acute poliomyelitis. Consequently, in the unlikely event that a physician would encounter a case of acute polio associated with ventilatory failure, positive pressure ventilation would be recommended. A more likely scenario would be the patient with PPS who develops late symptoms of ventilatory insufficiency. In this setting, noninvasive positive pressure ventilation would be recommended. Should it become evident that an acute polio victim, or a patient with PPS, has become ventilator dependent, the decisions, from medical, financial, and ethical perspectives, become more complex. Discussion of this complex issue is beyond the scope of this chapter.

The role of exercise in chronic neuromuscular disease remains a matter of controversy. In general, low-level, aerobic, and conditioning exercise is felt to convey more benefit than harm. There are at least nine studies that support this contention in the postpolio population.[7]

▶ SUMMARY

Although poliomyelitis is and will hopefully remain a disease of largely historical interest, physicians remain responsible for the care of many of the disease's victims. In addition, other less prevalent virions have the same apparent affinity for anterior horn cells and the capability of producing an identical or near-identical acute poliomyelitis phenotype. As a result, neurologists should

remain aware of both the acute and the chronic features of these illnesses.

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CHAPTER 8

Neural Disorders of Skeletal Muscle Overactivity: Cramps and Fasciculations, Neuromyotonia, Tetanus, Tetany, Satayoshi, and Stiff-Person Syndrome

▶ INTRODUCTION

Complaints of muscle pain and stiffness are a common and confounding occurrence in the practice of medicine. Muscle cramping, tenderness, involuntary limb movement and posturing, fatigue, and exercise intolerance frequently occur in unison. Conceptualization of the disorders that produce these symptoms is difficult for a number of reasons. Most of these complaints are nonspecific, defining neither disease locus, pathogenetic mechanism nor etiology. The principles of neurological localization are difficult to apply to these disorders. Distinction between intracranial, spinal, neuronal cell body, axon, or muscle as the site of symptom origin is not readily accomplished through assimilation and formulation of clinical clues. Despite extensive evaluation, a large proportion of these individuals with symptoms referable to muscle discomfort and undesired muscle activity defy diagnosis.

Some of the disorders that present with ill-timed, excessive, and unwanted muscle activity not of neural origin are addressed in other chapters of this book. Disorders of muscle producing physiologic contracture, myotonia, and "rippling muscle disease" are considered in Chapters 24, 26, and 29. Spasticity as the primary manifestation of corticospinal tract pathology is touched upon briefly in Chapters 4 and 5, devoted to the discussion of ALS and hereditary spastic paraparesis. Disorders of abnormal muscle posture and tone related to disorders of extrapyramidal system are not considered in this text.

This chapter is devoted to disorders of diverse cause that have the shared characteristic of unwanted muscular activity due to altered function of motor axons or their cell bodies. The discussion will include cramps, which are commonplace and associated with either benign or sinister implication. The cramp–fasciculation syndrome may represent an intermediate disorder between muscle cramps and neuromyotonia. Although initiated by different mechanisms, tetanus and stiff-person syndrome (SPS) share a common pathophysiology, that being impaired function of inhibitory spinal motor interneurons resulting in motor neuron hyperactivity. As such, these are considered here, along with cramps, in the section on motor neuron diseases. Neuromyotonia, also known as Isaac syndrome (IS), is considered to be a disorder of peripheral nerve. In many cases, circulating antibodies specific for voltage-gated potassium channels (VGKCs) can be demonstrated in the serum of patients who are affected, suggesting an autoimmune etiology. Satoyoshi syndrome (SS) is another rare disorder, characterized by painful muscle spasms. Little is known of its pathogenesis, but there is reason to believe that it too is an autoimmune disorder associated with disordered spinal inhibition.

▶ CLINICAL FEATURES

CRAMPS AND FASCICULATIONS

Cramps are sudden, involuntary, and painful shortening of muscle accompanied by a squeezing sensation and visible, palpable muscle hardening. Often, there is associated abnormal posturing of joints. Cramps are relieved by massage or stretching. They have a tendency to recur if the muscle is prematurely returned to its unstretched position. They spontaneously remit within minutes without continued provocation.

Cramps are ubiquitous and are most commonly associated with a benign etiology. Their weekly prevalence in a normal population is estimated at 35%.[1] They occur with greater frequency in the elderly and in pregnant females, as well as in those who have

recently begun unaccustomed exercise. Familial, benign cramp syndromes have been reported. The gastrocnemius/soleus complex is the most common location of benign cramps, particularly in the elderly at night. They are often elicited in the EMG laboratory, while trying to activate the gastrocnemius–soleus complex. Even if benign in etiology, cramps may provide significant morbidity if persistent.

Cramps are less commonly associated with potentially serious neuromuscular pathology. Although they may associate with disorders of any level of the motor unit, their most notorious association is with the motor neuron (i.e., anterior horn cell) diseases. Cramps are common in ALS although are rarely a major complaint or source of morbidity. These are commonly provoked during isometric manual muscle testing in these patients. They occur in other lower motor neuron disorders affecting either anterior horn cells, e.g., Kennedy's disease where these may represent the earliest symptom, or motor axons such as multifocal motor neuropathy.[2–4] Exertional cramping or contracture may occur in muscle disease as well. They occur most commonly with metabolic disorders of muscle associated with disorders of glycogen, lipid, or mitochondrial metabolism. They may represent an uncommon phenotype of the x-linked Becker's muscular dystrophy.[5]

Fasciculations represent the random spontaneous discharge of all muscle fibers belonging to a given motor unit. These may or may not be felt or seen by a patient. As in cramps, these have a frequently benign, although occasionally ominous, etiology. As in cramps, they are more likely to be benign when confined to a singular muscle belly at any given period of time or when they occur in isolation.[6] Cramps and fasciculations together or fasciculations occurring in multiple muscles/limbs simultaneously are disconcerting. Fasciculation potentials represent the electrodiagnostic signature of fasciculations.

The clinical approach to cramps and fasciculations involves identifying other potential clues of an underlying disease. Chronological association with a new drug exposure or any potential metabolic disturbance should be sought for (Table 8–1). Cramps occurring in isolation, particularly if isolated to the calf muscles, are frequently benign. Conversely, cramps that are multifocal or occur in association with muscle weakness, atrophy, hypertrophy, muscle rippling, or chronic elevations of resting serum creatine kinase are more likely to represent an expression of an underlying neuromuscular disorder. Electrodiagnosis is frequently used to identify or exclude evidence of an associated neuromuscular disorder.

CRAMP–FASCICULATION SYNDROME

The cramp–fasciculation syndrome has been proposed as a disorder consisting of myalgias, cramps, stiffness, myokymia, fasciculations, and exercise intolerance in otherwise healthy people. Despite the seemingly benign nature of the syndrome, eight of original nine reported cases were vocationally disabled.[7] Its classification remains in flux and its acceptance as a unique syndrome is not universal. It may represent nothing more than a more severe expression of the benign cramps and fasciculations mentioned above. On the opposite extreme, circulating anti-voltage-gated K^+ channel antibodies have been demonstrated in the serum of some patients with this disorder, suggesting that it may be a limited expression of neuromyotonia.[8,9]

▶ TABLE 8–1. DRUGS AND METABOLIC DISTURBANCES THAT PROMOTE MUSCLE CRAMPING

1.	Ethanol
2.	Nifedipine
3.	Cimetidine
4.	Terbutaline
5.	Salbutamol
6.	Clofibrate
7.	Penicillamine
8.	Hypothyroidism
9.	Hypoadrenalism
10.	Cirrhosis
11.	Diuretics
12.	Pregnancy
13.	Uremia/hemodialysis
14.	Intensive exercise/excessive sweating
15.	Diarrhea
16.	Emesis

Adapted with permission from Miller TM, Layzer RB. Muscle cramps. Muscle Nerve 2005;32:431–442.

NEUROMYOTONIA (ISAAC, SYNDROME OF CONTINUOUS MUSCLE FIBER ACTIVITY, IDIOPATHIC GENERALIZED MYOKYMIA)

In 1961, Isaacs described two patients with a history of progressive muscle stiffness associated with continuous muscle fiber activity.[10] This syndrome has been referred to by a number of names including IS, the syndrome of continuous muscle fiber activity, generalized myokymia, and acquired neuromyotonia. Generalized myokymia term emphasizes both the neural origin of the abnormality and the pseudomyotonic muscle contraction that differentiates it from clinical myokymia. The latter refers to a phenotype in which undulating waves of muscular rippling without the stiffness, contraction, and occasional abnormal posturing that help define the clinical syndrome of neuromyotonia.[8,11,12] Clinical manifestations of IS include a combination of diffuse muscle stiffness, widespread and continuous muscle twitching (clinical myokymia), and cramps.[13] Abnormal posturing may occur including carpopedal spasm, plantar flexion

of the feet, enhanced spinal curvature, facial grimacing, and flexion of the elbows, wrists, hips, and knees.[14] The excessive muscular activity may be either focal or generalized. Unlike SPS, the excessive muscular activity has a predilection for distal rather than axial and proximal muscles, is not particularly painful, and persists during sleep. On occasion, acquired neuromyotonia may present as a strikingly focal disorder.[15,16] The muscle stiffness worsens with voluntary activity of the affected body segment, and patients may experience difficulty relaxing muscles following maximal contraction, i.e., the aforementioned pseudomyotonia.

IS may affect the central nervous system manifesting as confusion, hallucinations, or insomnia.[12,17–20] Neuromyotonia with an associated encephalopathy was first described by Morvan as fibrillary chorea but is now preferentially referred to as Morvan syndrome. Dyspnea may occur due to involvement of the respiratory muscles. Talking (hoarseness), eating, and swallowing may be affected. The patients also develop excessive sweating, most likely due to muscle activity, with a constant feeling of excessive warmth. Affected individuals may lose considerable weight during the course of the illness, potentially attributable to both increased caloric expenditure and decreased caloric intake. Ocular neuromyotonia has been implicated as a cause of intermittent, spasmodic diplopia, occurring either spontaneously or in response to sustained eccentric gaze.[21–23] This may occur either as a component of the generalized syndrome or as an isolated event following parasellar radiation. Genitourinary complaints are rare. Nonspecific complaints of numbness and paresthesia, may represent either an associated peripheral neuropathy or an analogous overactivity of sensory nerves. The latter concept is supported by microneurographic recordings demonstrating the same spontaneous activity of sensory axons that occurs in their motor counterparts.[24]

Physical examination of the IS patient generally reveals a somewhat stiff posture with slight trunk flexion, shoulder elevation and abduction, and elbow flexion.[14] Widespread fasciculations and myokymia are seen and appear as a continuous undulating or quivering of the underlying muscles.[25] Myokymia is particularly prominent in the facial, pectoral, and calf muscles following attempts at strong muscle contraction. Delayed relaxation of eye or hand opening following forceful eye closure or a strong grip (pseudomyotonia) may be demonstrable. Sensation is normal unless there is an underlying demyelinating or axonal neuropathy, in which case there may also be varying degrees of weakness as well as sensory loss. Muscle stretch reflexes can be normal or reduced.[26,27] Plantar responses are normal. Chvostek's and Trousseau's signs may be appreciated despite normal calcium levels.[24,28]

Affected individuals are typically adolescent or adult, although a newborn case has been reported.[29] Most patients develop this disease sporadically. Several families with apparent autosomal-dominant inheritance have been reported.[30] Disease associations include a number of neoplasms and autoimmune diseases (see "Pathogenesis" section below).

SATOYOSHI SYNDROME

SS was initially described as a progressive, presumed autoimmune disorder of adolescents.[31] It is a rare disorder, which is twice as common in females as in males. Although cases of it have been reported worldwide, its greatest prevalence appears to be in the Japanese.[32] It is characterized by painful muscle spasms of the extremities, typically beginning in the legs, progressing to involve the trunk, neck, and masticatory muscles. The spasms typically last for a few minutes and recur after short intervals. The commonly result in distortions of posture. SS is also associated with alopecia, diarrhea, and various endocrine abnormalities including growth retardation and amenorrhea.[33] The latter occur, at least in some cases, as a result of hypergonadotrophic hypogonadism resulting from primary ovarian failure.[32] Cases with restricted patterns of muscle spasm have also been described.[34] SS is also associated with bony deformities, which have been hypothesized to result from the trauma of repeated forceful muscle spasm on developing bone. Adults may be affected.[35] The disorder may be lethal in some cases.

SPS (MOERSCH–WOLTMAN SYNDROME)

Stiff-man syndrome was first described in 1956 by Moersch and Woltman.[36] They elaborated on their experience with 14 patients with a syndrome of fluctuating but progressive muscle rigidity and spasm affecting predominantly the axial musculature. Although many continue to refer to it by the original designation of stiff-man syndrome, others, particularly in consideration of its increased prevalence in women,[37] have referred to it by the gender neutral designation (SPS).[38]

SPS is typically diagnosed in middle age. Women are twice as likely as men to have antibodies directed against glutamic acid decarboxylase (GAD). Diagnosis occurs on average of 6 years after recognition of the original symptom.[37] All individuals with SPS develop the insidious onset of muscle stiffness, frequently associated with extremely painful muscle spasms that commonly occur in response to movement, tactile, emotional, or auditory stimuli.[39] The rigidity and spasm of SPS concomitantly affect agonist and antagonist muscles. The spasms are typically relieved by general anesthesia, neuromuscular blocking agents, and sleep, although the latter is by no means absolute. During paroxysms, associated features of dysautonomia may occur, including diaphoresis, hypertension, tachycardia, tachypnea,

and pupillary dilatation.[38] Rarely, the dysautonomia may result in sudden death.[40,41] The spasms may be powerful enough to produce osseous fracture, joint dislocation, or rhabdomyolysis and may mimic the opisthotonic posturing of tetanus.[40] Associated dysphoria, anxiety, phobias, and depression have been frequently reported. This coupled with occasional unusual disease manifestations, e.g., pelvic thrusting as a manifestation of axial muscle spasm, may lead to an erroneous diagnosis of hysteria. Current thinking holds that behavioral anomalies in this disorder represent an understandable reaction to the illness rather than an associated encephalopathic feature.[42]

Nonetheless, the clinical manifestations of SPS are to some extent heterogeneous.[37,43] In the classic form of the disease, the disorder begins in and most severely affects the lower axial muscles. Paraspinal and abdominal wall spasm and rigidity promote hyperlordotic posturing of the lumbar spine, which is arguably the most helpful clinical finding. Flexibility and mobility are consequently impaired. Measuring the distance between fingertips and toes with attempted forward flexion is one means of measuring disease response to treatment. Other symptoms attributed to trunkal rigidity include symptoms of ventilatory insufficiency (dyspnea on exertion and exercise intolerance) and impaired gastric distention (early satiety). Facial involvement resulting in facial masking has been described in some cases, leading to the erroneous diagnosis of Parkinson's disease.[37] Impairment of ocular motility has rarely been described, which may or may not indicate concomitant myasthenia gravis.[40] Clinical features that should dissuade a clinician from the diagnosis of SPS would include significant extrapyramidal, lower motor neuron, sensory, or cognitive impairments.

Progressive encephalomyelitis with rigidity and myoclonus or "jerking SPS" is arguably the most malignant phenotype of the disease.[43–46] Axial and lower extremity stiffness and spasm evolve into a more widespread central nervous system disorder.[23,47] Associated features include myoclonus, nystagmus, opsoclonus, and other forms of impaired ocular motility, dysarthria, and dysphagia. Patients may have hyperactive deep tendon reflexes to the extent that a pyramidal tract disorder may be suspected. Sustained clonus and extensor plantar responses can occur.[41] Seizures may occur in up to 10% of cases. The course is relentless. Death may occur within weeks to months of onset.

On the opposite end of the spectrum, SPS may begin with focal involvement of a single limb (stiff limb syndrome).[43,48–50] It may or may not progress into a more generalized or even encephalomyelitic disorder. If the phenotype remains focal, SPS may not be readily suspected. The differential diagnosis may overlap considerably with other noncompressive myelopathic disorders. Fortunately, many of these patients are seropositive for GAD antibodies, making the diagnosis easier if clinically suspected.

SPS is associated with malignancy in 5% of individuals. Patients with paraneoplastic SPS may have a preferential involvement of the upper extremities. Muscles in the lower extremities and those innervated by cranial nerves are relatively spared. Related malignancies include Hodgkin's disease, thymoma, colon, breast, and small-cell carcinoma of the lung.[51–56,57]

As in other disorders of autoimmunity, patients with SPS appear to have an increased incidence of concomitant immune-mediated disorders both within and outside of the nervous system. This is particularly true in those who possess GAD antibodies. The prevalence of these comorbidities may be as high as 80%. Encephalomyelitis, which may include seizures (10%) or a cerebellar syndrome, and myasthenia gravis have been reported in addition to systemic disorders such as hypo- and hyperthyroidism, pernicious anemia, celiac disease, adrenal insufficiency, systemic lupus erythematosis, rheumatoid arthritis, ovarian failure, and vitiligo.[37,40,58,59] Diabetes mellitus is particularly prevalent and may exist in up to 70% of patients with SPS.[60]

TETANUS

Tetanus is a painful disorder of sustained muscle rigidity with superimposed painful spasms. It is usually, but not always, associated with a recognized penetrating wound, resulting in inoculation with the anaerobic organism *Clostridium tetanus*. The incubation period between spore deposition and symptom onset is quite variable, ranging from hours to 2 months with a mean of 8 days.[61] The majority of those afflicted become symptomatic within 30 days of exposure. Disease progression typically lasts 10–14 days. A shorter duration between exposure and symptom onset portends the development of severe disease with intense spasms and bulbar symptoms. If the patient survives, recovery typically begins in approximately 1 month.[61]

The clinical manifestations of tetanus depend, in large part, on the wound site, the extent of toxin spread, as well as the patient's premorbid immunization status. In generalized tetanus, the initial symptoms may be nonspecific, including irritability, akasthesia, diaphoresis, and tachycardia. The predominant, if not most distinctive, symptom of tetanus is painful muscle stiffness. More often than not, it begins in the paraspinal and masseter muscles, leading in the latter to one of its most notorious manifestations, trismus or "lockjaw." Involvement of facial muscles produces a characteristic facial posture known as risus sardonicus (Fig. 8–1), resulting from contraction of the muscles that straighten the normal bowed appearance of the upper lip. Masseter spasm may also result from tactile stimulation of the posterior pharyngeal wall. This reflex is thought to represent both a sensitive and a specific bedside test for tetanus.

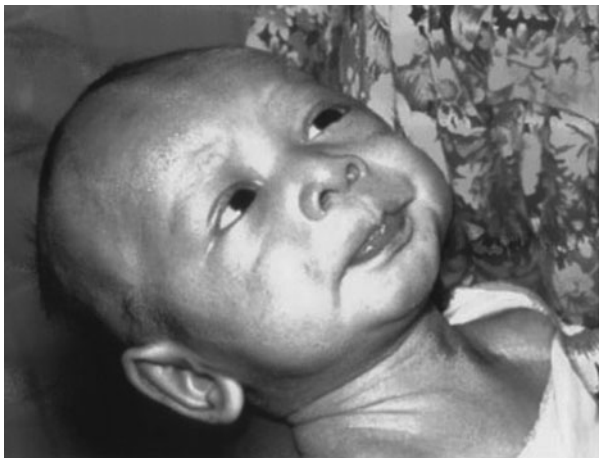

Figure 8–1. Risus sardonicus in infantile tetanus. (Photograph reproduced with permission from the Immunization Action Coalition, St. Paul, MN.)

Cranial, trunk, and limb muscles are usually affected in that order presumably due to nerve length and the retrograde transport of the neurotoxin. Tetanus may begin and remain local in proximity to the wound site producing "local" or "cephalic" tetanus. These are artificial distinctions as the majority of these patients will progress to a generalized form of the disease. If the disease remains localized, diagnosis may be difficult. For example, localized tetanus may mimic an acute abdomen or one or more cranial nerve palsies. In the latter instance, evidence of impaired function due to muscle overactivity rather than underactivity provides a valuable clue, as does involvement of the autonomic nervous system (pupils) and the extraocular muscles.

In generalized tetanus, rigidity of the abdominal and back muscles may contribute to ventilatory insufficiency. In severe cases, violent stimulus-induced spasms occur, leading to opisthotonus, a dramatic overarching of the back resulting in body contact at the head, shoulders, and heels along with a fisted posture of the hands (Fig. 8–2). The spasms are often triggered by an emotional or sensory stimulus, or by attempted patient movement. Spasms of the bulbar muscles may preclude effective speech and swallowing and may contribute to impaired ventilation through a laryngospastic mechanism. Dysautonomia, primarily expressing itself through excessive adrenergic influence, manifests as hypertensive crises, arrhythmia, and hyperhydrosis. Prominent sialorrhea can further compromise the airway. Fever is a frequent accompaniment. Alteration of consciousness, if it occurs, represents an indirect effect of hypoxia. The sensorium, if accessible, remains clear. The tetanus toxin (tetanospasmin) does not cause permanent neurologic injury. Complete recovery may occur if the patient can be spared from significant hypoxia and other secondary consequences of the disease.

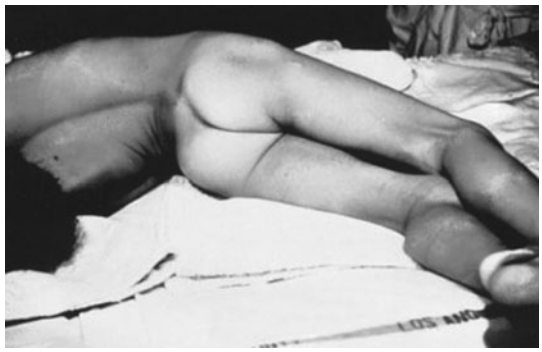

Figure 8–2. Opisthotonus. (Photograph reproduced with permission from the Immunization Action Coalition, St. Paul, MN.)

Uncommonly, tetanus may result from anaerobic infection of the middle ear or paranasal sinuses. This may result in "local" tetanus, producing trismus as well as motor cranial nerve dysfunction including ophthalmoparesis. Tetanus may also proliferate in the uterus and represents a feared complication of instrumentation during parturition or abortion in nonhygienic facilities.

Neonatal tetanus is predominantly a disease of underdeveloped countries. The typical pathogenesis is umbilical stump infection in a child born of an unimmunized mother. Local customs that include application of substances to the umbilical stump, which unknowingly harbor spores, may contribute to risk of the disease. Symptom onset is typically within the first 2 weeks of life, manifesting as a poorly feeding infant with prominent muscle twitching. Changes in cranial musculature provide valuable clues. The jaw may clamp tight on a finger placed in the mouth. The upper lip stiffens, the eyelids are closed tightly, and the forehead is continuously wrinkled. Mortality in neonatal tetanus is high. Neonatal tetanus accounted for two-thirds of the 300,000 deaths attributed to tetanus worldwide in the year 2000.[62]

TETANY

Tetany is a disorder of neural hyperexcitability provoked by hypocalcemia or alkalosis. Its prevalence has decreased in comparison to historical estimates when vitamin D deficiency was more commonplace. The syndrome is characterized by the development of paresthesias, which initially occur in the digits and in a circumoral distribution. This is followed by spasmodic muscle contraction of muscle that provokes the characteristic extremity posturing, which includes thumb and finger adduction as well as digital flexion at the metacarpal–phalangeal joints. Unlike tetanus, the effects of tetany are more pronounced in limb as opposed to cranial and axial muscles. This posturing may be elicited in hypocalcemic patients by inflating a blood pressure cuff to greater than systolic blood pressure for ≤3 minutes (Trousseau's

sign). Alternatively, spasm of facial muscles may be provoked in hypocalcemic patients by digital percussion of the facial nerve at the angle of the jaw (Chvostek's sign). Lower extremity posturing in tetany includes toe and ankle flexion as well as ankle inversion (equinovarus). Tetany of the laryngeal muscles may occur in mild cases, whereas involvement of the axial and paraspinal musculature occurs only in severe and protracted involvement.

▶ LABORATORY FEATURES

CRAMPS AND FASCICULATIONS

Electrophysiologically, cramps are associated with the involuntary discharge of multiple, normal-appearing different motor unit action potentials (MUAPs), a.k.a., cramp discharge.[56] Cramps may be clinically indistinguishable from the physiological contractures of metabolic muscle disease but are electrically distinct. Physiologic contracture is defined by muscle hardening and shortening associated with electrical silence. If persistent, cramps may produce an elevation of serum CK, which like any traumatic elevation of CK may take 3–8 days to normalize.[63]

Fasciculation potentials are readily recognized electromyographically by their morphology and firing pattern. These are MUAPs that fire in a singular, random fashion, unlike those that are voluntarily activated, (Fig. 8–3). Distinction between benign and pathological fasciculations and fasciculation potentials is, in large part, determined by the clinical and electrophysiologic company that these keep. Attempts to define the significance of fasciculation potentials by their morphology have been accomplished but are largely of academic interest.[64,65]

The electrodiagnostic findings in the cramp–fasciculation syndrome include fasciculation potentials and cramp discharges. In addition, repetitive stimulation of peripheral nerves led to the development of afterdischarges in some cases in a manner similar to IS. In the cramp–fasciculation syndrome, neuromyotonic, myokymic, and complex repetitive discharges; fibrillation potentials and positive waves; and morphological changes of MUAPs suggesting chronic partial denervation and reinnervation are notable for their absence.[7,66]

ISAACS SYNDROME

In acquired neuromyotonia, radioimmunoassay may identify antibodies directed against VGKCs in the serum and cerebrospinal fluid (CSF).[8,12,67,68] Patients may have other markers of autoimmunity including increased protein, immunoglobulins, and oligoclonal bands within the CSF.[12]

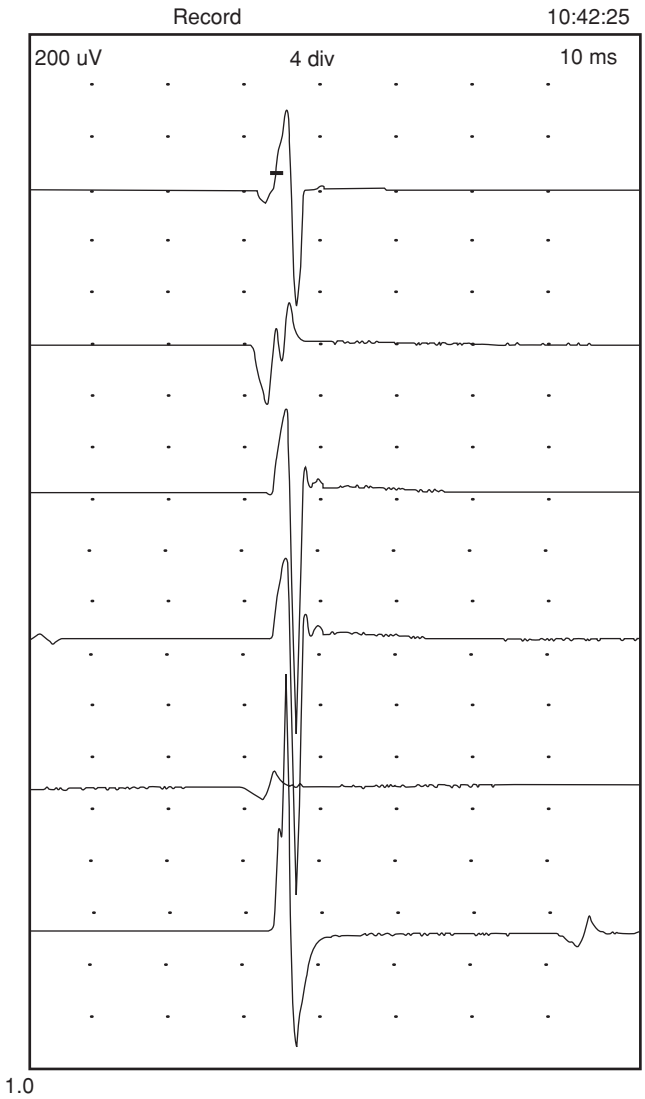

Figure 8–3. Fasciculation potential—single, random, and spontaneous discharges of normal appearing but differing motor unit action potentials.

Motor and sensory NCS are often normal in patients with the idiopathic or familial form of Isaacs' syndrome although may reflect a concomitant polyneuropathy in some patients.[12,14,24,28,69–72] However, if one looks closely or turns up the gain, repetitive afterdischarges are often evident following standard motor conduction and F-wave studies similar to organophosphate poisoning (Fig. 8–4).[30] Microneurographic recordings demonstrate afterdischarges not only in motor nerves but also in sensory nerves.[24]

Neuromyotonic discharges are the defining but not sole electromyographic finding in IS.[73] These discharges occur in the majority of skeletal muscles, including the facial and external ocular muscles.[66] They are very high frequency (200–300 Hz) and therefore high-pitched discharges provoked by needle movement or muscle

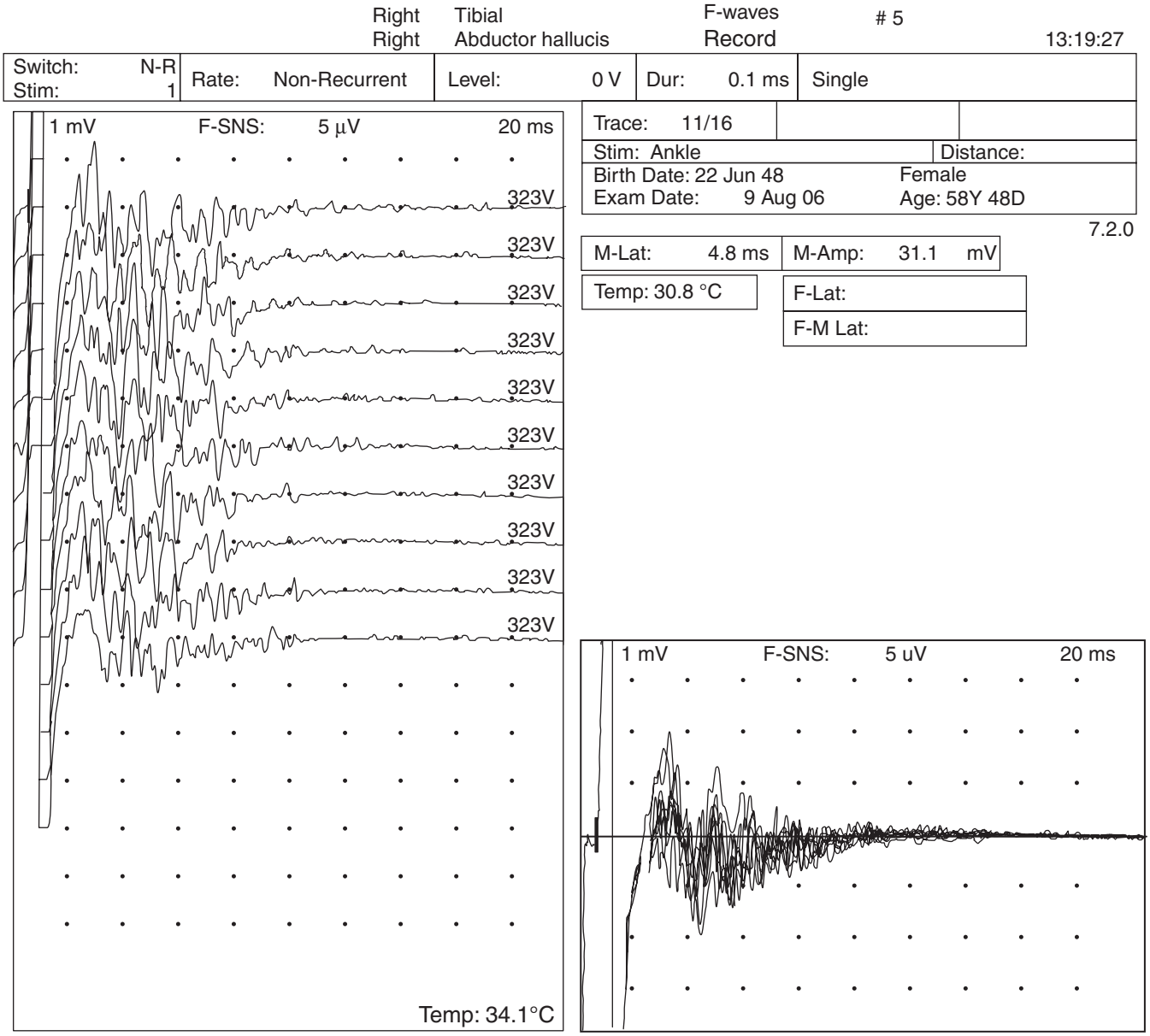

Figure 8–4. Rastered CMAPs from the tibial nerve in response to single stimuli resulting in repetitive afterdischarges. (Reproduced with courtesy permission of Steven Vernino, MD, and Alpa Shah, MD, UT Southwestern Medical Center, Dallas, TX.)

contraction that cannot sustain themselves and rapidly dissipate.[74] They have a typical abrupt onset, with decrescendo pitch and equally abrupt cessation with a duration measured typically in seconds (Fig. 8–5).

Myokymic discharges are even less specific for IS than neuromyotonic discharges but occur more frequently.[14] These are characterized by grouped discharges of a single motor unit that fire spontaneously in bursts with intervening periods of electrical silence (Fig. 8–6). The associated sound has been likened to troops marching in unison. These have interpotential intervals of greater than 10 milliseconds or interburst frequencies of less than 100 Hz. In contrast, neuromyotonic discharges are defined by interpotential intervals in the 2–5 milliseconds range, with interburst frequencies of greater than 150 and up to 500 Hz. These discharges may be triggered by exercise, needle movement, mechanical nerve stimulus, or limb ischemia.

In IS, any combination of individual or grouped discharge waveforms may occur, including fasciculation potentials, doublets, triplets, multiplets, and complex repetitive discharges as well as myokymic and neuromyotomic discharges.[12,70,75] Motor point block or neuromuscular blockade diminishes these neuromyotomic discharges, substantiating the impression that the abnormality arises in the terminal nerve arborization.[12]

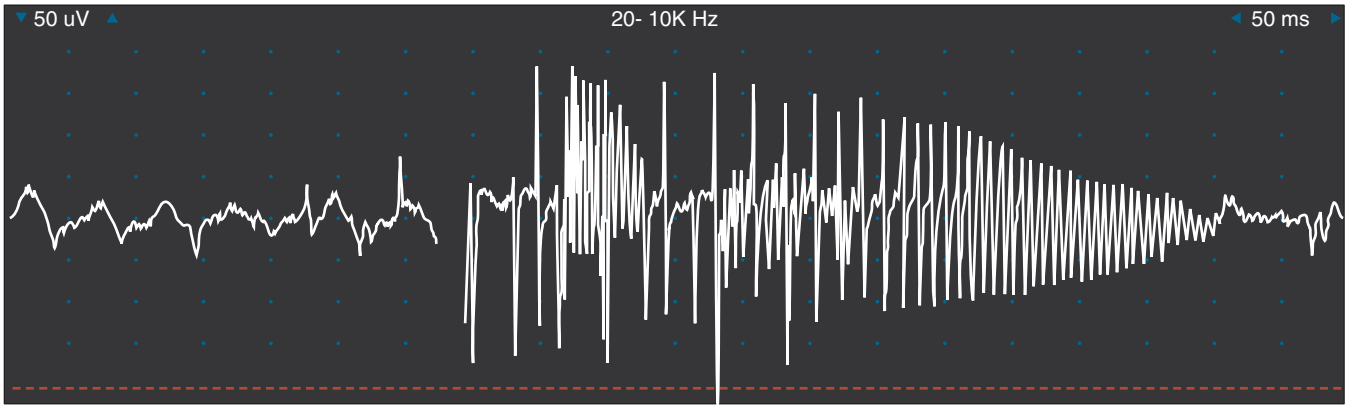

Figure 8–5. Neuromyotonic discharge—abrupt onset, high frequency and high pitched, and rapidly dissipating. (Reproduced with courtesy permission of Devon Rubin, MD, Mayo Clinic, Jacksonville, FL.)

A number of patients have demonstrated a reduction in the muscle fiber activity following peripheral nerve block, suggesting that there may be numerous impulse generators both in the peripheral and central nervous system.[72,76–78]

The involuntary MUAP discharges in IS may well obscure the visualization of voluntarily activated MUPs. If MUAPs can be isolated and visualized, they may have prominent small amplitude and short duration. These potentials may appear morphologically identical to fibrillation potentials with the exception of their firing pattern. These most likely represent single muscle fiber discharges secondary to activation of individual terminal nerve twigs. Additionally, MUAPs may be fragmented as the initiating electrical impulse may originate in the terminal arborization of the nerve and result in the activation of small groups of muscle fibers sequentially, as opposed to the more usual synchronous spread of neural activity from a common peripheral nerve trunk branch point. The net result may be short-duration, small-amplitude MUAPs larger than the single fiber potentials (fibrillation-like potentials) yet smaller than the complete MUAP, thus resembling "myopathic" MUAPs. In the absence of a superimposed peripheral neuropathy, there should be an absence of fibrillation potentials and positive sharp waves.

Both myokymic and neuromyotonic discharges may be associated with the anti-VGKC antibodies in the serum, suggesting that both represent a continuum of a similar pathophysiology.[11] Neuromyotonic discharges are not specific for IS and have been reported in association with myasthenia gravis, amyloidosis, chronic inflammatory demyelinating polyneuropathies, graft vs. host disease, lymphoma, radiation therapy to central and peripheral nervous systems, hereditary neuropathies, pontine demyelination, rattlesnake envenomation, and penicillamine exposure and even in amyotrophic lateral sclerosis.[11,12,14,21,22,24,79,80–84]

SATOYOSHI SYNDROME

In postpubescent young women with SS, female sex hormones may be reduced and gonadotropin

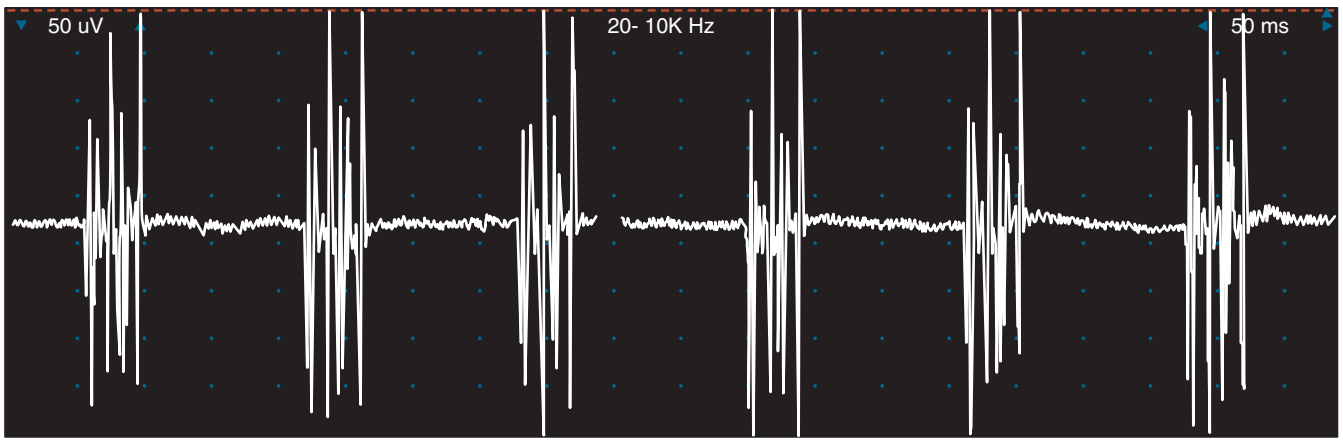

Figure 8–6. Myokymic discharges—semirhythmic-grouped discharges. (Reproduced with courtesy permission of Devon Rubin, MD, Mayo Clinic, Jacksonville, FL.)

levels elevated in keeping with hypergonadotrophic hypogonadism.[32] Although a number of circulating autoantibodies have been anecdotally reported in this disorder, there has been no consistent pattern identified to date.[85,86] Mild elevations of CK may occur, probably resulting from muscle injury as a result of the spasm.[85] Interical, routine EDX studies in Satoyoshi patients are normal. Surface EMG recordings during involuntary muscle contraction reveals high amplitude, synchronous motor unit discharges that are pervasive throughout the entire muscle belly.[87]

STIFF-PERSON SYNDROME

Sixty percent to 80% of SPS cases are associated with high titers of antibodies to the 65 kD isoform of GAD in serum or spinal fluid.[88,89] If only patients with the classic phenotype are considered, the prevalence of anti-GAD antibodies in SPS may exceed 90%.[43] Anti-GAD antibodies are not specific for SPS. They have been identified in individuals with cerebellar ataxia, palatal myoclonus, localization-related epilepsy, and ceroid lipofuschinosis.[40] As in myasthenia gravis, the antibody titers do not correlate with either the severity or the duration of the disease.[90] It is not clear whether titer decline in response to treatment provides a meaningful marker of treatment efficacy.

Individuals with breast cancer may have antibodies directed against a 128 kD protein, called amphiphysin, localized to neuronal synapses.[51,53] SPS associated with other malignancies are typically seronegative to currently recognized antigens. Occasional patients with the encephalomyelitic form of SPS with opsoclonus may have anti-Ri antibodies. Whether anti-GAD and anti-amphiphysin antibodies occur concurrently in the same patient is unknown.

There have been individual case reports linking SPS with antibodies directed against gephyrin and Ri antigens.[91,92] The former is of particular interest, as gephyrin is a protein associated with receptors for two major inhibitory neurotransmitters: glycine and gamma aminobutyric acid (GABA). Additionally, knockout of the gephyrin gene in mice results in an SPS phenotype. Oligoclonal bands in the CSF are common in SPS.[93] Their presence may provide valuable support for the diagnosis of SPS in an individual who does not possess the more specific biomarkers of anti-GAD or amphiphysin antibodies in either serum or their CSF. Other organ-specific autobodies may be found in SPS. Routine testing is not suggested, as these offer little diagnostic specificity for SPS and more likely representative of the underlying autoimmune diathesis. The decision regarding potential evaluation for underlying malignancy should probably depend on the context of the individual patient. A strong family history of breast or ovarian cancer, a strong smoking history, and predominant upper extremity involvement are features that might increase the diagnostic yield of identifying an underlying malignancy.

The role of electrophysiology in SPS is complex. Routine nerve conduction studies are normal. Needle electromyography of symptomatic muscles will reveal the spontaneous discharge of normal-appearing MUAPs, which has neither diagnostic sensitivity nor specificity. More importantly, simultaneous recording from an agonist/antagonist pair may reveal these same morphologically normal MUAPs discharging simultaneously. This should not occur in normal individuals. As this phenomenon can be feigned, it should not be used as the sole basis for diagnosis. Arguably, the greatest value of standard needle electromyography in this patient population is to exclude other waveforms that would not be expected in SPS, including myotonic, myokymic, and neuromyotonic discharges. In addition, electrical silence in the setting of muscle hardening (physiologic contracture) suggesting metabolic muscle disease can be excluded as well.

A number of other electrophysiological techniques not routinely applied in clinical settings may demonstrate hyperexcitability of the reflex arc in SPS. Vibration-induced inhibition of H reflexes is a GABAergic phenomenon that may be suppressed in SPS. Exteroceptive reflexes such as the blink reflex may be enhanced in SPS, leading to recruitment of muscles not typically activated by the stimulation paradigms used. Excessive muscle activation in response to auditory stimuli (startle response) both in degree and in distribution can be recorded in SPS.[40] With the blink reflex, it may be possible to demonstrate a contralateral R1 response.

Experimentally, magnetic resonance spectroscopy has been reported to demonstrate reduced GABA levels in both the sensorimotor and the posterior occipital cortices.[94,95]

TETANUS

The diagnosis of tetanus is made clinically, based on the appropriate phenotype occurring in the context of an inadequately immunized individual. A history of a dirty wound within the last month increases the index of suspicion but may not be available in some cases. It is estimated that *Clostridium tetani* can be cultured from wounds in a third of cases but usually only if deep necrotic tissue is harvested. There are no effective bioassays for the tetanus toxin either in blood or in CSF. Elevated levels of CSF protein and immunoglobulins may occur but are nonspecific and of little clinical value. In the same nonspecific vein, electromyography will demonstrate continuous firing of motor units of normal morphology in affected agonist and antagonist muscles. Inappropriate secretion of antidiuretic hormone, rhabdomyolytic renal failure, and spinal compression fracture are all secondary complications of the disorder

that should be considered and tested for in the appropriate clinical context. Numerous attempts have been made to identify a characteristic electrodiagnostic signature for tetanus, including measurement of silent periods and single fiber electromyographic measurements intended to identify disordered neuromuscular transmission. None appears to have adequate specificity or sensitivity for practical clinical application. Normal-appearing MUAPs appearing simultaneously and continuously in agonist and antagonist muscles are characteristic but not pathognomonic.

TETANY

A diagnosis of tetany can be supported by a reduced level of serum-ionized calcium with or without a reduced serum 25 hydroxy-vitamin D level. Tetany induced by hyperventilation will be associated with an arterial blood gas pattern consistent with acute respiratory alkalosis, i.e., a reduced PCO_2 and elevated pH. The electrodiagnostic signature of tetany is spontaneous grouped discharges of normal-appearing, single MUAPs (doublets, triplets, and multiplets).

HISTOPATHOLOGY

In general, tissue biopsy has a limited diagnostic role in disorders discussed in this chapter. Some insight into the pathogenesis of these disorders has been gained by postmortem analysis. Patients with the cramp–fasciculation syndrome may have features of neurogenic atrophy with muscle biopsy.[7] As neurogenic atrophy can be accurately and less invasively be predicted by electromyographic examination, and as the histological features do not identify etiology, muscle biopsy is rarely performed. In neuromyotonia, sural nerve biopsies may be normal, revealing a reduction in myelinated fibers or demyelination.[24] Grouped atrophy and fiber-type grouping suggesting denervation with subsequent reinnervation may be appreciated on muscle biopsy.[28,77,96,97] Histologic findings in SPS are limited and inconsistent. Postmortem examination may reveal loss of anterior horn cells, interneurons, and small alpha and gamma motor neurons within the spinal cord. In addition, there may be perivascular inflammation in the cord and, in the encephalomyelitic or progressive encephalomyelitis with rigidity and myoclonus variant, similar inflammation within the brain and brainstem as well.[40]

▶ PATHOGENESIS

CRAMPS AND FASCICULATIONS

The weight of experimental evidence supports a neurogenic origin for both cramps and fasciculations. Specifically, the generator appears to be located within distal nerve terminals. There are many lines of evidence in support of this.[6] Cramps usually occur in a single muscle at any given time, making an anterior horn cell or CNS generator unlikely. In normal humans, cramps can be provoked by repetitive stimulation of motor nerves distal to a complete, pharmacologically induced nerve block.[98]

ISAACS SYNDROME

In many if not most cases, IS appears to be an autoimmune, occasionally paraneoplastic disorder.[12,68,99] If sensitive immunostaining techniques are used, such as those capable of binding to individual subunits of potassium subunits in *Xenopus* oocytes, a large proportion of IS and approximately half of the patients with Morvan syndrome will be found to have anti-VGKC antibodies.[42,100] Divalent VGKC antibodies appear to accelerate and degrade potassium channels by a cross-linking mechanism independent of complement.[101] Experimental passive transfer of serum from patients with acquired neuromyotonia into mice results in resistance of ex vivo phrenic nerve-diaphragm preparations to D-tubocurarine.[102] Other passive transfer experiments demonstrated increased quantal content and repetitive firing of dorsal root ganglia cells in mice injected with sera from patients with Isaacs' syndrome compared to normal control sera.[68] Immunoglobulins from patients with Isaacs' syndrome suppress outward-bound currents at VGKCs but have no effect on their inward-bound sodium channel currents.[103] Blocking these VGKC reduces the hyperpolarizing influence of the channel on the axonal membrane, leading to hyperexcitability of the neurons.[83]

IS has been reported to occur in association with small-cell carcinoma of the lung, thymoma, plasmacytoma, and Hodgkin's disease.[12,26,57,104–106] IS may also associate with other autoimmune disorders, including myasthenia, systemic lupus, and celiac disease.[12,19,52,55,107–111] Responsiveness to immunomodulating agents lends further support to an immune-mediated pathogenesis.

SATOYOSHI SYNDROME

SS is suspected to have an autoimmune mechanism. The existence of both antiacetylcholine receptor[86] and anti-GAD antibodies[85] have been reported in single cases. As titers of anti-GAD antibodies are frequently markedly elevated in SPS, the significance of low-level titers of these antibodies in this singular observation in SS awaits further clarification.

The pathophysiology of muscle contraction in SS is unknown. It appears to differ from cramps in that surface EMG recordings of motor unit discharges that

are synchronous rather than random and that occur in uniform rather than spreading pattern throughout the muscle belly. 130 rather than

STIFF-PERSON SYNDROME

SPS presumptively occurs on an autoimmune basis. Anti-GAD antibodies have been shown to impair the synthesis of GABA, a major inhibitory neurotransmitter within the central nervous system.[112,113] By doing so, the balance or interneuronal influence on motor neurons is tipped in favor of excitation both in the spinal and in the cortical gray matter. Anti-GAD antibodies may occur in individuals with SPS who have an underlying malignancy. These have been reported in patients having both breast cancer and thymoma.[61,114,115]

Amphiphysin is a 128 kD synaptic membrane protein involved in synaptic-vesicle endocytosis and found in breast cancer cells. Along with GAD, it is the only other protein located on the cytoplasmic surface of synaptic vesicles in nerve terminals that are known targets of CSF autoimmunity.[40] Antiamphiphysin antibodies have been most closely associated with breast cancer-associated SPS.[51,53] These are nonspecific, having been described with other phenotypes and other malignancies but rarely found in males. These may exist in association with other paraneoplastic syndromes including non-SPS encephalomyelitis, limbic encephalitis, cerebellar degeneration, and sensory neuronopathy. These have been found in the sera of individuals harboring thymoma and small-cell lung and ovarian carcinomas.[40] A causal relationship between antiamphiphysin antibodies and SPS is supported by the production of a similar clinical response in animals to whom antiamphiphysin antibodies have been passively transferred.[116] Response to immune-modulating treatment in some cases offers further support for the autoimmune hypothesis in both anti-GAD- and antiamphiphysin-associated SPS.

TETANUS

Tetanus results from infection with *C. tetani*, a gram-positive anaerobic rod. It is commonly introduced by contaminated puncture wounds including parenteral drug abuse. Septic abortion, infected umbilical stumps, burns, and compound fractures provide other common portals of entry. Outside of the human body, the organism is resilient, being able to exist in the spore form for decades. These spores are particularly prevalent in warm, moist soil contaminated by animal fecal material. Germination and proliferation occurs under optimal conditions, including those provided by wounds with tissue necrosis, foreign bodies, tissue ischemia, or ongoing infection with other organisms. The adverse effects of the organism result from the release of the neurotoxin tetanospasmin. The role of a second neurotoxin tetanolysin in clinical tetanus is unknown. Tetanospasmin may have local effects by diffusing to nearby peripheral nerve terminals. Generalized disease results from retrograde axonal transport in motor nerves providing access to the central nervous system as well as by hematogenous dissemination. The early involvement of cranial muscles is presumptively due to their shorter length and early arrival of neurotoxin to brainstem via this retrograde transport mechanism. Transynaptic migration from the perikaryon of motor nerves to presynaptic terminals then allows irreversible binding to the presynaptic inhibitory interneurons in the brainstem and spinal cord. The primary effect is to inhibit release of GABA in the brainstem and glycine in the spinal cord, thereby removing an inhibitory effect on motor nerves from descending cortical and afferent sensory stimuli, thus promoting muscle overactivity. A similar effect on cell bodies in the intermediolateral cell column may promote sympathetic overactivity. The tetanospasmin that gains access to the intermediolateral cell column is thought to travel in an anterograde manner in sensory axons. The early development of dysautonomia may be explained by greater velocity of toxin transport in sensory nerve axons than in their motor analogues. Recovery from tetanus is dependent on the genesis of new presynaptic nerve terminals of inhibitory interneurons.[61,117]

DIFFERENTIAL DIAGNOSIS AND RECOMMENDED EVALUATION (Table 8–2)

Dental infection and paraneoplastic brainstem encephalitis are two considerations in the differential diagnosis of trismus. Drug-induced dystonias frequently affect ocular movements and are often dominated by writhing rather than tonic contraction of muscle. A prompt and dramatic response to anticholinergic drugs can be anticipated. Other extrapyramidal disorders in which dystonia is a prominent feature are typically chronic and result in distorted postures that are recognizably different from those of the disorders described above, e.g., torticollis. Trimus and painful spasms are not typical of most dystonias.

Hyperekplexia is a term derived from the Greek word ekplexis, meaning surprise. It is a familial disorder characterized by an excessive startle response to unanticipated auditory or tactile stimuli. In addition, affected patients experience generalized stiffness during the attack. Hyperekplexia varies in phenotypic severity. It commonly manifests as a neonatal disorder where interrupted breathing and swallowing may be fatal. Nose tapping may produce the characteristic response in an

▶ TABLE 8–2. NON-NEURAL DISORDERS OF SKELETAL MUSCLE OVERACTIVITY NOT CONSIDERED IN THIS CHAPTER

Trismus
Brainstem encephalitis (paraneoplastic)
Dental infection
Movement disorders
Parkinsonian syndromes
Dystonias
Pyramidal tract disorders
Muscle disorders
Neuroleptic malignant syndrome
Malignant hyperthermia
Glycogen storage disease
Lipid storage disease
Myotonic disorders
Rippling muscular disease
Brody disease

affected neonate but should be done cautiously due to the morbidity and occasional mortality it may induce. Affected adults often experience drop attacks as their major manifestation. Autosomal-dominant inheritance is a disorder of the alpha-1 subunit of the glycine receptor gene located on chromosome 5q33–35. The less frequently occurring recessively inherited form of the disease results from mutations of the beta subunit of the same gene. Nonfamilial cases resulting from brainstem pathology have been described. Clonazepam is an effective treatment and is currently the drug of choice. Forced flexion of the head, trunk, hips, and knees may interrupt an attack associated with apnea in a neonate.[118]

Meningoencephalitis may be associated with prominent nuchal and paraspinal rigidity. Associated seizures may further contribute to tonic and phasic increases in trunk and limb tone. Lumbar puncture with CSF examination should be strongly considered in a patient with increased paraspinal tone, fever, and/or altered sensorium occurring in the absence of trismus.

Metabolic muscle disease is characterized by exercise-induced muscle pain and stiffness, with or without associated fixed muscle weakness. Serum CK values are usually strikingly elevated. An initial attack in a previously undiagnosed patient could be potentially confused with tetanus. Significant involvement of cranial and paraspinal muscles would be unlikely in metabolic muscle disease. EMG of a rigid muscle in metabolic muscle disease would demonstrate electrical silence, the hallmark of a physiologic contracture.

Multiple sclerosis is often the initial consideration or even the erroneous diagnosis given to some individuals with SPS. This is particularly likely to occur in a young woman with heightened deep tendon reflexes who has oligoclonal bands within her CSF. SPS should be considered in any individual with upper motor neuron signs, without other clinical features of multiple sclerosis, with normal or near-normal brain and spinal cord imaging.

Neuroleptic malignant syndrome produces profound muscular rigidity and significant dysautonomia. Nonspecific but significant elevations in serum CK values are the rule. A history of exposure to an inciting agent, fever, and altered mental status are the basis for distinction from the majority of disorders discussed in this chapter.

Peritonitis and localized tetanus affecting the abdomen may be confused for each other. The context in which the symptoms have occurred, and the presence or absence of fever and point tenderness may be helpful in distinguishing features.

Rabies needs to be considered in the differential diagnosis of cephalic tetanus when dysphagia is part of the symptom complex. Patients with rabies are frequently encephalopathic, have dysautonomic symptoms that are more likely to be cholinergic in nature (sialorrhea), do not tend to have continuous muscular rigidity, and have a CSF pleocytosis if tested.

Spasticity is never acute, although spasms and involuntary jerking of the extremities may occur. The pattern of increased muscle tone is usually distinctive, affecting flexors in the upper extremities and extensors in the lower extremities preferentially. The limbs are affected more so than the trunk and head in contrast to tetanus. Hyperactive reflexes, sustained clonus, and Babinski signs are frequent signatures of corticospinal tract involvement although are not etiologically specific. Hyperactive deep tendon reflexes and sustained clonus may occur, e.g., in SPS.

Strychnine is a CNS glycine antagonist, used primarily as a rat poison. It impedes postsynaptic inhibition of motor neurons in the spinal cord. The phenotype is almost identical to tetanus other than the absence of trismus and the onset that occurs within minutes to hours of exposure. The diagnosis is dependent on a history of exposure in addition to the expected clinical manifestations. Reflex spasms are superimposed upon tonic rigidity affecting upper extremity flexors, lower extremity extensors, and facial muscles resulting in risus sardonicus. Strychnine assays can be performed by specialized laboratories.

▶ TREATMENT

CRAMPS AND FASCICULATIONS

Treatment of cramps may involve avoidance of offending drugs, ample hydration and electrolyte replacement, prophylactic diurnal stretching, and various pharmacological interventions. These include quinine sulfate, phenytoin, carbamazepine, gabapentin, calcium, magnesium, botulinum toxin, creatine, L-carnitine, verapamil,

baclofen, and vitamin E. Of these, quinine (260 mg), carbamazepine (100–200 mg), phenytoin (100–200 mg), gabapentin (300 mg), and vitamin E (1000 units) have been used most frequently at the starting doses listed.[1] Typically, these agents are dispensed at night, as sleep interruption is the usual period of greatest morbidity. No one of these drugs clearly stands out as the most effective or best tolerated. Any decision to employ pharmacological treatment for cramps has to be tempered with the realization that there is a 40–50% efficacy rate for placebo.[1] Although quinine has been the historical mainstay of treatment for cramps, concerns exist regarding its side-effect profile, which includes cinchonism, visual loss that may be permanent, thrombocytopenia, and interactions with warfarin. In view of these safety concerns, quinine has recently been disapproved by the FDA for any use other than the treatment of malaria.

In patients who are psychologically troubled by an apparent benign fasciculation syndrome, informing them of the natural history data from Mayo Clinic addressing this issue would appear to be helpful in reassuring them that their risk of developing motor neuron disease is negligible.[116]

ISAACS SYNDROME

Various forms of immunotherapy have partial efficacy in patients with IS. Immunomodulating treatments such as plasmapheresis, IVIG, azathioprine, and corticosteroid treatment have all been reported to provide benefit.[12,69,102,120–123] Symptomatic treatment with antiepileptic medications (e.g., phenytoin, carbamazepine, baclofen, mexilitine, and gabapentin) may be useful by blocking sodium channels and decreasing neuronal excitability.[12,30,70,97,124] Symptomatic treatment seems to be most effective when coupled with immunosuppression. As in other autoimmune diseases, patients may seemingly enter a period of protracted remission following treatment or may require prolonged maintenance therapy.

STIFF-PERSON SYNDROME

The treatment of SPS involves the use of both symptomatic agents to enhance GABAergic influences and immunomodulating treatments aimed at suppressing unwanted immune-mediated effects. Many patients will respond to treatment, although complete eradication of symptoms is the exception rather than the rule. Benzodiazepines have been the historical mainstay of symptomatic treatment. Patients often both require and tolerate large doses, with daily doses of up to 100 mg of diazepam being used and tolerated. Baclofen, as a GABA antagonist, is theoretically attractive and has been used both orally and intrathecally. Despite this promise, significant benefit from oral administration is uncommon. A number of anticonvulsants have been tried with anecdotal report of benefit including gabapentin, valproic acid, levetiracetam, vigabatrin, and tiagabin. Botulinum toxin may benefit individual patients as well but is limited by the symptomatic nature of its effects, its cost, and the need for large doses to adequately address large axial muscle groups.

There have been many reports describing anecdotal responses to immunomodulating therapies but a limited evidence basis to judge which, if any, of these treatments is most effective. The largest controlled trial involved 16 patients whose morbidity and anti-GAD antibody titers both seemed to decline with IVIG treatment.[125] Plasma exchange has benefited some patients. There is a case report of a dramatic, protracted response to rituximab.[126] A controlled trial of rituximab is underway, but a recent report of two treated individuals developing progressive multifocal leukoencephalopathy may quell enthusiasm for its use, even if found to be effective. Corticosteroids are less attractive than in other diseases, in view of the high incidence of diabetic comorbidity. As in other paraneoplastic syndromes, successful treatment of the underlying malignancy may lessen the morbidity of the associated SPS. Conversely, the use of immunomodulating agents in paraneoplastic SPS is associated with the theoretical concern that tumor control may be compromised as a result.

SATOYOSHI SYNDROME

In view of its rarity, there is no standardized approach to the treatment of SS. A variety of agents have been used unsuccessfully for the treatment of spasms. Botulinum toxin may be locally effective (e.g., masticatory spasm) but is impractical for widespread application. Carbamazepine was effective in at least one case.[32] Immunomodulation has been used with varying degrees of success, with anecdotal reports of benefit (tacrolimus,[86] corticosteroids,[85,86] intravenous immunoglobulin,[127] and methotrexate[32]) as well as failure with corticosteroids and IVIG.[32]

TETANUS

The primary treatment strategy for tetanus is prevention. Tetanus toxoid was developed in the 1940s. In the United States, five doses of tetanus toxoid is recommended for vaccination at 2, 4, and 6 months of age, as well as at 15–18 months and 4–6 years. Typically, it is combined with pertussis and diphtheria vaccines for the first five doses. Following these initial five doses, pertussis is deleted and tetanus toxoid/diphtheria boosters

are recommended at 10-year intervals. The incidence of tetanus has declined dramatically where vaccination is routinely and completely practiced. In the United States, the incidence is greatest in older individuals, presumably due to the waning effects of childhood vaccination.[61] Although extremely effective, rare individuals may develop tetanus even with a complete and up-to-date tetanus vaccination program and demonstration of preexisting tetanus antibodies.[128] In inadequately immunized individuals with an at-risk tetanus wound, intramuscular injection of 250 units of human tetanus immune globulin is recommended.

With symptomatic tetanus, the goals are to (1) limit further production of tetanospasmin by wound debridement and antimicrobial therapy; (2) neutralize, if possible, the effects of existing, unbound toxin; (3) actively immunize and provide symptomatic treatment of painful spasms, impaired ventilation, and swallowing; and (4) treat symptoms referable to dysautonomia. Patients having tetanus have a frequent need for extended ventilation and nutrition. Attempted manipulation of these patients who are prone to stimulus-induced spasms may be difficult. For these reasons, early placement of a nasogastric or percutaneous feeding tube and tracheostomy should be considered.

Elimination of the toxin source involves removal of any foreign body, debridement of any necrotic tissue, and delivery of antibiotics with anaerobic efficacy. Metronidazole, penicillin, third-generation cephalosporins, clindamycin, or erythromycin are typically administered and appears to reduce the need for muscle relaxants and sedatives. Penicillin G is given in doses ranging from 2 to 10 million units per day. Metronidazole appears to be equally effective and may be preferential in view of penicillin's stimulatory effect on the cortex. The customary dose is 500 mg IV Q6H for 10 days. Neutralization of unbound circulating toxin is attempted with human tetanus immune globulin administered as soon as possible, ideally before the wound is manipulated. The standard dose is 500 units delivered intramuscularly. The benefit of delivering human tetanus immune globulin in proximity to the wound or intrathecally at a dose of 250 units is unknown.[61] Equine-derived tetanus immune globulin may be used if human-derived immune globulin is not available. Infection with *C. tetani* does not stimulate active immunity by the host. For that reason, three doses of tetanus toxoid (with Diphtheria) should be administered immediately and at 2 weeks' intervals in anyone whose vaccination history is suspect.

Symptomatic treatment of spasms is important for patient comfort, to improve ventilation and to prevent thermal and mechanical injury from excessive and sustained muscular contraction. Treatment should be titrated to patient response. Benzodiazepines (up to 80 mg a day of lorazepam), neuromuscular blocking agents, and/or baclofen are most commonly used. Vecuronium at a dose of 6–8 mg/h is preferred over pancuronium, as the latter has catecholamine reuptake-blocking properties that may contribute to autonomic instability. Baclofen may be administer orally or intrathecally. The initial dose is 40–200 μg followed by a continuous infusion of 20 μg/h.[129,130] Meticulous catheter care is required to minimize the risk of meningitis from prolonged intrathecal catheter placement. Labetolol (0.25–1.0 mg/min), morphine (0.5–1.0 mg/kg/h), magnesium sulfate, atropine, clonodine, and epidural bupivicaine have all been used with some degree of reported benefit for hyperadrenergic and other autonomic manifestations.[117] As with all illnesses associated with protracted recovery periods, vigorous supportive care is required to minimize the risk of secondary complications that these patients are susceptible to.

▶ SUMMARY

With the exception of cramps and fasciculations, the disorders described in this chapter are uncommon. Most of these disorders have, to some extent, overlapping clinical features. Successful diagnosis requires a heightened index of clinical suspicion, detailed knowledge concerning each disorder's phenotypic characteristics, and awareness of the serological and electrodiagnostic features of each syndrome. Many of these disorders appear to have an autoimmune pathogenesis, some of which are in turn related to underlying malignancies. No singular treatment paradigm exists for any of these disorders. In many cases, both immunomodulating therapies and symptomatic measures will provide considerable relief from disease morbidity.

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CHAPTER 9

Charcot–Marie–Tooth Disease and Related Disorders

Hereditary neuropathies may account for as many as 50% of previously undiagnosed peripheral neuropathies referred to large neuromuscular centers. Charcot–Marie–Tooth (CMT) disease is the most common type of hereditary neuropathy, but, rather than one disease, CMT is a syndrome of several genetically distinct disorders (Table 9–1). In this chapter, we discuss CMT and related neuropathies. In the subsequent chapters, we will review other less common hereditary neuropathies (Chapters 10 and 14 for familial amyloid polyneuropathy).

The various subtypes of CMT are classified according to the nerve conduction velocities (NCVs) and presumed pathology (e.g., demyelinating or axonal), mode of inheritance (autosomal dominant or X linked), age of onset (e.g., infancy or childhood/adulthood), and the specific mutated genes (Table 9–1).[1–6] Updated information including recent mutations causing CMT can be found on the Internet: http://www.molgen.ua.ac.be/CMTMutations/DataSource/MutByGene.cfm. Type 1 CMT or CMT1 refers to inherited demyelinating motor and sensory neuropathies, while the axonal motor and sensory neuropathies are classified as CMT2. Both CMT1 and CMT2 usually begin in childhood or early adult life; however, onset later in life can occur, particularly in CMT2. Both are typically associated with autosomal-dominant inheritance, with a few exceptions. CMT3 is an autosomal-dominant neuropathy that appears in infancy and is associated with severe demyelination or hypomyelination. CMT4 is an autosomal-recessive motor and sensory neuropathy that typically begins in childhood or early adult life. Unfortunately, classification of these neuropathies is not as straightforward as it may seem. Some neuropathies are associated with nerve conduction studies (NCS) and histopathology that may reflect either a primary demyelinating or an axonal process. Further, there is overlap between CMT and hereditary sensory and autonomic neuropathy (HSAN), hereditary motor neuropathy (distal spinal muscular atrophy), and hereditary spastic paraplegia (Fig. 9–1). There are no medical therapies for any of the CMTs, but physical and occupational therapy can be beneficial as can bracing (e.g., ankle–foot orthotics for foot drop) and other orthotic devices.

▶ CMT DISEASE TYPE 1 (CMT1)

CLINICAL FEATURES

CMT1 is the most common form of hereditary neuropathy, with the ratio of CMT1:CMT2 being approximately 2:1. Individuals with CMT1 usually present in the first to third decades with distal leg weakness, although patients may remain asymptomatic even late in life. There is an early predilection for the anterior compartment (peroneal muscle group), thus resulting in progressive foot drop. This leads to poor clearance of the toes when walking particularly on uneven surfaces. People with CMT1 often present with frequent tripping, falling, and recurrent ankle sprains. Individuals who are affected generally do not complain numbness or tingling, which can be helpful in distinguishing CMT from acquired forms of neuropathy.

Although people with CMT1 usually do not complain of sensory loss, reduced sensation to all modalities is apparent on examination. Muscle stretch reflexes are unobtainable or reduced throughout. There is often atrophy of the muscles below the knee (particularly the anterior compartment), leading to the so-called inverted champagne bottle legs. However, rare individuals have asymmetric pseudohypertrophy of the calves.[7] Most will have pes cavus, equinovarus, or hammertoe deformities (Fig. 9–2), which lead to aching in the feet. Rather than having a heal strike while ambulating affected people land flat-footed or on their toes and thus use a steppage gait to help prevent toes from catching on the ground. Approximately two-thirds of individuals with CMT1 also have distal weakness and atrophy of the arms. Claw–hand deformities of the hands may develop in the most severely affected. Mild-to-moderate proximal weakness can develop over time as well, which can lead to diagnostic confusion with chronic inflammatory demyelinating polyneuropathy. In addition, some individuals manifest with phrenic nerve involvement leading to respiratory weakness.[8] Rarely, patients with hypertrophy of nerve roots can be severe enough such that it leads to compression of the spinal cord or cauda equina. Approximately one-third of patients with CMT1 have an essential tremor (Roussy–Levy syndrome). Hypertrophy

▶ TABLE 9–1. CLASSIFICATION OF CHARCOT–MARIE–TOOTH DISEASE AND RELATED NEUROPATHIES

Name	Inheritance	Gene Location	Gene Product
CMT1			
CMT1A	AD	17p11.2	PMP-22 (usually duplication of gene)
CMT1B	AD	1q21–23	MPZ
CMT1C	AD	16p13.1–p12.3	LITAF
CMT1D	AD	10q21.1–22.1	ERG2
CMT1E (with deafness)	AD	17p11.2	Point mutations in PMP-22 gene
CMT1 F	AD	8p13–21	Neurofilament light chain
CMT1X	X-linked dominant	Xq13	Connexin-32
HNPP	AD	17p11.2	PMP-22
		1q21–23	MPZ
CMT2			
CMT2A1	AD	1p36.2	Microtubule motor kinesin-like protein
CMT2A2 (allelic to HMSN VI with optic atrophy)	AD	1p36.2	MFN2
CMT2B	AD	3q13–q22	RAB7
CMT2B1 (allelic to LGMD 1B)	AR	1q21.2	Lamin A/C
CMT2B2	AD	19q13	?
CMT2C (with vocal cord and diaphragm paralysis)	AD	12q23–24	?
CMT2D (allelic to distal SMA5)	AD	7p14	Glycine tRNA synthetase
CMT2E (allelic to CMT1F)	AD	8p21	Neurofilament light chain
CMT2F	AD	7q11–q21	Heat-shock 27-kDa protein-1
CMT2G (may be allelic to CMT4 H)	AD	12q12–q13	? frabin
CMT2H	AD	8q21.3	? (may be GDAP1)
CMT2I (allelic to CMT1B)	AD	1q22	MPZ
CMT2K (allelic to CMT4A)	AD	8q13–q21	GDAP1
CMT2L (allelic to distal hereditary motor neuropathy type 2)	AD	12q24	Heat-shock protein 8
CMT2X	X-linked	Xq24	?
DI-CMT			
DI-CMTA	AD	10q24.1–q25.1	?
DI-CMTB	AD	19p12–p13.2	Dynamin-2
DI-CMTC	AD	1p34–p35	Tyrosyl-tRNA synthetase
CMT3 (Dejerine–Sottas disease,	AD	17p11.2	PMP-22
congenital hypomyelinating	AD	1q21–23	P_0
neuropathy)	AR	10q21.1–22.1	ERG2
	AR	19q13	Periaxon
CMT4			
CMT4A	AR	8q13–21.1	GDAP1
CMT4B1	AR	11q23	MTMR2
CMT4B2	AR	11p15	MTMR13
CMT4C	AR	5q23–33	SH3TC2
CMT4D (HMSN–Lom)	AR	8q24	NDRG1
CMT4E (congenital hypomyelinating neuropathy)	AR		Probably includes PMP22, MPZ, and ERG-2
CMT4F	AR	19q13.1–13.3	Periaxin
CMT4G	AR	10q23.2	?
CMT4H	AR	12q12–q13	Frabin
Other Hereditary Neuropathies			
HNA	AD	17q24	SEPT9
HMSN-P	AD	3q13–q14	?

CMT, Charcot–Marie–Tooth; DI-CMT, dominant intermediate CMT; HNNP, hereditary neuropathy with liability to pressure palsies; HNA, hereditary neuralgic amyotrophy; SMA, spinal muscular atrophy; LGMD, limb girdle muscular dystrophy; HMSN-P, hereditary motor and sensory neuropathy-proximal; AD, autosomal dominant; AR, autosomal recessive; PMP-22, peripheral myelin protein-22; P_0, myelin protein zero protein; ERG2, early growth response-2 protein; LITAF, lipopolysaccharide-induced tumor necrosis factor-alpha factor; MFN2, mitochondrial fusion protein mitofusin 2 gene; MTMR2, myotubularin-related protein-2; NDRG1, N-myc-downstream-regulated gene; KIF1B β, microtubule motor kinesin-like protein; GDAP1, ganglioside-induced differentiation-associated protein-1; SH3TC2, SH3 domain and tetraticopeptide repeats 2; SEPT9, Septin 9.

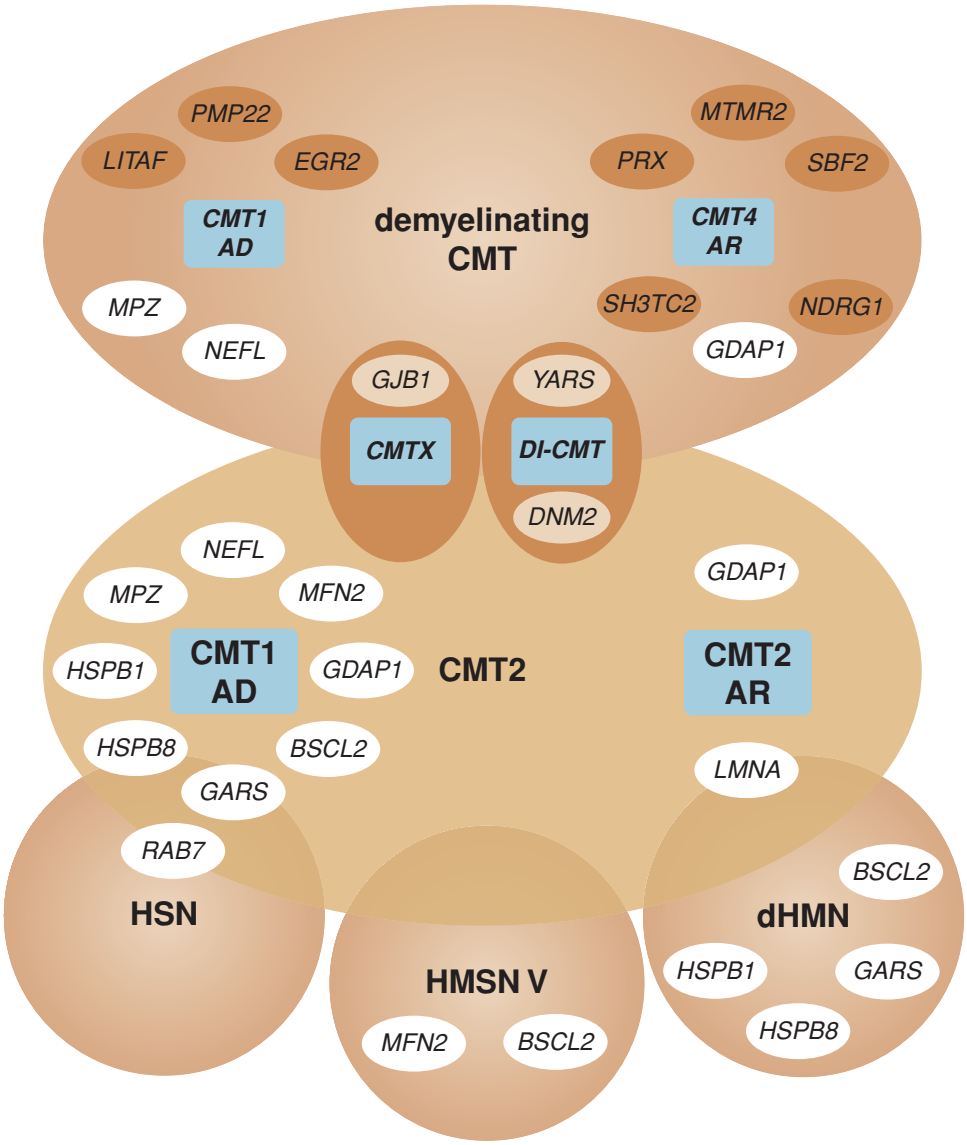


Figure 9–1. The various types of Charcot–Marie–Tooth disease and their areas of overlap. Identified causative genes are also shown. Diseases: CMT, Charcot–Marie–Tooth disease (CMT1, demyelinating, autosomal dominant; CMT2, axonal, autosomal dominant or recessive; CMT4, demyelinating, autosomal recessive; CMTX, X-linked; DI-CMT, dominant intermediate); dHMN, distal hereditary motor neuropathies; HSN, hereditary sensory neuropathies; HMSN V, hereditary motor and sensory neuropathy V (CMT with pyramidal involvement). Inheritance: AD, autosomal dominant; AR, autosomal recessive. Genes: BSCL2, Berardinelli–Seip congenital lipodystrophy type 2; DNM2, dynamin 2; EGR2, early-growth response 2; GARS, glycyl-tRNA synthetase; GDAP1, ganglioside-induced differentiation-associated protein 1; GJB1, gap junction B1/connexin-32; HSPB1 (or HSP27), heat-shock 27-kDa protein 1; HSPB8 (or HSP22), heat-shock 22-kDa protein 8; LITAF, lipopolysaccharide-induced tumor necrosis factor-alpha factor; LMNA, lamin A/C nuclear envelope protein; MFN2, mitofusin 2; MTMR2, myotubularin-related protein 2; SBF2, SET binding factor 2; SH3TC2, SH3 domain and tetratricopeptide repeat domain 2; NDRG1, N-myc downstream-regulated gene 1; NEFL, neurofilament light chain; MPZ, myelin protein zero; PMP-22, peripheral myelin protein-22; PRX, periaxin; RAB7, small GTPase late endosomal protein RAB7; YARS, tyrosyl-tRNA synthetase. (With permission from Pareyson D. Axonal Charcot–Marie–Tooth disease: The fog is only slowly lifting. Neurology 2007;68:1649–1650, Fig. 1, p. 1650.)

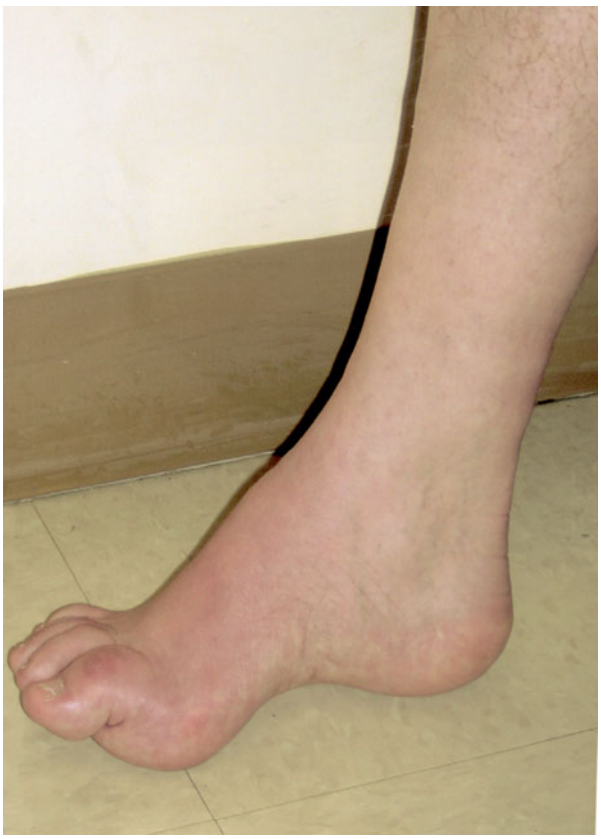


Figure 9–2. CMT1. Note the high arch (pes cavus) of the foot and hammertoes of a patient with CMT1.

of the nerves, especially posterior to the ear and arm regions, may be visualized and palpated. Some individuals who are affected also develop deafness or Adie's pupils.

It is important to examine family members of patients with possible CMT. Although there may be no family history of CMT, careful examination of the family may demonstrate other members with features of the neuropathy. This can be important in clarifying a diagnosis and in providing genetic counseling.

LABORATORY FEATURES

Cerebrospinal fluid (CSF) protein levels may be elevated. Besides genetic testing, NCS are the most important laboratory tests in the evaluation of people suspected of having CMT. The NCS are invaluable in determining if patients have a demyelinating or axonal neuropathy and, if demyelinating, if it is uniform or multifocal, which is useful in distinguishing CMT from chronic inflammatory demyelinating polyneuropathy.[2,9,10] At birth and in infancy, NCVs may be normal or only minimally slowed in children with CMT1. However, the NCVs rapidly decline, and, by 3–5 years of age, the nadir in NCV slowing is achieved and remains stable throughout the rest of the person's life. However, the compound muscle action potential (CMAP) amplitudes continue to diminish over time, reflecting ongoing loss of axons. Distal motor latencies at birth are commonly borderline abnormal. These latencies continue to increase until approximately the age of 10 years, at which time there is little further prolongation of the distal latencies. A detailed discussion of specific nerve conduction abnormalities in CMT1 follows.

Motor NCS

Motor NCVs by definition are slowed to less than 38 m/s, but in most cases the NCVs are in the 20–25 m/s range.[2,9–11] Patients with point mutations in peripheral myelin protein-22 (PMP-22) and myelin protein zero (MPZ) genes can have even slower conduction velocities (CVs) approaching that seen in CMT3 (10 m/s or less).[12,13] As will be discussed in the subsequent section, some people with MPZ mutations have only slightly slow or normal NCVs and thus by NCV criteria can be classified as having CMT2.[10,14] Demyelination is generally uniform; therefore, patients with CMT1 do not usually demonstrate conduction block or temporal dispersion.[11,15] However, there are well-documented cases of genetically proven CMT1A with nonuniform slowing and CVs over 42 m/s and thus might mimic an acquired neuropathy.[7] Further, temporal dispersion of nerve conduction and irregularity of conduction slowing have been reported in CMT1C.[16]

Distal motor latencies are usually markedly prolonged. The CMAPs may be absent when recordings are attempted from severely atrophic muscles. It is useful in people with wasted foot intrinsics to perform motor NCS in the lower limb by recording from the tibialis anterior muscle. F-waves latencies are usually absent but, when obtainable, are extremely prolonged.

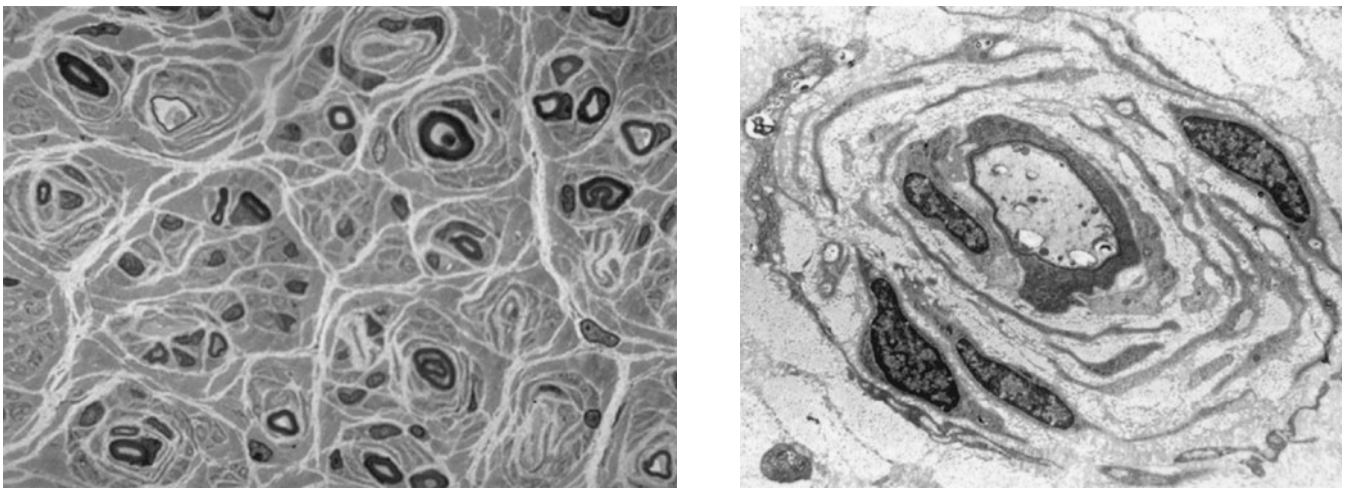
There is no correlation between the NCVs and the clinical severity of the neuropathy.[17] The NCVs are quite slow in childhood, even when there are minimal clinical deficits. Further, asymptomatic adults can have prolonged distal motor latencies and slow NCV. It is apparent that weakness and loss of function are more related to the degree of axon loss, rather than the extent of demyelination and slowing of nerve conduction.

Motor Nerve Unit Estimates

Motor nerve unit estimates can assess motor unit loss in CMT and may better reflect axonal loss than CMAP amplitude.[18]

Sensory NCS

The sensory nerve action potentials (SNAPs) are usually unobtainable or very low in amplitude.[19–27] When recordable, the distal latencies are very prolonged and NCVs are markedly slow.



A B

Figure 9–3. CMT1 Nerve biopsy demonstrates a reduction of myelinated nerve fibers, thinly myelinated fibers, and onion bulb formations (A, semithin section). Electron microscopy reveals proliferation of Schwann cell processes surrounding demyelinated fiber forming a so-called onion bulb (B). (From www.neuropathologyweb.org/chapter12.)

Evoked Potentials

Somatosensory-evoked potentials have demonstrated slowing of central conduction in CMT. Visual-evoked potentials also reveal similar slowing of the optic pathways.

Needle Electromyography

Electromyography (EMG) reveals positive sharp waves and fibrillation potentials along with reduced recruitment of long-duration, high-amplitude, and polyphasic motor unit action potentials (MUAPs) in the distal legs and lesser and arms.[22] Evidence of active denervation and reinnervation may also be found in some the proximal muscles.

HISTOPATHOLOGY

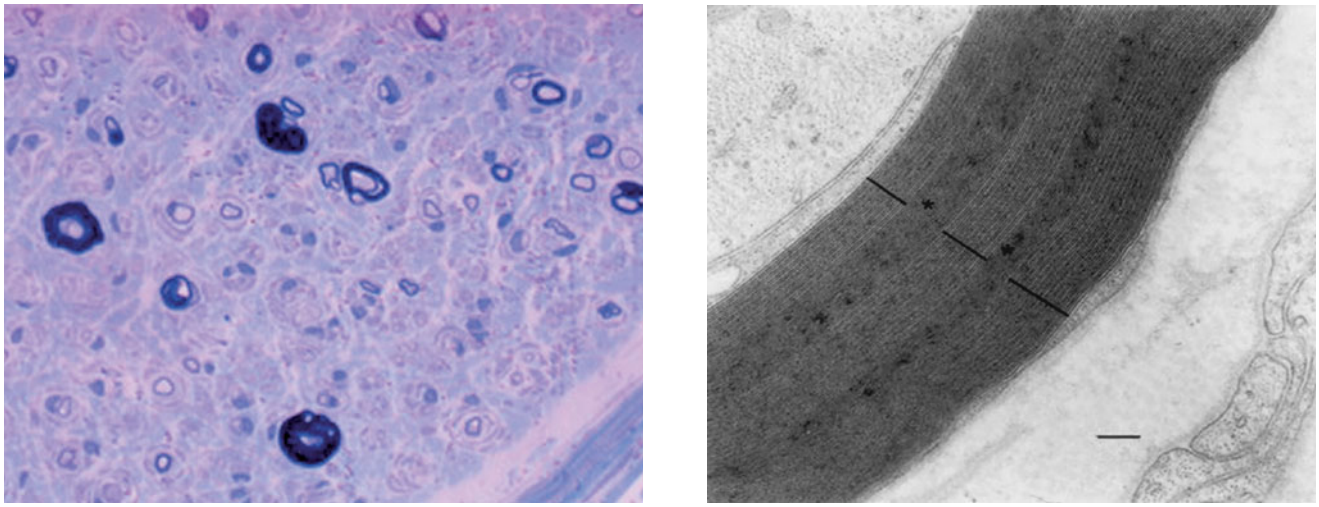
We do not perform nerve biopsies on people suspected of having CMT1 anymore, as the diagnosis can usually be made by less invasive testing (e.g., NCS and genetic studies). Nevertheless, nerve biopsies are strikingly abnormal.[10,23,24] The enlarged gross appearance of the peripheral led to the early designation of CMT1 as a hypertrophic neuropathy. Light microscopy reveals reduction of myelinated nerve fibers with a predilection for the loss of the large-diameter fibers.[23,24] The diameters of the axons are also decreased; on the whole there is an increase in the density of neurofilaments within these atrophic axons. Early in life, the peripheral nerves may appear normally myelinated, but over time axons become thinly myelinated. Recurrent demyelination and remyelination lead to reduced internodal length, while Schwann cell proliferation results in the formation of the so-called onion bulbs (Fig. 9–3). In patients with CMT1B, occasionally biopsies reveal tomacula, uncompacted myelin, and focally folded or widened myelin sheaths (Fig. 9–4).[4,12,25] Demyelination, neuronal loss, and axonal atrophy are slightly more prominent distally. Autopsy studies demonstrate the loss of myelinated fibers in the posterior columns in the spinal cord.

MOLECULAR GENETICS AND PATHOGENESIS

CMT1 is a genetically heterogeneic disorder (Table 9–1). In addition, there is phenotypic heterogeneity associated with mutations in specific genes. CMT1A is by far the most common form of CMT1, representing 70% of cases, while 20% have CMT1B, and 10% have one of the other subtypes.[3]

CMT1A

Approximately 85% of people with CMT1A have a 1.5-megabase (MB) duplication within chromosome 17p11.2–12 wherein the gene for PMP-22 lies.[26,27] Thus, these individuals carry three copies of the PMP-22 gene rather than two (Fig. 9–5). In contrast, inheritance of the chromosome with the deleted segment results in affected individuals having only one copy of the PMP-22 gene and leads to hereditary neuropathy with liability to pressure palsies (HNPP). Although these mutations are inherited in an autosomal-dominant fashion, de novo mutations do occur. Most de novo duplications are paternally inherited and are believed to arise due to



A B

Figure 9–4. CMT1B. Semithin section reveals rarefaction of myelinated fibers, foldings of myelin, and onion bulb proliferations of Schwann cells (A). Note the alternate disposition of normal (stars) and uncompacted myelin lamellae (lines), Bar = 0.2 μm (B). (With permission from Vallat JM, Magy L, Lagrange E, et al. Diagnostic value of ultrastructural nerve examination in Charcot–Marie–Tooth disease: Two CMT1B cases with pseudo-recessive inheritance. Acta Neuropathol (Berl) 2007;113(4):443–449, Fig. 3, p. 445.)

unequal crossover during meiosis. De novo mutations of female origin are probably caused by intrachromosomal rearrangement.[28] In keeping with this abnormal dosage effect of PMP-22, people affected with trisomy 17p (thus, containing three copies of the PMP-22 gene) also have a demyelinating sensorimotor polyneuropathy.[29]

Some individuals with CMT1A have point mutations in the PMP-22 gene.[30] These individuals can more closely resemble Dejerine–Sottas or CMT3 phenotypically, in which they are more severely affected at an earlier age, demonstrate slower NCV (less than 10 m/s), and have more prominent histopathology than those with the classic duplication.[13] Other individuals present with a milder phenotype with pressure-induced palsies (e.g., HNPP as discussed in a subsequent section).

The pathogenic basis for CMT1A is likely due to a toxic gain of function of PMP-22. This protein accounts for 2–5% of myelin protein and is expressed in compact portions of the peripheral myelin sheath. An increased expression of PMP-22 mRNA and the protein itself in the myelin sheaths has been demonstrated on nerve biopsies in CMT1A; however, late in the course PMP-22 expression actually decreases.[31–34] The exact function of PMP-22 in the peripheral nerves is not known, but it may be important in maintaining the structural integrity of myelin, acting as an adhesion molecule, or regulating the cell cycle. Regeneration-associated remyelination is delayed in nerve xenografts implanted from individuals with CMT1A into mice.[35] Further, PMP-22 must also be essential for maintaining the integrity of the axon itself, as there is evidence of axonal atrophy on nerve biopsies in people with CMT1A.

CMT1B

Approximately 20% of people with CMT1 have CMT1B, which is caused by mutations in the MPZ gene located on chromosome 1q22–23.[36–38] CMT1B is for the most part clinically, electrophysiologically, and histologically indistinguishable from CMT1A. However, patients with MPZ mutation are more likely to have more "axonal" physiology on NCS than those patients with PMP-22 mutations. Also, CMT associated with Adies' pupils are more common in patients with MPZ mutations. MPZ is an integral myelin protein and accounts for more than half of the myelin protein in peripheral nerves. It is a member of the immunoglobulin superfamily and consists of an extracellular immunoglobulin-like domain, a transmembrane domain, and a cytoplasmic domain.[1] MPZ localizes to the tight compact regions of myelin, where it may play a role in maintaining tight compaction by forming links between adjacent myelin layers. Nerve biopsies in people with CMT1B reveal abnormalities similar to that noted in CMT1A. However, occasionally tomaculae and uncompacted myelin are apparent, which are not typically seen on nerve biopsy in CMT1A.[4,12,39] Immunohistochemistry and ultrastructural studies on nerve biopsy specimens may demonstrate decreased expression of MPZ protein.[40] Some mutations in the MPZ gene have been associated with a severe demyelinating CMT3 phenotype, while others are associated with NCS suggestive of an axonopathy or CMT2. The specific location of the mutations in the MPZ gene and how these affect the function of the myelin protein probably account for the phenotypic heterogeneity.

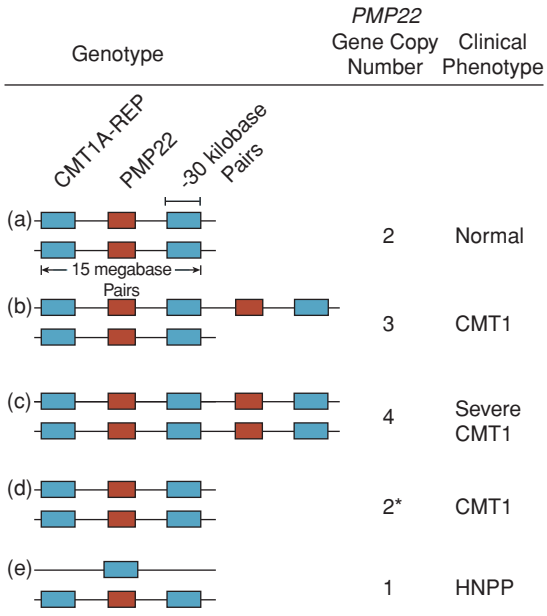


Figure 9–5. The origin of Charcot–Marie–Tooth syndrome type 1A (CMT1A) and hereditary neuropathy with liability to pressure palsies (HNPP). Relative locations of the CMT1A repeat sequence (CMT1A-REP) and the peripheral myelin protein-22 gene (PMP-22) in chromosome 17p11.2–12 are shown. Normally only one copy of the PMP-22 gene is present on each chromosome. However, misalignment of the CMT1A-REP sequence during meiosis may lead to tandem duplication in CMT1A (three copies of the PMP-22 gene) or an interstitial deletion in HNPP (one copy of PMP-22 gene). Rare cases inheriting duplicated copies of PMP-22 gene (four copies) in both chromosomes are associated with a severe CMT1 clinical phenotype. (With permission from Lupski JR, Chance PF, Garcia CA. Inherited primary peripheral neuropathies: Molecular genetics and clinical implications of CMT1 A and HNPP. JAMA 1993;270(19):2326–2330, Fig. 1, p. 2327.)

CMT1C

This rare neuropathy is caused by mutations in LITAF gene (lipopolysaccharide-induced tumor necrosis factor-alpha factor) located on chromosome 16p13.1–p12.3.[16,41,42] In a large study of 968 unrelated cases of CMT1, the percentage of patients with LITAF mutations was only 0.6%.[42] LITAF, also known as SIMPLE (small integral membrane protein of the lysosome/late endosome), is expressed on Schwann cells and may play a role in protein degradation pathways.[43]

CMT1D

Mutations in the early growth response 2 (ERG2) gene on chromosome 10q21.1–q22.1 are responsible for CMT1D.[44] ERG2 is believed to be a transcription factor that binds DNA through three zinc finger domains and likely has an important action in regulating myelin genes in Schwann cells. CMT1D accounts for <1% of molecular-defined cases of CMT1.

CMT1E

This refers to kinships with CMT1 associated with deafness. It has been demonstrated to be allelic to CMT1A and caused by point mutations in PMP-22 gene.[5]

CMT1F

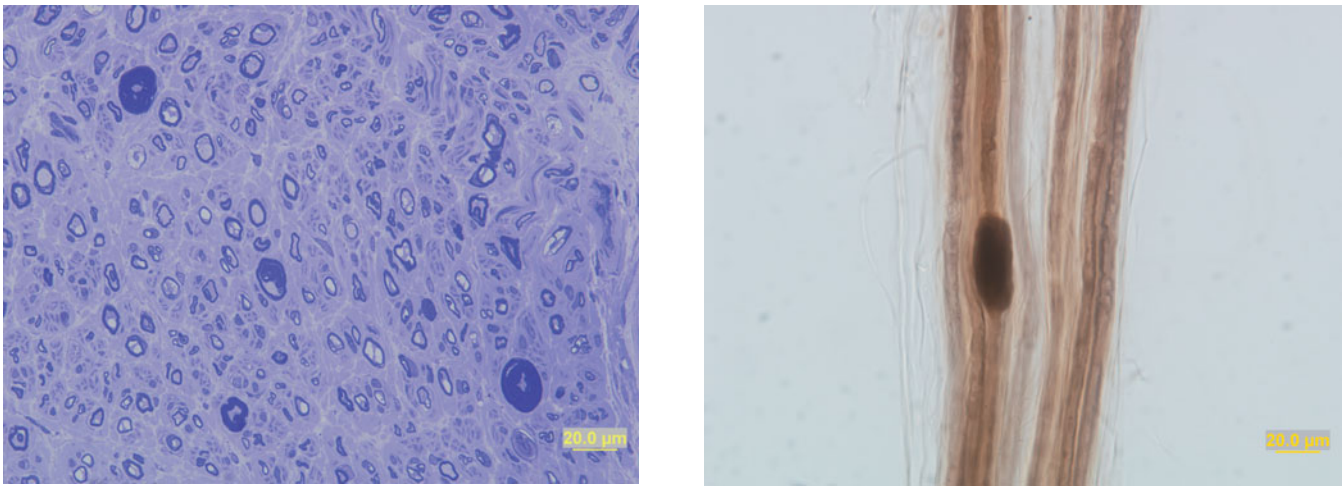
Mutations in the neurofilament light chain (NF-L) gene located on chromosome 8p13–21 are usually associated with low-amplitude CMAPs and normal or only slightly slow NCVs and thus are often categorized as an axonal form of CMT (CMT2E). However, some cases have been reported with motor NCVs in the mid-twenties and thus have been classified as a CMT1F.[45,46]

▶ HEREDITARY NEUROPATHY WITH LIABILITY TO PRESSURE PALSIES

Because HNPP is associated with mutations affecting PMP-22 and less commonly MPZ, we discuss it here before moving on to CMT2.

CLINICAL FEATURES

HNPP or tomaculous neuropathy is inherited in an autosomal-dominant manner.[19,47–57] The neuropathy usually manifests within the second or third decade, although some individuals who are affected present earlier and others remain asymptomatic their entire life. People usually describe painless numbness and weakness in the distribution of a single peripheral nerve, although multiple mononeuropathies and cranial neuropathies can occur. Symptomatic mononeuropathy or multiple mononeuropathies are often precipitated by trivial compression of nerve(s), as it can occur with wearing a backpack, leaning on the elbows, or crossing one's legs for even a short period of time. These pressure-related mononeuropathies usually resolve, although it may take several weeks or months. The most commonly affected sites are the median nerve at the wrist (carpal tunnel syndrome), ulnar nerve at the elbow (cubital tunnel syndrome), radial nerve in the arm (spiral groove insult), and peroneal nerve at the fibular head. In addition, the brachial plexus can be involved after carrying a heavy shoulder bag or backpack. Further, some individuals who are



A B

Figure 9–6. HNPP nerve biopsy. Transverse section of toluidine blue-stained epon-embedded sural nerve from a patient with HNPP reveals scattered thinly myelinated nerve fibers and fibers with redundant myelin swellings (A). Teased Fiber preparation demonstrates a sausage-shaped myelin swelling or tomacula (B).

affected manifest with a progressive or relapsing, generalized, and symmetric sensorimotor peripheral neuropathy that resembles CMT or even chronic inflammatory demyelinating polyneuropathy.[19,47,50] On examination, there is decreased sensation to all modalities, particularly large fiber functions. Muscle stretch reflexes are usually reduced throughout, but these can be normal. Pes cavus deformities and hammertoes are often evident as seen in CMT.

LABORATORY FEATURES

Although the clinical symptoms and signs are typically focal, NCS often reveal diffuse abnormalities.[19,47–51,53–55,58,59,60] Sensory and motor NCS usually demonstrate moderately prolonged distal latencies and slightly slow NCV with normal or reduced amplitudes. Slowing of NCVs, conduction block, and temporal dispersion are accentuated across typical sites of entrapment or compression (i.e., the carpal and cubital tunnel, Guyon's canal, and across the fibular head) and can also be demonstrated across sites of compression. In addition, there also appears to be a distal accentuation of nerve conduction slowing, irrespective of possible compression.[47,48,55]However, this length-dependent slowing has not been appreciated by all.[56,57] NCS may also be abnormal in asymptomatic family members who carry the mutation.

Histopathology

Nerve biopsies demonstrate focal globular thickening of the myelin sheath, which is best appreciated on teased fiber preparations.[47,52,58,61] The thickened myelin resembles as a sausage, hence the name tomaculous neuropathy (Latin: sausage) (Fig. 9–6). These tomaculae represent redundant loops of myelin. In addition, nerve biopsies reveal a reduction in large myelinated fibers, segmental demyelination and remyelination, and axonal atrophy and degeneration similar to but not as severe as that seen in CMT1.

MOLECULAR GENETICS AND PATHOGENESIS

Approximately 85% of cases of HNPP are caused by an inverse of the mutation that is responsible for most cases of CMT1A.[19,47,62] While CMT1A is usually associated with a 1.5-MB duplication in chromosome 17p11.2, an extra copy of PMP-22 gene, HNPP is caused by inheritance of the chromosome with the corresponding 1.5-MB deletion of this segment and thus have only one copy of the PMP-22 gene (Fig. 9–5). De novo deletions are usually paternally inherited and arise due to unequal crossing-over during meiosis, while rare de novo mutations are of female origin and the result of intrachromosomal rearrangements.[28] In addition, as with CMT1A, mutations within the PMP-22 gene itself can cause HNPP.[63] Why some point mutations in the PMP-22 gene result in a CMT1A clinical phenotype and other are associated with a HNPP phenotype is not known. It is speculated that mutations causing CMT1A produce a gain of function of the PMP-22 protein, while mutations causing HNPP cause a loss of function of the PMP-22. Nerve biopsies demonstrate an underexpression of PMP-22

mRNA and the protein[31,33] that inversely correlate with the mean diameter of the axons and clinical severity.[64] Normal expression of PMP-22 appears important for proper axonal development.

▶ CMT DISEASE TYPE 2 (CMT2)

CLINICAL FEATURES

CMT2 refers to the "axonal" hereditary motor and sensory neuropathies. Most of these are associated with autosomal-dominant inheritance. The prevalence of CMT2 is about half that of CMT1. There are several well-defined subtypes based on the clinical features and genetic localization (Table 9–1).[9,21–23,65,66–70] CMT2A2 caused by mitofusin-2 mutations is the most common subtype accounting for approximately one-third of CMT2 cases overall.[70–72] The different subtypes can be difficult to distinguish from one another and even from CMT1; however, there are clinical features that may be helpful. CMT2 tends to present later in life compared to CMT1. Individuals who are affected usually become symptomatic in the second decade but some remain asymptomatic into late adult life while others present in the first decade of life.[69,74] People with CMT2 tend to have less severe involvement of the intrinsic hand muscles than that appreciated in CMT1. In contrast, CMT2 is associated with more profound atrophy and weakness of both the anterior compartments (peroneal and anterior tibial) and the posterior compartments (gastrocnemius and soleus) of the distal legs compared to CMT1. Generalized areflexia is rare in CMT2, while it is rather common in CMT1. Ankle reflexes are usually absent in both types of diseases. Individuals with CMT2 are less likely to have a tremor (Roussy–Levy syndrome) than people with CMT1. Although patients generally do not complain of sensory loss or paresthesia, 50–70% of those with CMT2 have significant reductions in light touch, pain, joint position, and vibration sense. While pes cavus and hammertoe deformities may be seen in CMT2, these are less frequent than in CMT1.

There are some features that also help distinguish the different subtypes of CMT2. For example, optic atrophy, hearing loss, pyramidal tract, and subcortical white matter abnormalities on brain magnetic resonance imaging findings are sometimes seen in CMT2A2, which was previously reported as hereditary motor and sensory neuropathy type 6 (HMSN VI).[75,76] Severe mutilating neuropathic ulcerations similar to those typically seen in HSAN type 1 (HSAN1) sometimes complicate CMT2B.[77,78–80]

CMT2B1 caused by homozygous mutations involving lamin A/C is allelic to limb-girdle muscular dystrophy 1B.[81–84] Most of the reported cases have been from North Africa and the Middle East, where consanguineous marriages are not uncommon. The age of onset has ranged from 6 to 27 years in these small series, and the course of the neuropathy is variable. The neuropathy can progress rapidly with severe distal and proximal weakness of the arms and legs evolving in a few years, while other affected individuals have only mild weakness two decades after onset of symptoms.

CMT2C is associated with vocal cord paralysis and diaphragmatic weakness in addition to limb involvement.[3,85–87] The age of onset and symptoms are variable, and it can begin in infancy when it may manifest with breathing difficulties and stridor. Laryngeal weakness is more often insidious in onset and presents as progressive hoarseness. In addition, the phrenic nerves may be affected, leading to diaphragm weakness and reduced respiratory function, particularly with the affected individual being supine. Some people will require tracheostomy and mechanical ventilation. Severe atrophy of the distal limbs is common. Individuals who are affected can develop proximal weakness as well. There is mild sensory loss to all modalities and deep tendon reflexes are reduced. Pes cavus can be appreciated in some patients, but such foot deformities are not as common as seen in CMT1, CMT2A, or CMT2B. Similar cases have been reported in the literature as hereditary distal spinal muscular atrophy with vocal cord paralysis.[85,87] However, because of concurrent sensory abnormalities most authorities consider this a subtype of CMT category rather than spinal muscular atrophy.[3,85]

CMT2D is another genetically distinct autosomal-dominant form of CMT2.[89–93] The hands are more severely affected than the distal legs. Selected wasting of the first interosseus muscles is often appreciated. Onset of weakness is usually appreciated in the late teens (range between the ages of 12 and 36 years) and the neuropathy has a slowly progressive course. Distal hypesthesia to all sensory modalities and areflexia are appreciated. Pes cavus, hammertoes, and scoliosis are variably present. Enlarged palpable nerves are not appreciated. This disorder is allelic to distal spinal muscular atrophy type 5.[90–92]

CMT2E is a rare neuropathy usually manifested in the second or third decade of life with progressive distal leg weakness.[45,46,94] Some patients develop deafness. Sensory loss, pes cavus, and areflexia are also often appreciated on examination.

CMT2F was reported in a Russian family with symmetric weakness and atrophy of the distal legs greater than the arms, with onset age 15–25 years.[95,96]

CMT2G was described in a large Spanish kinship with typical CMT2 phenotype, with an age at onset being 9–76 (mean 29) years. Most patients developed symptoms in the second decade of life.[97] This disorder links may be allelic with CMT4H.

CMT2H may be allelic to CMT 4A.

CMT2I is associated with late-onset axonal neuropathy, Adie's pupil, and hearing loss and is caused by mutations in *MPZ* gene that are more typically associated with demyelinating neurophysiology (CMT1B).

CMT2J with a late-onset neuropathy (usually fifth or sixth decade) associated with hearing loss and pupillary abnormalities (Adie's pupil) is also allelic to CMT1B and caused by mutations in MPZ gene.

CMT2K is allelic to CMT4A and usually manifests early in childhood. Some individuals who are affected have vocal cord paralysis. They may have axonal or demyelinating abnormalities on NCS.

CMT2L was reported in a large Chinese family.[98] Onset of the disease was between 15 and 33 years of age with symmetric weakness of the distal lower limbs, mild-to-moderate sensory impairment including pain and touch, and absent muscle stretch reflexes.

LABORATORY FEATURES

The similarities between the CMT1 and CMT2 make it difficult to definitely distinguish between these neuropathies on clinical grounds only; thus, NCS are invaluable. It is usually not too difficult to differentiate CMT2 from the more common chronic idiopathic axonal neuropathy. Although there is electrophysiologic evidence of motor involvement in chronic idiopathic axonal neuropathy, sensory symptoms predominate the clinical picture in this neuropathy, while motor signs and symptoms are the major clinical features in CMT2.[99]

NCS can help distinguish CMT1 from CMT2[9,22,65–67,79]; however, these do not help ascertain the various subtypes of CMT2. Sensory NCS reveal reduced or absent SNAP amplitudes in both the upper and the lower limbs. CVs are normal or only slightly reduced. Likewise, the distal sensory latencies are either normal or only mildly prolonged. The motor NCS demonstrate reduced CMAP amplitudes, particularly in the legs, except in CMT2D in which the distal arms are affected more than the legs. Distal motor latencies are normal or only mildly prolonged. NCVs are normal or only slightly slow, usually greater than 37 m/s. However, cases of CMT2E have been reported with motor NCVs in the mid-twenties and thus may be classified as a subtype of CMT1.[46,100] Needle EMG reveals fasciculation and fibrillation potentials, particularly in distal extremity muscles. A few patients with CMT2 have been reported to have continuous MUAP firing resembling neuromyotonia in that it is abolished with peripheral neuromuscular blockade.[101,102] The MUAPs can be increased in amplitude and duration with a higher-than-normal number of polyphasic potentials. Recruitment is reduced in weak muscles as well.

HISTOPATHOLOGY

Nerve biopsies in CMT2 demonstrate a generalized reduction in myelinated fibers, particularly the large myelinated fibers.[79,103] Axonal atrophy, Wallerian degeneration, and small clusters of thinly myelinated fibers representing regenerating axons can be appreciated. As opposed to CMT1, onion bulbs are not a prominent feature in CMT2. Abnormal accumulations of mitochondria may be appreciated on electron microscopy (EM) in CMT2A2 (Fig. 9–7). Some forms such as CMT2E are associated with giant axons and accumulation of disorganized neurofilaments.[45]

MOLECULAR GENETICS AND PATHOGENESIS

CMT2 is a genetically heterogeneic group of disorders (Table 9–1).

CMT2A1 is caused by mutations in a microtubule motor kinesin-like protein, *KIF1Bbeta* gene located on chromosome 1p36.2.[104,105] The kinesin superfamily is involved in axonal transport and likely impairment of this function leads to axon degeneration. Subsequent to the discovery of mutations in the *KF1Bbeta* gene, missense mutations in the mitochondrial fusion protein mitofusin 2 gene, *MFN2*, also located on chromosome 1p36.2, were found.[106] Now, it is appreciated that the majority of patients with CMT2A have MFN2 mutations (CMT2A2), which account for one-third of CMT2 cases overall.[71,73] MFN2 localizes to the outer mitochondrial membrane, where it regulates the mitochondrial network architecture by fusion of mitochondria. Mitochondria undergo a dynamically regulated balance between fusion and fission reactions of its tubular and branched membrane network in order to maximize cell functions, such as equilibrating mitochondrial gene products to overcome acquired somatic mutations of mitochondrial DNA and establishing a uniform membrane potential at the mitochondrial double membrane and regulation of apoptosis.[106] Mutations in MFN2 leads to abnormal mitochondrial tracking, which may explain the length-dependent severity of the associated neuropathy (Fig. 9–7).[73,107]

CMT2B (3q13–q22) is caused by mutations in a small GTPase late endosomal protein encoded by the *RAB7* gene.[79,108] This protein serves as a guanine-nucleotide exchange factor for the Rho family of GTPase enzymes (RhoGTPases). Rho guanine-nucleotide exchange factors regulate the activity of small RhoGTPases by catalyzing the exchange of bound GDP by GTP. In turn, RhoGTPases play a pivotal role in regulating the actin cytoskeleton by their ability to influence cell polarity, microtubule dynamics, membrane-transport

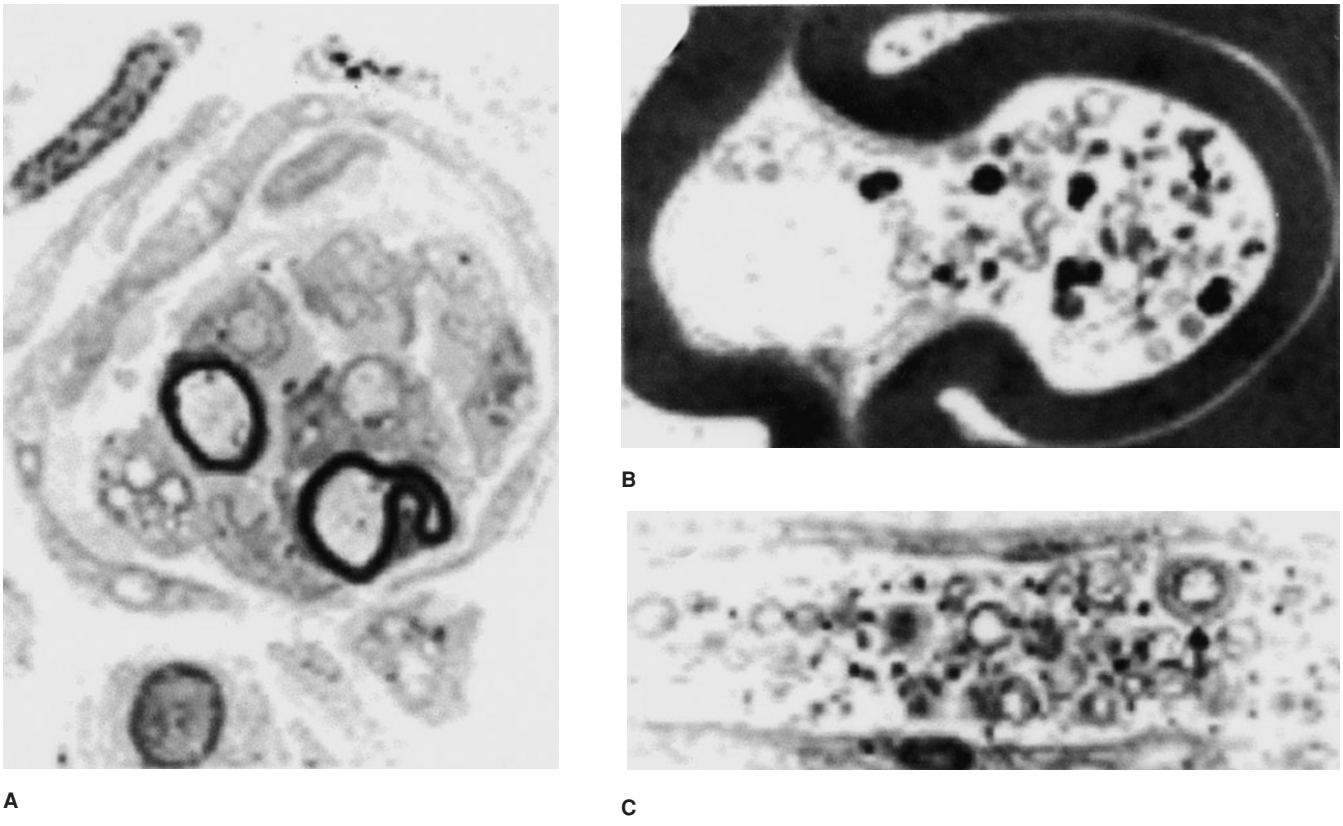


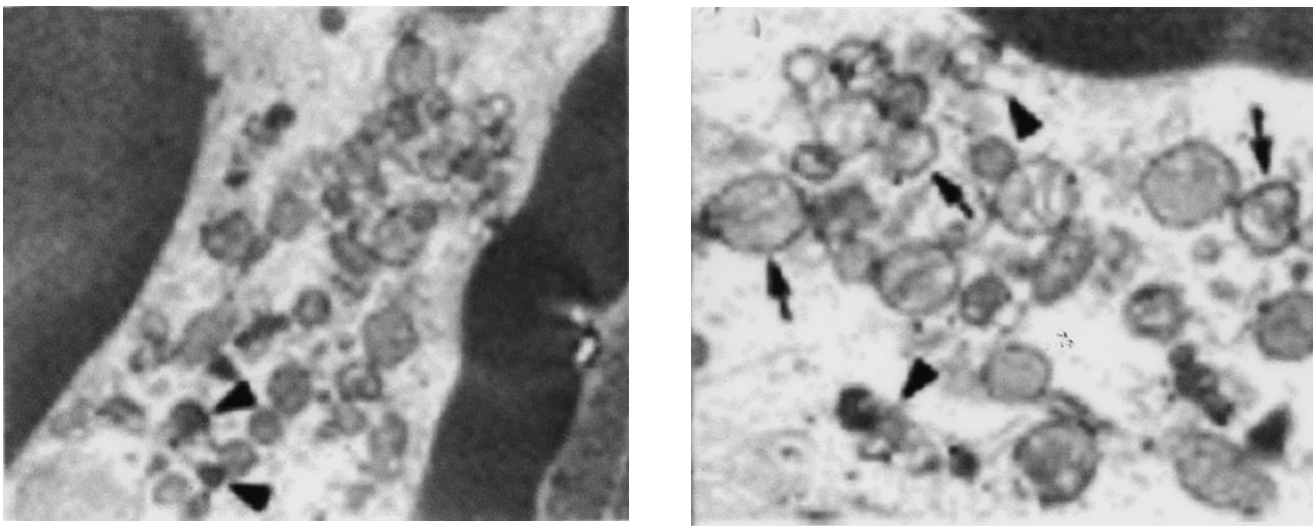
Figure 9–7. CMT2A2. (A) Electron micrograph of a sural nerve biopsy reveals a large reinnervated band of Büngner with two remyelinated and at least six unmyelinated sprouts at the site of a distally degenerated and regenerated nerve fiber. There are a large number of Schwann cell processes with no evidence of degeneration. The collagen filaments inside and outside this band of Büngner have similar diameters. Fibroblastic cells or macrophages are apparent inside and outside, but only the inner one shows an increased number of (artificially swollen) mitochondria. Original magnification: ×13,000. (B) This fortuitous section through an axon protruding into a paranodal myelin loop shows considerable accumulation of normal and abnormal mitochondria. There are various degenerative changes such as swelling, transformation into membranous whorls, suggestive splitting or fusion (arrow), or dissolution. Only some mitochondria appear to be well preserved. (C) This unmyelinated axon shows further mitochondrial changes such as uneven density of the inner and outer membranes, or a concentric inner component with somewhat collapsed intracristal space, despite normal appearance of the outer "double membrane" (arrow) or wavy mitochondrial membranes. In some small mitochondria, the matrix appears to be dissolved and the outer and the inner membrane fused. In between are neurosecretory granules, glycogen granules, components of the axoplasmic reticulum, neurofilaments, and microtubules. Primary magnifications: (B) ×28,000 and (C) ×35,000. (*continued*)

pathways, and transcription-factor activity, as well as RhoGTPases in neuronal morphogenesis, including cell migration, axonal growth and guidance, dendrite elaboration and plasticity, and synapse formation.[79]

CMT2B1 is caused by mutations in the *LMNA* gene located on chromosome 1q21.[81–84] This gene encodes for the nuclear envelop protein, lamin A/C. This gene is also mutated in patients with LGMD (limb girdle muscular dystrophy) 1B (see "Muscular Dystrophies," Chapter 24).

CMT2B2 has been linked to chromosome 19q13, but the gene has not been identified. Likewise, the gene for CMT2C maps to 12q23–24, but the gene product is unknown.[87] Both CMT2B1 and CMT2B2 are inherited in an autosomal-recessive rather than autosomal-dominant manner.

CMT2D and distal spinal muscular atrophy type V are allelic disorders caused by mutations in the glycyl-tRNA synthetase gene on chromosome 7p14.[88,91–93] Glycyl-tRNA synthetase is a member of the family of aminoacyl-tRNA synthetases, responsible for charging tRNAs with their cognate amino acids. The pathogenic mechanism by which mutations in this gene lead CMT2D/distal spinal muscular atrophy type V is not as yet clear.



D E

Figure 9–7. (Continued) (D and E) Electron microscopic findings in sural nerve of an affected patient: intra-axonal accumulation of mitochondria showing, on high magnification, several irregular arrangements of cristae (arrows) and degenerative features (arrowheads). Furthermore, in panel (E), uncommon swollen intra-axonal mitochondria with ruptured cristae are visualized as well as normal-appearing mitochondria. Magnification: (D) ×108,000 and (E) ×164,000. (With permission from Verhoeven K, Claeys KG, Zuchner S, et al. MFN2 mutation distribution and genotype/phenotype correlation in Charcot–Marie–Tooth type 2. Brain 2006;129(Pt 8):2093–2102, Fig. 4, p. 2100.)

CMT2E is caused by mutations in the NF-L gene located on chromosome 8p13–21.[45,46,94,100,109] Neurofilaments are important for proper organization, function, and regeneration of axons as well as for axonal transport. Further, NF-L plays a major role in regulating the expression and function of other neurofilament proteins.

CMT2F is caused by mutations in the gene encoding 27-kDa small heat-shock protein B1 (HSPB1, also called HSP27) located on chromosome 7q11–q21.[95,96] Mutations in this gene are also responsible for some patients categorized as having distal spinal muscular atrophy.[96]

CMT2G has been localized to chromosome 12q12–q13, but the gene has not been identified.[97] It may be allelic to CMT4H, which links to the same region and is caused by mutations in the gene that encodes for frabin (*FGD4*). Frabin (FGD1-related F-actin binding protein) is a GDP/GTP nucleotide exchange factor (GEF) it may have a role in mediating actin cytoskeleton changes during cell migration, morphogenesis-polarization, and division.[109a,109b]

CMT2H has been localized to chromosome 8q21.3, but the gene has not been identified. It is inherited in an autosomal-recessive fashion and is likely allelic to CMT4A, which is discussed in a separate section.

CMT2I refers to late-onset cases with mutations in MPZ gene (CMT1B) but in which the neurophysiology and nerve biopsies look more axonal and thus can be mistakenly classified as CMT2.[14,110] Likewise, CMT2J, which is associated with hearing loss and Adie's pupil, is also associated with mutations in MPZ gene.

CMT2K refers to early-onset neuropathy (usually before the age of 2 years), which is caused by mutations in ganglioside-induced differentiation-associated protein 1 (GDAP1) gene located on chromosome 8q13–q21. This is allelic to CMT4A.[84] Some individuals who are affected have vocal cord paralysis. The mechanism by which this causes axonal degeneration is not known.

CMT2L is caused by mutations in the HSPB8 gene chromosome 12q2 that encodes for small heat-shock protein 22-kDa protein 8 (HSP22).[98,111] Mutations in this gene are also responsible for distal hereditary motor neuropathy type II. HSP 22 forms homodimers and larger oligomers with other HSPs. The mutation may lead to an increased tendency to form cytoplasmic protein aggregates.[111]

▶ DOMINANT INTERMEDIATE CMT DISEASE

Dominant intermediate CMT (DI-CMT) disease refers to forms of CMT in which the CVs show only mild slowing (>38 m/s) and in which there are both demyelinating and axonal features on nerve biopsies. The clinical features are otherwise similar to what was described previously in CMT1 and CMT2 sections. Different chromosomal loci have been linked with three autosomal-dominant, "intermediate" types of CMT: DI-CMTA (10q24.1–q25.1), DI-CMTB (19p12–p13.2), and DI-CMTC (1p34–p35). Mutations in dynamin-2 gene

have been found in DI-CMTB.[112] Of note, mutations in the same gene have been found in adult-onset centronuclear myopathy.[113] Dynamin-2 belongs to the family of large GTPases and is important in endocytosis, membrane trafficking, actin assembly, and centrosome cohesion.[113] DI-CMTC is caused by mutations in the gene that encodes for tyrosyl-tRNA synthetase.[114,115] Tyrosyl-tRNA synthetase appears to be localized to axon terminals and probably plays a role in protein biosynthesis.

▶ CMT DISEASE TYPE 3 (DEJÉRINE–SOTTAS DISEASE, CONGENITAL HYPOMYELINATING NEUROPATHY)

CLINICAL FEATURES

CMT3 was originally described by Dejérine and Sottas as a hereditary demyelinating sensorimotor polyneuropathy presenting in infancy or early childhood.[77,116] Although initially CMT3 was believed to be an autosomal-recessive disorder because of a lack of family history,[9,117] most cases are due to spontaneous heterozygous mutations in the PMP-22, MPZ, or ERG2 genes.[118–120] Further, most cases of the so-called congenital hypomyelination neuropathy[121,122] also represent a severe form of CMT3.[123]

CMT3 usually manifests as generalized weakness at birth or in early childhood. Affected infants can be hypotonic and often have distal contractures (arthrogryposis multiplex). Respiratory distress and swallowing difficulties can develop in severe cases, leading to death in several months. In less severe cases, infants may appear normal at birth, but motor milestones are delayed. Some children achieve independent ambulation, although it may take several years. Distal muscles are affected more than proximal muscles. Weakness can progress and render some ambulatory patients to a wheelchair.

The peripheral nerves may be visible or palpably enlarged. There is a reduction in all sensory modalities, particularly those conveyed by large myelinated fibers (i.e., vibration and proprioception) and generalized reflexia. Sensory ataxia of the limbs and trunk can be profound. Sensorineural hearing and abnormal pupillary reaction to light can be detected in some children. Skeletal deformities (e.g., pes cavus and kyphoscoliosis) are common.

LABORATORY FEATURES

CSF protein levels are usually elevated. Motor NCV are markedly slow, typically 5–10 m/s or less; the distal motor latencies are markedly increased; and the amplitudes are reduced.[2,21,121,124–125] Sensory responses are usually unobtainable. Needle EMG demonstrates increased insertional activity with variable degrees of positive sharp waves and fibrillation potentials, and reduced recruitment of MUAPs.[127] In milder cases of CMT3 in which reinnervation can occur, large-amplitude, long-duration, polyphasic MUAPs are apparent. However, in severe cases with poor innervation, and much less reinnervation, the MUAPs can appear small and almost "myopathic" in appearance.

HISTOPATHOLOGY

Nerve biopsies in CMT3 are markedly abnormal.[123,128–130] One can see hypomyelination with basal lamina or classical onion bulbs as well as amyelination. There is an increase in the size of nerve fasciculi with a reduction in the numbers of myelinated fibers, while unmyelinated nerve fibers are less affected.

The most common histopathological abnormality is hypomyelination with basal lamina onion bulbs. There is marked loss of myelinated nerve fibers, with the remaining axons surrounded by onion bulbs composed of multiple layers of basement membranes, with only one or two thin Schwann cell lamella in the outer ring. These abnormalities are typically found in cases of infantile or early-onset neuropathy. Although, some of the infants have respiratory and swallowing problems, nearly all survive. However, affected children rarely achieve independent ambulation and most are wheelchair dependent.

Occasionally, nerve biopsies reveal hypomyelination, with classical onion bulbs composed of concentrically arranged thin Schwann cell lamellae, enclosing nearly all the fibers. This histopathological appearance is associated with a more benign neuropathy. Affected children can appear normal at birth but subsequently fail to meet normal motor milestones. They usually are eventually able to ambulate but may require assistance over time.

Other cases are associated with a marked reduction of nerve fibers and remaining fibers have minimal myelin. Onion bulbs are not apparent. These so-called congenital amyelinating neuropathies are the most severe form of CMT3 and are usually lethal.

MOLECULAR GENETICS AND PATHOGENESIS

CMT3 is a genetically heterogeneic disorder. As previously discussed, CMT3 was initially felt to be an autosomal-recessive disorder. However, de novo heterozygous point mutations have been discovered in the

genes for PMP-22, MPZ, and ERG-2, which are also genes responsible for autosomal-dominant CMT1.[2,44,119,131] Further, a CMT3 phenotype was described in a child with four copies of the PMP-22 gene as a result of both parents having the typical CMT1A duplication of 17p22.[26] Thus, there exists a wide spectrum of clinical, electrophysiolgical, and histological phenotypes associated with mutations in PMP-22, MPZ, and the ERG2 genes. Some individuals who are affected have a mild CMT1 phenotype with only asymptomatic slowing of NCV, while others manifest with severe congenital amyelinating neuropathy, resulting in severe generalized weakness and death in infancy. The severity of CMT3 is probably related to the exact locations of the mutations in the PMP-22, MPZ, and ERG2 genes and how these mutations specifically affect the function of the myelin proteins or how these interact with one another and the axons.

▶ CMT DISEASE TYPE 4

CLINICAL FEATURES

This subgroup of CMT is characterized by a severe, childhood-onset, sensorimotor polyneuropathy that is usually inherited in an autosomal-recessive fashion. The electrophysiological and histological features can have demyelinating or axonal features.[132]

CMT4A was initially reported in Tunisian families but has subsequently been reported elsewhere.[84,133–140] Distal weakness is usually noted within the first 2 years of life. Motor development is generally delayed, and progressive weakness involving the proximal muscles is apparent by the end of the first decade. Some individuals who are affected become wheelchair dependent by the third decade of life. Vocal cord paresis and diaphragm paralysis can occur.[134,141] Mild sensory loss and areflexia are evident on clinical examination, as are scoliosis, pes cavus, and other skeletal deformities.

CMT4B is characterized clinically by distal greater than proximal weakness affecting the legs more than the arms and histologically by the abundance of focally folded myelin sheaths on nerve biopsy.[142–144] Weakness is usually apparent at birth or within the first year of life but may not be apparent until the third decade. Motor milestones are often delayed but children do generally become ambulatory. Weakness is slowly progressive and the ability to ambulate without a wheelchair may be lost over time. Sensation is reduced, particularly large fiber function, and muscle stretch reflexes are generally unobtainable. Some people develop scoliosis.

CMT4C was initially described in two Algerian kinships.[145] The main clinical features are delay in walking until 18–24 months, deformities in the feet and spine by 5 years of age, and distal greater than proximal leg and arm weakness. Reduced sensation primarily affects large fiber modalities and is evident prominently in patients with severe motor weakness. Some patients develop sensorineural hearing loss. Muscle stretch reflexes are reduced or absent. Hypertrophy of the nerves may be appreciated.

CMT4D is probably allelic to hereditary motor and sensory neuropathy with deafness—Lom (HMSNL) (discussed in a subsequent section).

CMT4E is another name for congenital hypomyelinating neuropathy and most of these cases have mutations in PMP-22, MPZ, or ERG2 genes. So we feel that these are better classified as CMT3, which is discussed previously.

CMT4F is an autosomal-recessive neuropathy that otherwise resembles CMT3 clinically and electrophysiologically.[146–148] Individuals who are affected manifest in early childhood, with weakness leading to developmental motor delay, sensory loss, and areflexia. Pes cavus and kyphoscoliosis are common.

CMT4G has been reported in several gypsy kinships. Distal lower extremity weakness develops in the first two decades of life followed by distal upper extremity weakness.[149]

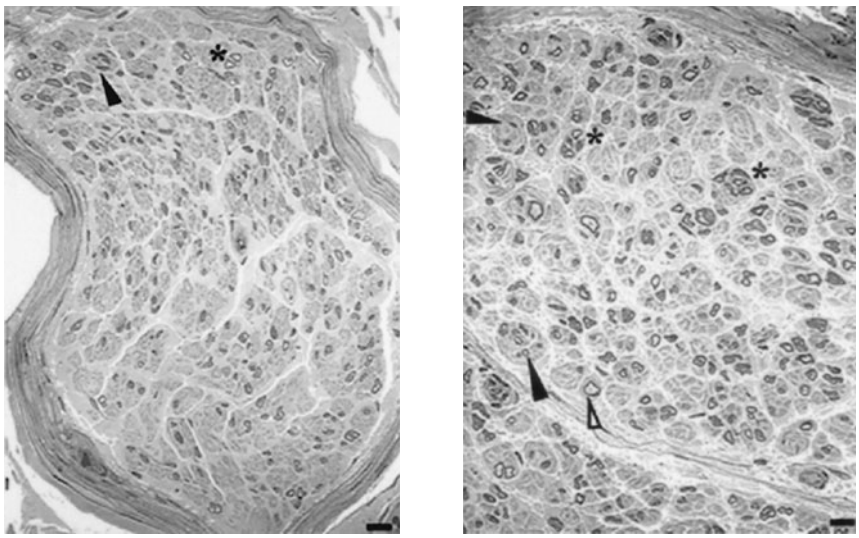
CMT4H presents in the first 2 years of life with severe weakness and resembles CMT3 clinically and electrophysiologically.[150]

LABORATORY FEATURES

CSF protein is reportedly normal in CMT4A and CMT4C but has been elevated in some reported cases of CMT4B. NCS are markedly abnormal in the various subtypes of CMT4.[133,142,143,151] SNAPs are generally unobtainable, while CMAPs are usually reduced in amplitude. In CMT4A, the CVs can range from being quite slow (less than 20 m/s) to being normal. Thus, electrophysiologically, CMT4A can appear to be a primary demyelinating neuropathy in some patients and an axonal neuropathy in others.[84,133–139,140] Motor NCVs are often less than 10 m/s in CMT4B.[142–144] In CMT4C, motor NCVs are slightly faster (ranging from 14 to 32 m/s, mean 24 m/s in the median nerve).[144] CMT4F is associated with marked slowing of motor NCV.[152]

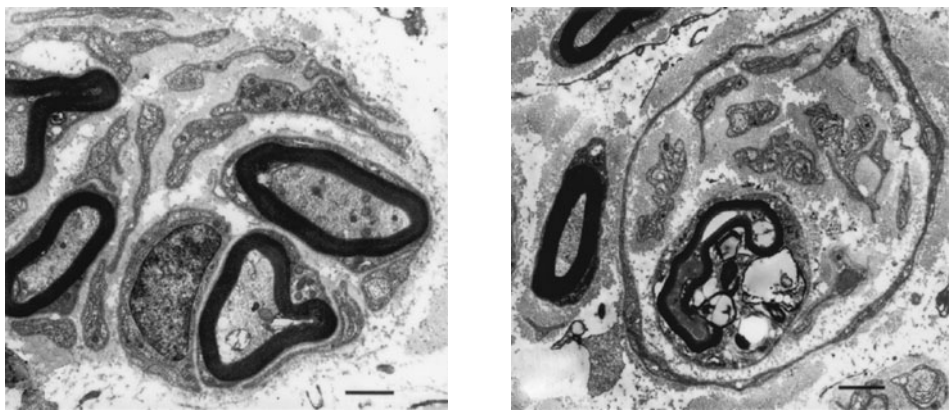
HISTOPATHOLOGY

In CMT4A, nerve biopsies reveal a marked reduction of myelinated nerve fibers, severe hypomyelination, and basal lamina onion bulbs (Figs. 9–8 and 9–9).[133,135–140] Hypomyelination, loss of myelinated



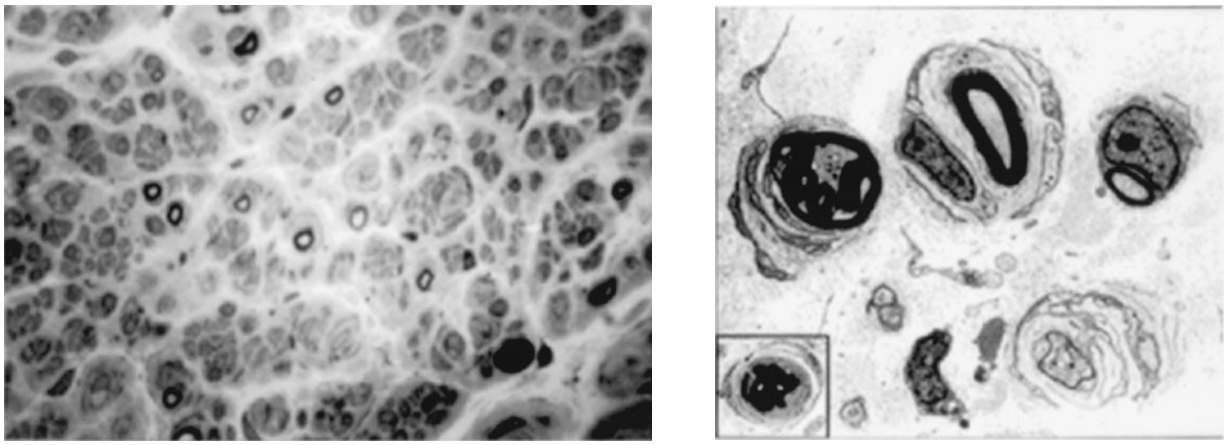
A B

Figure 9–8. CMT4 A. Semithin transverse section through sural nerve from two patients (A and B), showing a pronounced depletion of myelinated fibers. Remaining fibers are of very small size, sometimes assembled in regenerative clusters. *Note the proliferation of Schwann cells in circular fashion forming onion bulbs, particularly around cluster (black arrowhead). Some fibers are thinly myelinated (open arrowheads). Bar = 10 μm. (With permission from Sevilla T, Cuesta A, Chumillas MJ, et al. Clinical, electrophysiological and morphological findings of Charcot–Marie–Tooth neuropathy with vocal cord palsy and mutations in the GDAP1 gene. Brain 2003;126(Pt 9):2023–2033, Fig. 2, p. 2027.)



A B

Figure 9–9. CMT4 A. EM. (A) A cluster of small myelinated fibers is surrounded by a concentric array of Schwann cell processes with which numerous unmyelinated axons are associated. (B) A myelinated fiber undergoing active axonal degeneration along with several groups of unmyelinated fibers fully encircled by a single Schwann cell. Bars = 2 μm. (With permission from Sevilla T, Cuesta A, Chumillas MJ, et al. Clinical, electrophysiological and morphological findings of Charcot–Marie–Tooth neuropathy with vocal cord palsy and mutations in the GDAP1 gene. Brain 2003;126(Pt 9):2023–2033, Fig. 5, p. 2029.)



A B

Figure 9–10. CMT4 F. (A) Light microscopy. Cross semithin–epon section of the sural nerve. Loss of myelinated fibers of all diameters, small onion bulb structures, and tomacula. (B) Electron microscopy. Onion bulb formations, fiber with focally folded myelin. Inset: A naked axon with myelin infoldings surrounded by an onion bulb of mixed type. (With permission from Kabzinska D, Drac H, Sherman DL, et al. Charcot–Marie–Tooth type 4F disease caused by S399fsx410 mutation in the PRX gene. Neurology 2006;66(5):745–747, Fig. 1, p. 746.)

nerve fibers, basal lamina onion bulbs, and numerous fibers with excessively folded myelin sheaths are features of CMT4B.[25,142,143] Some have characterized these focal myelin thickenings as tomacula,[142] while others have advocated that these are histologically distinct from tomacula.[143] In CMT4C, there is a marked reduction of large-diameter myelinated nerve fibers with relative sparing of small- and intermediate-diameter fibers.[145] The remaining axons are thinly myelinated and surrounded by Schwann cell proliferation forming classic onion bulbs. CMT4F is characterized by severe axonal loss, with remaining axons being hypomyelinated and associated with onion bulbs (Fig. 9–10).[146–148] In addition, occasional tomacula formation with focal myelin thickening, abnormalities of the paranodal myelin loops, and focal absence of paranodal septate-like junctions between the terminal loops and the axon are appreciated in CMT4F.[152]

MOLECULAR GENETICS AND PATHOGENESIS

CMT4A is caused by mutations in the GDAP1 gene located on chromosome 8q13–q21.[84,133–141,154] Both neurons and Schwann cells express GDAP1, which may explain why mutations may be associated with electrophysiological and histopathological features of either an axonal or a demyelinating neuropathy.[155,156] GDAP1 is located in the mitochondrial outer membrane and helps regulate the mitochondrial network and belongs to a group of proteins, such as mitofusion-2, which when abnormal lead to CMT.

CMT4B with focally folded myelin sheaths appears to be genetically heterogeneic.[151,153,157,158] Focally folded myelin sheaths are not specific for CMT4B, as these have also been described in patients with point mutations in the MPZ gene, which is the causative gene in CMT1B.[159] CMT4B1 are caused by mutations in the myotubularin-related protein-2 (MTMR2) gene located on chromosome 11q23[157,158] MTMR2 is a dual specificity phosphatase, and its deficiency may lead to the phosphorylation of an as-yet-unknown substrate that results in Schwann cell proliferation and abnormal myelinogenesis.[157] Of note, a related member of this same protein family, MTM-1, is responsible for X-linked myotubular myopathy (see "Congenital Myopathies," Chapter 25). Mutations in MTMR2 may lead to malfunction of neural membrane recycling, membrane trafficking, and/or endocytic or exocytotic processes, combined with altered axon–Schwann cell interactions.[160] Studies suggest that the loss of MTMR2 in patients, by decreasing Schwann cells proliferation and survival, may impair the first stages of myelination of the peripheral nervous system.[161]

CMT4B2 is caused by mutation in the myotubularin-related 13 gene, MTMR13, also known as SET-binding factor 2 (SBF2) on chromosome 11p15.[144,162] MTMR13 is a member of the pseudophosphatase branch of myotubularins and bears striking homology to MTMR2. Myotubularin-related proteins have been suggested to work in phosphoinositide-mediated signaling events, which may also convey control of myelination.

CMT4C localizes to chromosome 5q23–33.[163] CMT4D is better known as HSMNL, which is discussed in the next section. CMT4E is another name for congenital hypomyelinating neuropathy, but most of

these cases have mutations in PMP-22, MPZ, or ERG2 genes.

CMT4F is caused by mutations in the gene that encodes for periaxin located on chromosome 19q13.13–q13.2.[146,147,152] Periaxin normally localizes to the Schmidt–Lanterman incisures and paranodal membranes and is thought to be important in myelin–axon interactions and maintenance of normal myelin structure.

CMT4G has been linked to chromosome 10q23.2, but the gene has not been identified.[149]

CMT4H is caused by mutations in the gene that encodes for frabin (FGD4) on chromosome 12p11.21–q13.11.[150] This locus is similar to that of CMT2G. The mutation may lead to impaired Rho GTPase signaling. It may play a role in regulating the actin cytoskeleton.

▶ HMSNL/CMT4D

CLINICAL FEATURES

Lom (HMSNL) is a rare autosomal-recessive demyelinating neuropathy that was initially recognized in Bulgarian gypsies from the town of Lom[109,164]; however, not all affected people are of gypsy ancestry.[165] Individuals who are affected develop distal leg weakness in the first decade of life, which progresses to involve the hands by the second decade of life. Subsequently, hearing loss is generally noted in the third decade. Reduced sensation to all modalities and hyporeflexia are appreciated on examination. Pes cavus, hammer toes, clawing of the hands, and scoliosis are also common.

LABORATORY FEATURES

NCS reveal a demyelinating sensorimotor polyneuropathy.[109,164] Sensory studies are generally unobtainable, but when SNAPs are present, the distal latencies are prolonged and the NCVs are slow. Motor NCS are remarkable for markedly prolonged distal latencies and slow NCVs (ranging from 9 to 20 m/s) in the arms and legs. Active denervation changes are appreciated on needle EMG. Brainstem auditory-evoked potentials reveal both peripheral and central slowing of auditory conduction. Subcortical white matter abnormalities may be appreciated on magnetic resonance imaging of the brain.[165]

HISTOPATHOLOGY

Sural nerve biopsies reveal a loss of large and small myelinated nerve fibers with relative preservation of unmyelinated axons. Remaining axons are thinly myelinated, and onion-bulb formations may also be evident.

MOLECULAR GENETICS AND PATHOGENESIS

HMSNL is caused by mutations in the N-myc downstream-regulated gene 1 (NDRG1) located on chromosome 8q24.[109] NDRG1 may function as a signaling protein shuttling between the cytoplasm and nucleus and have role in growth arrest and cell differentiation.[109]

▶ X-LINKED CMT DISEASE

CMT DISEASE 1X

Clinical Features

CMT disease 1X (CMT1X) is an X-linked dominant disorder with clinical features similar to CMT1, except that the neuropathy is much more severe in men than in women.[10,166–170] CMT1X accounts for approximately 12% of the overall CMT cases. Men usually present in the first two decades of life with atrophy and weakness of the distal arms and legs, areflexia, pes cavus, hammertoes, and claw–hand deformities. Most do not complain of a sensory disturbance, although reduced sensation to all modalities can be demonstrated on examination. As opposed to men, obligate women carriers are frequently asymptomatic, onset is usually after the second decade of life, and the neuropathy is milder in severity. Rarely, patients with CMT1X can present with transient CNS symptoms and marked white matter lesions on magnetic resonance imaging scans.[171–173]

Laboratory Features

NCS reveal features of both demyelination and axonal degeneration, which are more severe in men compared to women.[2,10,166,167,169,170,174–177] SNAPs are reduced in amplitude or absent in the majority of patients but, when obtainable, the distal latencies are prolonged and CVs are slow. Peroneal CMAPs are absent in as many as two-thirds of patients, while median and ulnar CMAPs are often reduced in amplitude.[167,169] Distal motor latencies are prolonged in men more than in women with CMT1X.[167]

In men, motor NCVs in the arms and legs are moderately slow (median nerve 31 +/− 6 m/s; peroneal nerve 31.0 +/− 3.9 m/s).[169] These NCVs in men with CMT1X are approximately 10 m/s faster than that usually seen in autosomal-dominant forms of CMT1. In contrast, motor NCVs in women with CMT1X may be only slightly slow (median nerve 44.6 +/− 8.8 m/s; peroneal nerve 33.8 +/− 8.1 m/s).[169] As previously discussed, uniform slowing of motor NCVs is the rule in CMT1 and helps distinguish hereditary from acquired forms of demyelinating polyneuropathy.[15] However, nonuniform slowing

of conduction between different nerves and along different segments of individual nerves resulting in temporal dispersion has been described in some cases of CMT1X, particularly in women.[176,177] Motor unit nerve estimates demonstrate a reduction in units, which correlates with clinical severity.[170]

Histopathology

Sensory nerve biopsies reveal a loss of myelinated nerve fibers, especially of large-diameter fibers, along with axonal degeneration and atrophy, and clusters of thinly myelinated regenerating fibers.[10,167,174,176] A mild degree of Schwann cell proliferation (onion bulbs) can also be seen surrounding some of the thinly myelinated fibers. A mixture of demyelination and remyelination is evident on teased fiber preparations.

Molecular Genetics and Pathogenesis

CMT1X is caused by mutations in the connexin-32 gene located on chromosome Xq13.[2,168,170,178–180] Connexins are gap junction structural proteins, which are important in cell-to-cell communication. Connexin-32 oligomerizes into a hexameric structure on the Schwann cell lamella in the paranodal region and Schmidt–Lanterman incisures, where it forms intercellular channels, which allow diffusion of ions, nutrients, and other small molecules through the compact myelin to the inner most layers of the myelin sheath and the axon itself. The mutations in connexin-32 lead to demyelination and axonal degeneration.[176,181]

CMT 2X

CMT 2X is a rare X-linked recessive axonal motor and sensory neuropathy associated with deafness and mental retardation.[182] Distal limb weakness, atrophy, and sensory loss develop in early childhood. Affected males often develop significant hearing loss and may also have mental retardation, while female carriers are asymptomatic. CMT 2X links to Xq24–q25, although the specific gene has not yet been identified.

▶ MISCELLANEOUS HEREDITARY MOTOR AND SENSORY NEUROPATHIES

PROXIMAL HEREDITARY MOTOR AND SENSORY NEUROPATHY/ NEURONOPATHY

Clinical Features

Proximal hereditary motor and sensory neuropathy/ neuronopathy resembles Kennedy disease (see "Spinal Muscular Atrophies," Chapter 6), except that it is inherited in an autosomal-dominant inheritance rather than X linked.[183] Muscle cramps are the earliest symptoms. Individuals who are affected usually develop progressive proximal muscle atrophy, weakness, and fasciculations in the legs worse than in the arms after the age of 30 years (mean 45 +/− 6 years). People become nonambulatory 5–20 years after onset. Facial muscles are also slightly weak, but neck flexors and extensors remain relatively strong. The tongue may be slightly weak but dysphagia and dysarthria are not common. Nevertheless, bulbar and respiratory muscle weakness can develop late in the course of the disease. Some patients complain of mild dysesthesias in the distal legs and hands. Decreased sensation to all modalities, particularly vibratory preception and proprioception, is evident on examination. As in Kennedy's disease, muscle stretch reflexes are diminished or absent, neurogenic tremor is common, and there is an association with type 2 diabetes mellitus.

Laboratory Features

Serum creatine kinase (CK) levels are often mildly elevated. SNAPs are reduced in amplitude or unobtainable as in Kennedy's disease. CMAP amplitudes can be moderately decreased, while the distal latencies and NCVs are relatively preserved. Needle EMG reveals diffuse fasciculation and fibrillation potentials and decreased recruitment of long-duration, large-amplitude, polyphasic MUAPs.

Histopathology

Nerve biopsies show a loss of large and small myelinated nerve fibers with preservation of unmyelinated nerve fibers.[183] An autopsy demonstrated only a few remaining atrophic anterior horn cells along with significant loss off neurons in the spinal roots, cauda equina, and dorsal root ganglia.[183]

Molecular Genetics and Pathogenesis

This disorder has been linked to chromosome 3p14.1–q13, but the gene has not been identified (Table 9–1).[183]

HEREDITARY NEURALGIC AMYOTROPHY

Clinical Features

Hereditary neuralgic amyotrophy (HNA) is an autosomal-dominant disorder, characterized by recurrent attacks of pain, weakness, and sensory loss in the distribution of the brachial plexus often beginning in childhood.[184] These attacks are similar to those seen with idiopathic brachial plexitis (Parsonage–Turner syndrome), and most patients fully or at least partially recover over several weeks or months. Varying degrees of

hypotelorism, epicanthal folds, cleft palate, syndactyly, micrognathia, and facial asymmetry are seen in some patients. HNA can be distinguished from brachial plexopathy that can occur in HNPP because of the lack of severe pain in HNPP. Further, unlike HNPP, the neuropathy in HNA is restricted to the brachial plexus and is axonal in nature.

Laboratory Features

The electrodiagnostic findings are typically of classic brachial plexitis.[184] Amplitudes of SNAPs and CMAPs of the affected trunks, cords, divisions, and individual nerves are reduced while the distal latencies and CVs relatively preserved. Needle EMG reveals fibrillation and positive sharp waves in affect muscle groups along with decreased recruitment of MUAPs. Following reinnervation, especially after recurrent attacks of paresis, large polyphasic MUAPs become evident. NCS and EMG of the unaffected arm and the lower limbs are normal. The electrophysiological studies in HNA reflect an axonal process localized to the brachial plexus, while HNPP is a generalized or multifocal process, which is demyelinating in nature.

Histopathology

Sural nerve biopsies should be normal in patients with HNA. Although tomaculae have been reported in some patients,[52] these were most likely cases of HNPP rather than HNA.

Molecular Genetics and Pathogenesis

HNA is caused by mutations in the gene septin 9 (SEPT9) located on chromosome 17q25.[185] Septins may be important in formation of the neuronal cytoskeleton and have a role in cell division.

SCAPULOPERONEAL NEUROPATHY

Clinical Features

A scapuloperoneal distribution of weakness can be seen in several different myopathic and neurogenic disorders, including scapuloperoneal muscular dystrophy (some cases of which have also been termed myofibrillar myopathy (see "Muscular Dystrophy," Chapter 24), a scapuloperoneal neuropathy (Davidenkow syndrome), and perhaps even a pure motor neuropathy or spinal muscular atrophy form.[186–193] In regards to scapuloperoneal neuropathy or motor neuropathy, symptoms usually develop insidiously in the second or third decade of life. The early symptoms are related to progressive foot drop, with individuals complaining of tripping easily and recurrent ankle sprains similar to CMT. Gradually, proximal weakness of the legs and shoulder girdle arises. Examination reveals muscle wasting about the shoulder girdle (pectoralis, serratus anterior, rhomboids, supraspinatus, infraspinatus, trapezius, deltoid, and brachioradialis) muscles as well as the anterior compartment (peroneal innervated) muscles of the legs. Distal musculature of the arms is relatively spared. The unusual muscle distribution of proximal upper limb and distal lower limb muscles is the clinical distinguishing characteristic of the scapuloperoneal syndromes. Sensation may be normal or reduced. Muscle stretch reflexes may be normal or reduced and the plantar responses are flexor. Pes cavus and hammertoes are commonly appreciated.

Laboratory Features

Median and ulnar CMAPs and NCS are typically normal in the arms; however, peroneal CMAPs are usually reduced in amplitude with preservation of distal latency and CV. The SNAPs may be reduced in amplitude in the legs and arms, but individuals with scapuloperoneal motor neuropathy or spinal muscular atrophy (SMA) have normal sensory studies. The needle EMG examination reveals reduced recruitment of large-amplitude, long-duration, polyphasic MUAPs in weak muscle groups.

Histopathology

Sural and superficial peroneal nerve biopsies demonstrate axonal degeneration. Autopsies have demonstrated degeneration of the anterior horn cells. Muscle biopsy demonstrates small angulated fibers, grouped atrophy, and fiber-type grouping, which can help distinguish the neuropathy from cases of scapuloperoneal myopathy.

Molecular Genetics and Pathogenesis

The pathogenic basis for the different forms of scapulperoneal neuropathy or SMA is heterogeneic. Some cases appear to be inherited in an autosomal-dominant or autosomal-recessive pattern. One individual with Davidenkow syndrome was found to have the monochromosomic 17p11.2 deletion, which often is associated with HNPP.[194] In addition, an autosomal-dominant family with scapuloperoneal SMA has been linked to chromosome 12q24.1–q24.31, but the gene has not been identified.[193]

HEREDITARY SENSORY AND AUTONOMIC NEUROPATHIES

HSANs constitute a rare group of hereditary neuropathy in which sensory and autonomic dysfunction predominate over motor function loss unlike CMT in which motor findings are most prominent (Table 9–2).[78] Nevertheless, individuals who are affected can develop

▶ TABLE 9–2. HEREDITARY SENSORY AND AUTONOMIC NEUROPATHIES

Type	Inheritance	Chromosome	Gene	Onset	Clinical Features	Neurophysiology	Pathology
HSAN1	AD Rare AR and X-linked cases also reported	9q22	*SPTLC1*	Second to fourth decade	Loss of pain and temperature sensation; autonomic functions relatively spared (except for reduced sweating); arthropathies and foot ulcers are common; distal weakness may develop	Normal or only mildly reduced CMAPs and SNAPs amplitudes; near nerve recordings: reduced amplitudes of Aδ and C-fibers; abnormal QST (particularly temperature perception); SSR: absent	Distal greater than proximal loss of small myelinated and unmyelinated fibers more than large myelinated fibers
HSAN2	AR	12p13.33	*PRKWNK1*	Infancy to early childhood	Severe loss of sensation to all modalities (particularly touch-pressure/vibration); mutilation of hands and feet; impaired sweating, impotence, and bladder function	Absent SNAPs; normal or only mildly reduced CMAPs amplitudes; abnormal QST (particularly vibratory perception)	Virtual absence of large myelinated fibers; mild loss of small myelinated and unmyelinated fibers
HSAN3	AR	9q21	*IKAP*	Infancy	Severe autonomic dysfunction (labile BP, sweating, and temperature); decreased pain–temperature sensation more than touch/vibration; absence of fungiform papillae and taste; increased mortality	Decreased SNAP amplitudes; mild slowing of CMAP velocities; abnormal QST; normal SSR	Marked reduction of small myelinated and unmyelinated fibers and to a lesser extent large myelinated fibers; loss of neurons in sympathetic ganglia
HSAN4	AR	3q	*trkA/NGF* receptor	Infancy	Absence of pain and temperature sensation; episodic fevers, postural hypotension, and anhidrosis; self-mutilation; mental retardation	Mildly reduced amplitudes and slow CVs of SNAPs and to a lesser extent of CMAPs; abnormal QST (particularly temperature perception); SSR: intact	Virtual absence of small myelinated and unmyelinated fibers and a moderate loss of large myelinated fibers
HSAN5	AD or AR	1p11.2–p13.2	*NGFb*	Infancy	Congenital indifference to painful stimuli despite intact sensation to all modalities and normal deep tendon reflexes	Normal SNAPs, CMAPs, QST, and SSR	Normal nerve biopsies or only mild loss of small myelinated and unmyelinated fibers

HSAN, hereditary sensory and autonomic neuropathy; AD, autosomal dominant; AR, autosomal recessive; TrkA/NGF, tyrosine kinase A/nerve growth factor; SPTLC1, serine palmitoyltransferase long chain base 1; IKAP, I_KB kinase complex-associated protein; SNAP, sensory nerve action potential; CMAP, compound muscle action potential; QST, quantitative sensory testing; SSR, sympathetic skin response.

Modified with permission from Amato AA, Dumitru D. Hereditary neuropathies. In Dumitru D, Amato AA, Swartz MJ (eds). Electrodiagnostic Medicine, 2nd edn. Philadelphia: Hanley & Belfus, 2002, pp. 889–936, Table 22–3, p. 912.

motor weakness and thus can overlap with CMT (Fig. 9–1). There are no medical therapies available to treat these neuropathies, other than prevention and treatment of mutilating skin and bone lesions.

HSAN Type 1

Clinical Features

The HSAN1 is the most common of the HSANs and is inherited in an autosomal-dominant fashion. HSAN1 usually presents in the second through fourth decades and this later age of onset is helpful in distinguishing it from other subtypes of HSANs, which typically manifest in infancy or childhood.[195–197] HSAN1 is slowly progressive and predominantly affects the small myelinated and unmyelinated nerve fibers, resulting in the loss of pain and temperature sensation in the feet and hands. This can lead to the development of deep dermal ulcerations, recurrent osteomyelitis, Charcot joints, bone loss, gross foot and hand deformities, and amputated digits. Although most people with HSAN1 do not complain of numbness, they often describe burning, aching, or lancinating pains. Autonomic neuropathy is not a prominent feature, but bladder dysfunction and reduced sweating in the feet may occur.

On examination, there is reduced sensation to all modalities, particularly to pin prick and temperature. Mild-to-moderate distal arm and leg weakness develop over time. However, some individuals develop severe distal extremity weakness early in the course.[197] Muscle stretch reflexes are usually absent at the ankles but may be normal or reduced elsewhere. As with CMT, pes cavus and hammertoe deformities can be seen.

Laboratory Features

CSF examination is usually normal. Increased levels of IgA in the serum may be seen. Sensory NCS reveal normal or only mildly reduced amplitudes with normal distal latencies and NCVs.[197,198] Reduced amplitudes of Aδ and C potentials reflecting the loss of small myelinated and unmyelinated nerve fibers can be appreciated on near nerve recordings. Motor NCS are relatively spared; however, reduced amplitudes and of slight slowing of conduction develop over time. Needle EMG can demonstrate positive sharp waves and fibrillation potentials, with large MUAPs suggesting chronic reinnervation. Sympathetic skin responses are often unobtainable.[198]

Histopathology

Peripheral nerve biopsies demonstrate reduced density of all fiber sizes with a preferential loss of small myelinated and unmyelinated fibers (Fig. 9–11).[197] Muscle biopsies demonstrate features of neurogenic atrophy due to motor nerve involvement. Autopsy studies have revealed degeneration of dorsal root ganglia neurons and of the posterior columns, suggesting a primary sensory neuronopathy or ganglionopathy.[87]

Molecular Genetics and Pathogenesis

HSAN1A is caused by mutations in the serine palmitolytransferase long chain base-1 (*SPTLC1*) gene that is located on chromosome 9q22.[199–201] Serine palmitolytransferase catalyzes the rate-limiting, regulatory step in the biosynthesis of sphingolipids, and the autosomal-dominant inheritance suggests that the mutations either cause a gain of function of the enzyme or result in dominant-negative inhibition.[200] Mutations in SPTLC1 in lymphoblast cell lines cause an increase in the de novo synthesis of ceramide (a sphingolipid) that appears to trigger apoptotic cell death.[201]

There are reports of HSAN1-like neuropathy with either an autosomal-recessive or an X-linked form of inheritance, suggesting some genetic heterogeneity. HSAN1B associated with cough and gastroesophageal reflux in a large Australian family has been linked to chromosome 3p22–p24.[202]

HSAN Type 2

Clinical Features

HSAN2 is an autosomal-recessive disorder that manifests at birth or early childhood, with severe sensory loss to all modalities and areflexia.[24,203–206] Unlike HSAN1, patients with HSAN2 do not complain of lancinating pains. Autonomic dysfunction manifests with impaired sweating, bladder dysfunction, and impotence. However, postural hypotension is not common. Muscle strength is relatively normal. Scoliosis may be present. This severe sensory loss leads to pressure ulcers, Charcot joints, osteomyelitis, and bone resorption, and amputation of digits in the hands and feet can occur (Fig. 9–12).

Laboratory Features

NCS are remarkable for being absent, while the CMAPs are normal or have slightly reduced amplitudes.[24,203,205–208] Needle EMG can reveal positive sharp waves, fibrillation potentials, and a reduced recruitment of large, polyphasic MUAPs, particularly in the distal legs.

Histopathology

Nerve biopsies demonstrate a virtual absence of all myelinated fibers with less severe diminution of unmyelinated fibers (Fig. 9–13).

Molecular Genetics and Pathogenesis

HSAN2 is caused by mutations in the *PRKWNK1* gene on chromosome 12p13.33.[209] This protein may play a role

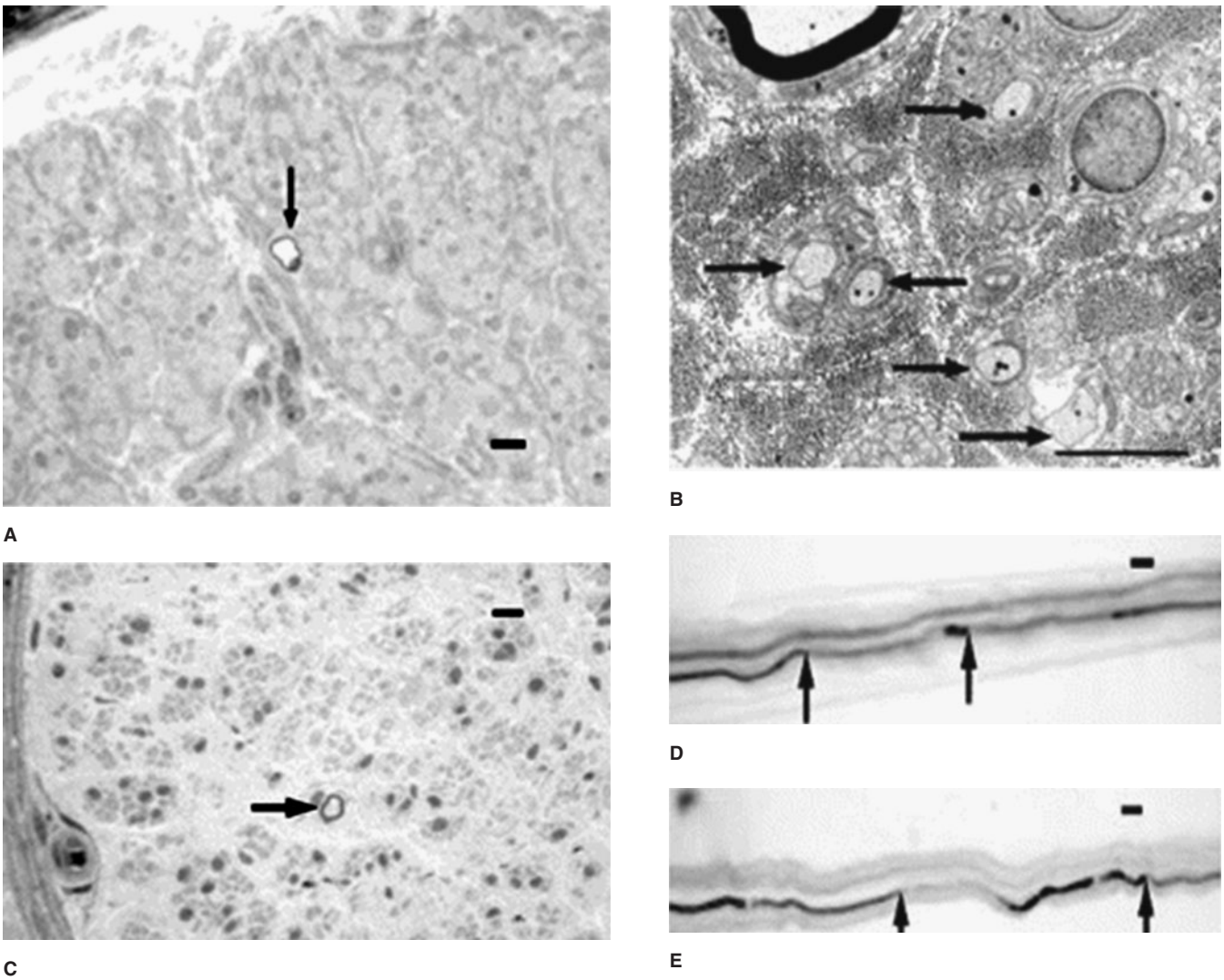


Figure 9–11. Hereditary sensory and autonomic neuropathy type 1. A 1-μm stained resin section (A) and electron micrograph (B) of a sural nerve biopsy. The single myelinated fiber in (A) (arrow) is visible at the top of (B); many more unmyelinated axons (arrows) remain than being myelinated. Scale bar = 10 μm (A) and 5 μm (B). A 1-μm stained resin section (C) and teased fiber preparation of the sural nerve biopsy from another patient with HSNA1 (D and E). There are around 50 myelinated fibers in the whole biopsy. At least two of them appear to have internodes that seem to be demyelinating in a segmental pattern (between arrows D and E). Scale bar = 10 μm (C) and 20 μm (D and E). (With permission from Houlden H, King R, Blake J, et al. Clinical, pathological and genetic characterization of hereditary sensory and autonomic neuropathy type 1 (HSAN I). Brain 2006; 129(Pt 2):411–425, Fig. 2, p. 420.)

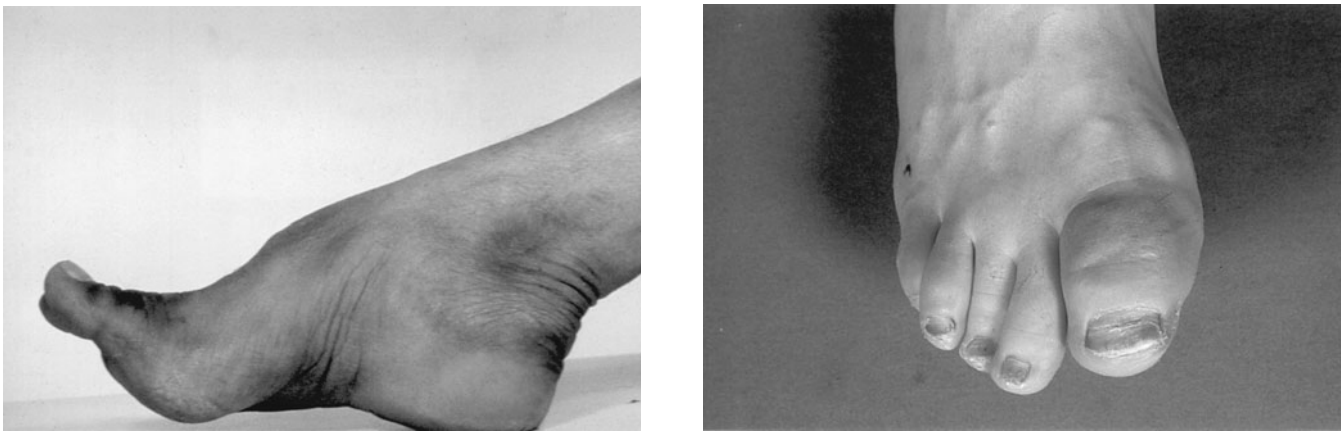
in the development and/or maintenance of peripheral sensory neurons or their supporting Schwann cells.

HSAN3 (Riley–Day Syndrome; Familial Dysautonomia)

Clinical Features

HSAN3 is a rare autosomal-recessive disorder that manifests in infancy with feeding difficulties due to poor suck, crying without tears (alacrima), blotchy skin, unexplained fluctuations in body temperature and blood pressure, and repeated vomiting.[118,210–212] Other autonomic features include esophageal and gastrointestinal dysmotility, excessive sweating, tonic pupils, and postural hypotension. Recurrent pulmonary infections are common. Developmental delay and seizures may also occur, although intelligence is normal. Most patients are of Ashkenazi Jews heritage in whom the incidence of the disease is 1:3700 live births and carrier frequency is 1:32.[213] HSAN3 is associated with an increased mortality, with a 30-year survival of approximately 50%.[213]

Examination reveals reduced pain and temperature perception and, to a lesser extent, a reduction in proprioception and vibration. Of note, there is an absence of fungiform papillae of the tongue and impaired taste



A B

Figure 9–12. Hereditary sensory and autonomic neuropathy type 2. Foot deformities such as pes cavus are common (A). Because of the severe lack of sensation, these patients are prone to developing neurogenic arthropathies (B). (With permission from Amato AA, Dumitru D. Hereditary neuropathies. In Dumitru D, Amato AA, Swartz MJ (eds). Electrodiagnostic Medicine, 2nd edn. Philadelphia: Hanley & Belfus, 2002, pp. 889–936, Fig. 22–7A and B, p. 913.)

sensation. Muscle strength is usually normal. Muscle stretch reflexes are reduced or absent. Corneal reflexes are also often absent. Mutilation and amputations of the distal extremities are not usually seen in HSAN3, but occasional Charcot joints occur. Short stature and scoliosis are common.

Laboratory Features

SNAPs have only slightly reduced amplitudes and slow CVs, while CMAPs are normal. Sympathetic skin responses are preserved, but quantitative sensory testing reveals impaired heat, cold, and vibratory perception.[118]

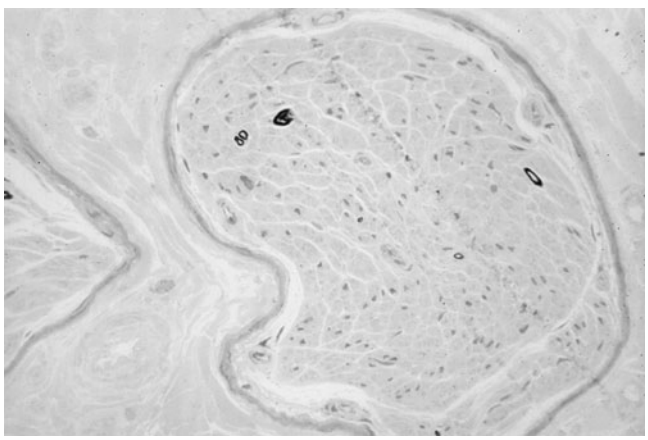


Figure 9–13. Hereditary sensory and autonomic neuropathy type 2. Sural nerve biopsy reveals a severe loss of myelinated and unmyelinated nerve fibers. Semithin, epoxy resin. (With permission from Amato AA, Dumitru D. Hereditary neuropathies. In Dumitru D, Amato AA, Swartz MJ (eds). Electrodiagnostic Medicine, 2nd edn. Philadelphia: Hanley & Belfus, 2002, pp. 889–936, Fig. 22–8, p. 913.)

Histopathology

Autopsy studies have demonstrated a loss of neurons within the cervical and thoracic sympathetic ganglia as well as in the dorsal root ganglia and trigeminal sensory nucleus. Sural nerve biopsies reveal a marked reduction of unmyelinated fibers (5–15% of normal) and less drop of the large myelinated fibers (15–50% of normal).

Molecular Genetics and Pathogenesis

HSAN3 is caused by mutations in the I_KB kinase complex-associated protein (IKAP) gene located on chromosome 9q31.[213–216] IKAP may activate genes important in the development of sensory and autonomic neurons. Importantly, carrier detection and prenatal diagnosis can be made.

HSAN4 (Congenital Sensory Neuropathy with Anhidrosis)

Clinical Features

HSAN4 is an extremely rare autosomal-recessive disorder that manifests in infancy or childhood with an insensitivity to pain, self-mutilation, anhidrosis, and reduced mentation.[118,217] Individuals who are affected can become extremely poikilothermic in hot temperatures due to the inability to sweat. In addition, they can develop severe postural hypotension. Sensory examination demonstrates a prominent loss of pain and temperature perception, while vibratory sensation and proprioception are less severely affected. Motor strength and reflexes are preserved.

Laboratory Features

NCS reveal normal or only slightly reduced SNAP and CMAP amplitudes and CVs. Quantitative sensory testing reveals markedly abnormal heat and cold perception and to a lesser extent vibratory perception.[118] Unlike HSAN3, sympathetic skin responses are unobtainable in HSAN4.[118,218]

Histopathology

As expected on the basis of the clinical examination, sural nerve biopsies reveal a virtual absence of unmyelinated and small myelinated fibers and to a lesser extent a reduction of large fibers to 45–65% of normal.[118,219]

Molecular Genetics and Pathogenesis

HSAN4 is caused by mutations in the tyrosine kinase A–nerve growth factor (trkA/NGF) receptor gene located on chromosome 3q.[220–222] However, no mutations in this gene have been identified in affected people, suggesting genetic heterogeneity of HSAN4. Tyrosine kinase receptors are ligands for neurotrophins. In this regard, NGF, a neurotrophin, binds to trkA receptors, which are highly expressed on dorsal root ganglia and sympathetic neurons. Once bound to the receptor, the trkA–NGF complex is internalized into the nucleus of the neuron, where it regulates the expression of genes important for neuronal maturation, growth, and survival. Mutations in the trkA/NGF receptor results in a loss of function of this receptor–ligand complex, which in turn leads to degeneration of sympathetic ganglion neurons and nociceptive sensory neurons derived from the neural crest.[220,222]

HSAN5 (Congenital Indifference to Pain)

Clinical Features

In contrast to other types of HSAN in which individuals who are affected may have an *insensitivity* to pain, patients with HSAN5 display an *indifference* to pain. Those with HSAN5 do not appear to recognize or react to painful stimuli (i.e., withdrawal) from birth despite having normal sensitivity to other sensory modalities, normal strength, and muscle stretch reflexes.[163,223,224] There is no obvious dysautonomia.

Laboratory Features

Motor and sensory NCS, quantitative sensory testing, and autonomic testing are all usually normal.

Histopathology

Reports of sural nerve biopsies have yielded mixed results. Some have reported normal densities of myelinated and unmyelinated nerve fibers,[163] while other studies have described a mild reduction of small myelinated and unmyelinated fibers.[223–226]

Molecular Genetics and Pathogenesis

Mutations in the NGFB gene on chromosome 1p11.2–p13.2 were identified in one family classified as having HSANV.[225] Some could argue that this family actually represents a more benign subtype of HSAN4 because the nerve biopsies were abnormal although neurophysiological testing was normal. In this regard, it is interesting that NGFB binds to trkA, which is mutated in HSAN4 (see "HSAN Type 4" section).

▶ SUMMARY

As one can see, there is marked variability in clinical phenotype associated with mutations in individual genes and the same clinical phenotype can be caused by mutation in various genes associated with CMT. Further, there is much overlap of CMT with distal motor neuropathies and HSAN. A practical approach to diagnosis is based on clinical and electrodiagnostic features. Clear autosomal-dominant, autosomal-recessive, or X-linked pattern of inheritance combined with data from NCS (e.g., demyelinating, axonal, or intermediate physiology) are helpful in directing which genes one should preferentially check for mutations. CMT1A is the most common form of CMT; therefore, these individuals suspected of having CMT with demyelinating NCS, unless there is clear X-linked pattern of inheritance, should have genetic testing beginning with screening for PMP-22 duplication. The next most common form of CMT is CMT1X, caused by mutations in connexin-32 gene. As discussed, CMT1X may have demyelinating or axonal neurophysiology. If screening for PMP-22 duplications and connexin-32 mutations are unrevealing then we would look for point mutations in the PMP-22 and MPZ. As discussed, there are many other genes that when mutated can cause a demyelinating neuropathy, but these are extremely rare. Genetic testing of an individual suspected of having a hereditary axonal neuropathy would begin with mutation analysis of MFN2, connexin-32, and MPZ. Again, most other described genetic mutations are very rare. Unfortunately, there are no medical treatments available at this time but genetic counseling and supportive therapies are important.

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CHAPTER 10

Other Hereditary Neuropathies

In Chapter 9, we reviewed Charcot–Marie–Tooth syndrome and related hereditary neuropathies. Here we discuss some of the more rare types of hereditary neuropathies (Table 10–1).

▶ NEUROPATHIES ASSOCIATED WITH LYSOSOMAL STORAGE DISORDERS

The lysosomal storage disorders are associated with abnormal accumulation of lysosomal products (e.g., sphingolipids, mucolipids, etc.) within neurons, leading to dysmyelination and axonal degeneration of both central and peripheral nerves (Table 10–1). Usually, the central nervous system (CNS) manifestations overshadow the peripheral neuropathy in most of these disorders. However, some patients present with peripheral neuropathy, which can be associated with significant disability.

METACHROMATIC LEUKODYSTROPHY

Clinical Features

There are three characteristic forms of metachromatic leukodystrophy (MLD) defined by age of onset: (1) late infantile, (2) juvenile, and (3) adult onset.[1–14] Most patients have the late-infantile-onset MLD variant and develop progressive generalized weakness, decline in mental functions, dysarthria, and worsening gait between 1 and 2 years of age. Children become quadriparetic, spastic, and cortically blind and often develop seizures. On examination, generalized muscle weakness, hypotonia, hyporeflexia, and extensor plantar responses are appreciated. Most children die within 5–6 years after onset of symptoms.

The juvenile form of MLD typically presents later in childhood or adolescence but is associated with clinical features similar to the late infantile form of the disease. Patients with adult-onset MLD usually develop slowly progressive dementia, psychosis, spasticity, ataxia, extrapyramidal signs, visual impairment, and incontinence in the third or fourth decade of life.[15]

Laboratory Features

Magnetic resonance imaging (MRI) of the brain often demonstrates increased signal on T2 weighted images in the subcortical white matter (Fig. 10–1).

The diagnosis is made by demonstrating decreased arylsulfatase A activity in urine, from leukocytes, or from cultured fibroblasts. Prenatal diagnosis can be made by amniocentesis. Cerebral spinal fluid (CSF) protein is usually markedly elevated in the 100–300 mg/dL range. Motor nerve conduction studies (NCS) reveal mild to moderately reduced amplitudes, prolonged distal latencies, and marked slow conduction velocities (NCVs) ranging from 10 to 20 m/s in the legs and 20 to 40 m/s in the arms.[1,2,4,5,7–12,15–17] Conduction block is not seen, but occasionally temporal dispersion is appreciated.[11] Sensory NCS are often unobtainable, but when recordable the sensory nerve action potentials (SNAPs) are reduced in amplitude with slightly to moderately prolonged latencies and slow NCVs. Visual, brainstem, and somatosensory-evoked potentials are delayed.

Histopathology

Autopsy studies reveal degeneration of myelin in the CNS and peripheral nerves (Fig. 10–2).[3,6,10,12] Nerve biopsies can also demonstrate a decrease in myelinated fibers with evidence of demyelination and remyelination (Fig. 10–3A). The characteristic abnormality is accumulation of metachromatically staining inclusions in cytoplasm of Schwann cells (Fig. 10–3B). On electron microscopy (EM), these inclusions appear as lamellated bodies within Schwann cells (Fig. 10–3C).

Molecular Genetics and Pathogenesis

MLD is an autosomal-recessive disorder caused by mutations in the arylsulfatase A or prosaposin genes.[18] Arylsulfatase A gene and prosaposin are both enzymes required for metabolizing galactosylsulfatide (cerebroside sulfatase), a glycolipid, present in myelin membranes. Deficiency of arylsulfatase A or the proteolytic product of prosaposin results in the accumulation of sulfatides (inclusions) in Schwann cells and oligodendrocytes resulting in dysmyelination.

Treatment

No specific medications are helpful, but bone marrow transplantation may be beneficial in some patients.[19]

▶ TABLE 10–1. RARE HEREDITARY NEUROPATHIES

Hereditary disorders of lipid metabolism
Metachromatic leukodystrophy
Krabbe disease (globoid cell leukodystrophy)
Fabry disease
Adrenoleukodystrophy/adrenomyeloneuropathy
Refsum disease
Tangier disease
Cerebrotendinous xanthomatosis
Hereditary ataxias with neuropathy
Friedreich ataxia
Vitamin E deficiency
Spinocerebellar ataxia
Abetalipoproteinemia (Bassen–Kornzweig disease)
Disorders of defective DNA repair
Ataxia-telangiectasia
Cockayne syndrome
Giant axonal neuropathy
Porphyria
Acute intermittent porphyria (AIP)
Hereditary coprophyria (HCP)
Variegate porphyria (VP)

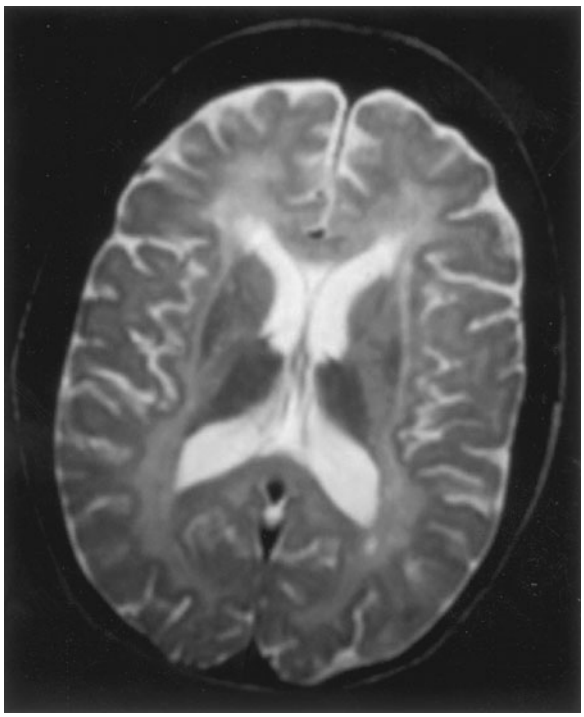


Figure 10–1. MRI of brain in a patient with MLD demonstrates widespread white matter disease on T2-weighted image. (With permission from www.uiowa.edu/~c064s01/nr287.htm.)

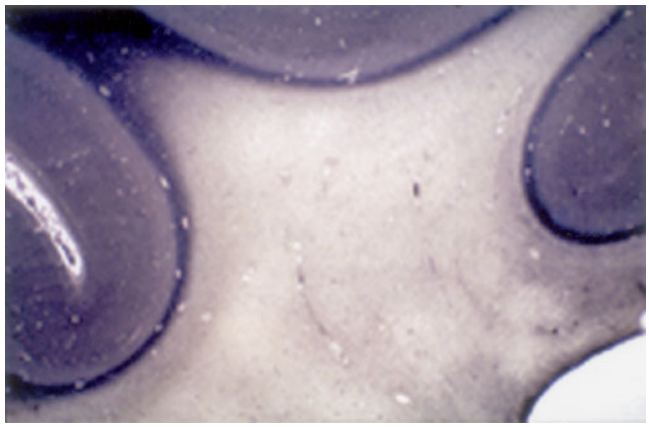


Figure 10–2. MLD pathology. Lysosomal storage of sulfatides kills oligodendrocytes and Schwann cells. Sulfatides discharged from dying cells are picked up by histiocytes. The white matter shows diffuse loss of myelin, which spares the subcortical fibers. (With permission from www.neuropathologyweb.org/chapter10/chapter10.)

KRABBE DISEASE (GLOBOID CELL LEUKODYSTROPHY)

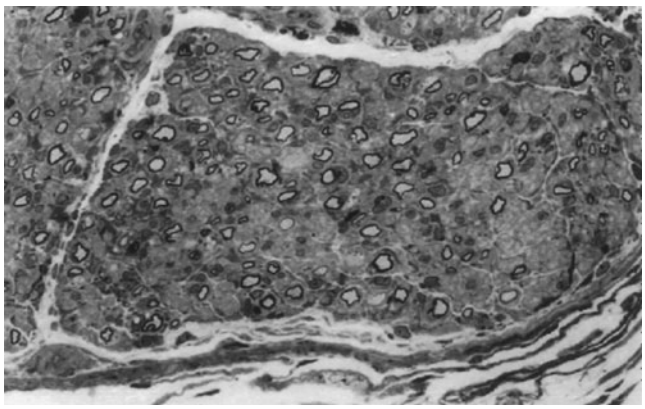
Clinical Features

Krabbe disease is another autosomal-recessive myelinopathy, affecting both the CNS and the peripheral nervous system (PNS). As with MLD, Krabbe can present early in infancy or in adulthood.[20–30] Krabbe disease usually presents between 3 and 8 months of age. Infants who are affected often appear normal at birth but later become extremely irritable and appear hypersensitive to various stimuli developing opisthotonos.[24] They develop feeding difficulties, recurrent vomiting, and often generalized tonic–clonic seizures. Progressive weakness and spasticity, blindness, and deafness ensue. Muscle stretch reflexes initially may bepathologically brisk but become hypoactive as concurrent polyneuropathy worsens. Plantar responses are extensor. Death generally occurs by the age of 2 years.

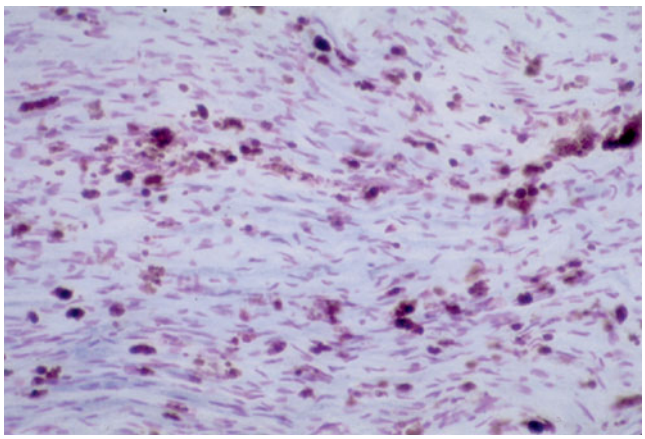
Less commonly, Krabbe disease presents later in childhood or adult life with progressive dementia, spastic paraparesis or hemiparesis, cerebellar ataxia, cortical blindness, and optic atrophy.[27,31–34] Although peripheral neuropathy is common, it is overshadowed by the CNS abnormalities. Pes cavus and scoliosis may be seen.

Laboratory Features

Diagnosis is confirmed by demonstrating decreased β-galactosidase activity in leukocytes and cultured fibroblasts. Chorionic villi can be biopsied for prenatal diagnosis. Approximately 50% of the individuals affected



A



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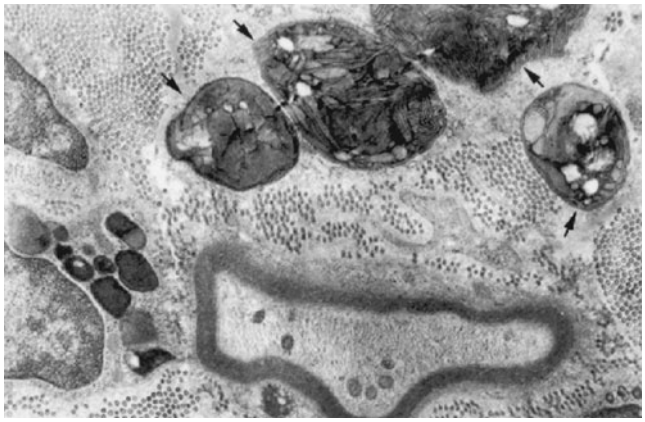


C

Figure 10–3. (A) Diffuse hypomyelination involving both large-and small-diameter fibers. Toluidine blue stain; original magnification, ×240. (B) Nerve biopsy stained with cresyl violet demonstrating dense metachromatic deposits within Schwann cells obscuring the nerve fibers in the endoneurium. With acid cresyl violet, these take on a brown color (brown metachromasia), hence the term metachromatic leukodystrophy. (C) Electron micrograph showing tuff stone inclusion bodies composed of stacks of lamellar discs and plates (arrows), enclosed within a membrane in the endoneurium. Original magnification, ×10 000. (With permission from Bindu PS, Mahadevan A, Taly AB, Christopher R, Gayathri N, Shankar SK. Peripheral neuropathy in metachromatic leucodystrophy. A study of 40 cases from south India. J Neurol Neurosurg Psychiatry 2005;76(12):1698–1701, Fig. 1, p. 1699, Fig. 3, p. 1700; and www.neuropathologyweb.org/chapter10/chapter10.).

have increased CSF protein concentrations.[27] MRI of the brain in early infantile Krabbe disease reveals diffuse and confluent demyelination in the cerebral and cerebellar white matter. In later-onset cases, the MRI scans show less diffuse demyelination, which may be restricted to the corticospinal tracts.[31,32] Motor NCS demonstrate mild to moderately reduced compound muscle action potential (CMAP) amplitudes, moderately prolonged distal latencies, moderately slow NCV, and delayed or absent F-waves.[20–25,27,28,30–32,34] Sensory NCS reveal absent responses or SNAPs with markedly reduced amplitudes and mildly prolonged distal latencies and slow CV.

Histopathology

Moderate cortical atrophy, loss of CNS white matter, gliosis, and globoid cells (macrophages filled with galactocerebroside) are appreciated on autopsy. Nerve biopsies also demonstrate a loss of myelinated fibers and segmental demyelination or hypomyelination, and macrophages filled with galactocerebroside.[21,27,31,32,34,35] The abnormal inclusions within macrophages stain positive with periodic acid Schiff (which indicates glycogen) and faintly with Sudan black (indicating lipid) and acid phosphate (suggesting that these are within lysosomes). Unlike MLD, the inclusions in Krabbe disease are not metachromatic. On EM, electron-dense granules and tubular crystalloid inclusions are evident in the cytoplasm of these histiocytes.

Molecular Genetics and Pathogenesis

Krabbe disease is autosomal recessive caused by mutations in the β-galactosidase gene located on

chromosome 14q24.3–q32.1.[31,32] β-Galactosidase metabolizes galactocerebroside to ceramide and galactose as well as catalyzing the hydrolysis of psychosine. The abnormal accumulation of galactocerebroside and psychosine leads to the degeneration of Schwann cells and oligodendrocytes.

Treatment

There is no proven effective therapy for Krabbe disease, although bone marrow and hematopoietic stem cell transplantation may prove to be a useful treatments.[19,36,37]

FABRY DISEASE

Clinical Features

Fabry disease (angiokeratoma corporis diffusum) is an X-linked disorder that usually affects males in their childhood or adolescence.[13,38–42] Individuals who are affected typically present with burning or lancinating dysesthesia in the hands and feet. Angiokeratomas, which appear as reddish purple maculopapular lesions, are characteristically found around the umbilicus, scrotum, inguinal, and perineum (Fig. 10–4). In addition, tiny red angiectasias may be visualized in the nailbeds, oral mucosa, and conjunctiva. The major cause of morbidity and mortality is related to premature atherosclerosis leading to hypertension, renal failure, cardiac disease, strokes, and death by the fifth decade of life. Occasionally, women develop a mild painful sensory neuropathy but only rarely do they have significant atherosclerotic disease.

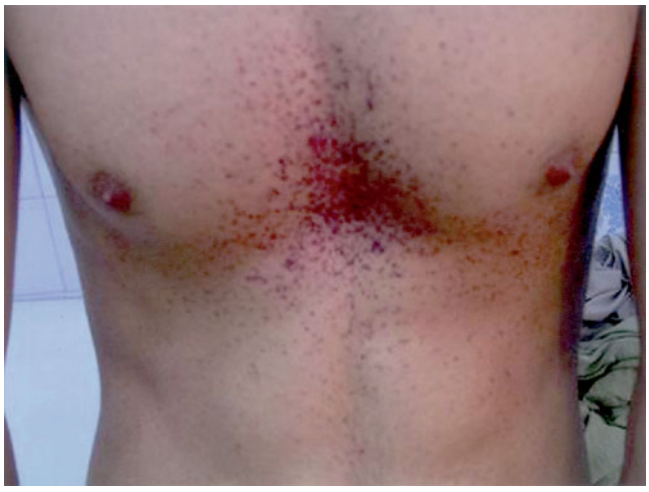


Figure 10–4. Fabry disease. Anterior chest with multiple, tiny, red, and hyperkeratotic papules. (With permission from Sodaifi M, Aghaei S, Monabati A. Cutaneous variant of angiokeratoma corporis diffusum associated with angiokeratoma circumscriptum. Dermatol Online J 10(1):20.)

Laboratory Features

A decrease in α-galactosidase activity can be demonstrated in leukocytes and cultured fibroblasts. Prenatal diagnosis can be made by amniocentesis. NCS are usually but mildly decreased amplitudes of motor, and sensory NCS may be seen.[38–44] Quantitative sensory testing reveals impaired temperature perception indicative of small fiber dysfunction.[42,43,45]

Histopathology

Nerve biopsies reveal a marked reduction of small myelinated and unmyelinated nerve fibers (Fig. 10–5). Glycolipid granules may be appreciated in ganglion cells of the peripheral and sympathetic nervous systems and in perineurial cells.[40,42] Reduced epidermal nerve fiber density may also be seen on skin biopsies.[44,46]

Molecular Genetics and Pathogenesis

Fabry disease is caused by mutations in the α-galactosidase gene located on chromosome Xq21–22. Decreased α-galactosidase enzyme activity leads to the accumulation of ceramide trihexoside in nerves and blood vessels.

Treatment

Enzyme replacement therapy with alpha-galactosidase beta can improve the neuropathy if patients are treated early prior to irreversible nerve fiber loss.[46,47]

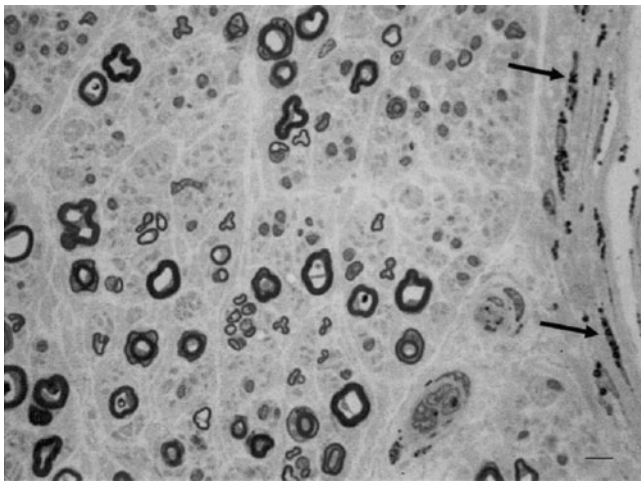
▶ PEROXISOMAL DISORDERS

Peroxisomes are organelles within the cytoplasm that contain enzymes essential in fatty acid oxidation (distinct from mitochondrial enzymes associated with beta-oxidation), bile acid and cholesterol synthesis, and amino acid metabolism. These disorders are the result of mutations in genes encoding for structural proteins or specific peroxisomal enzymes.

ADRENOLEUKODYSTROPHY/ ADRENOMYELONEUROPATHY

Clinical Features

Adrenoleukodystrophy (ALD) and adrenomyeloneuropathy (AMN) are allelic X-linked dominant disorders. ALD is more common and manifests in young males as progressive dementia, optic atrophy, cortical blindness,



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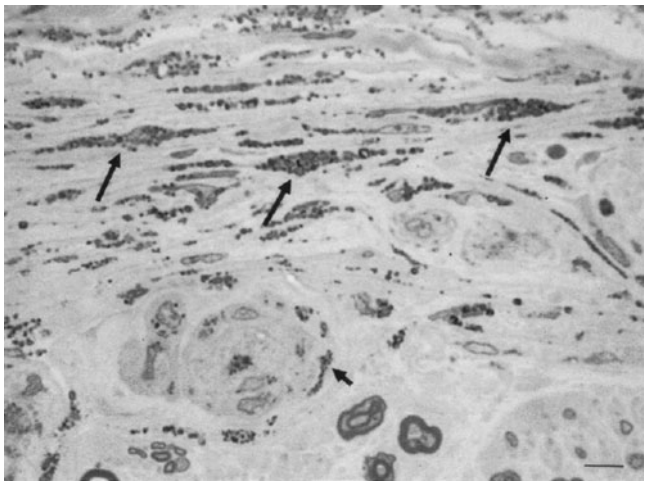

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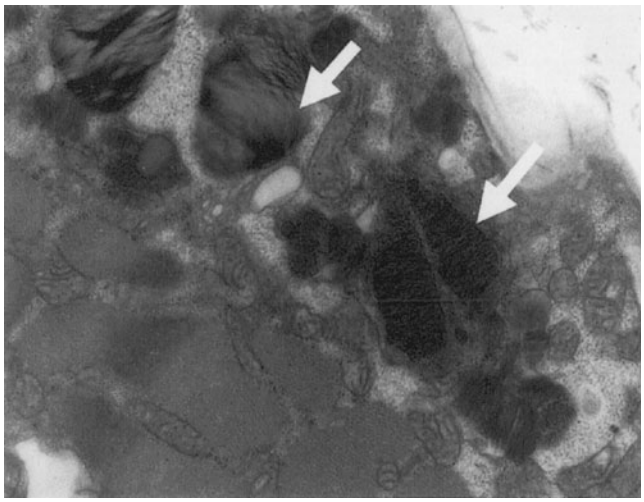

C

Figure 10–5. Fabry disease. Nerve biopsy. A toluidine blue-stained, semithin, plastic-embedded section reveals mild, patchy loss of large myelinated fibers, a few thinly myelinated axons, and several regenerative axon clusters (A). The perineurium (right edge) contains osmiophilic inclusions (arrows). Higher power reveals dark osmiophilic deposits in the perineurium (long arrows) and in association with blood vessels (short arrow) (B). An electron photomicrograph of the muscle biopsy specimen reveals electron-dense amorphous and lamellated inclusions in the perinuclear, subsarcolemmal region (C). (With permission from Lacomis D, Roeske-Anderson L, Mathie L. Neuropathy and Fabry disease. Muscle Nerve 2005;31:102–107, Figs. 1 and 2, p. 103 and 104.)

hearing loss, seizures, and spasticity.[13,48–54] At least 90% of patients with ALD also have adrenal insufficiency. The onset of symptoms in ALD is usually between the age of 4 and 8 years and death usually occurs within 2 years of onset of symptoms. Less commonly, ALD develops in adolescence or young adult life and progresses at a slower rate. Such patients may be misdiagnosed as having multiple sclerosis. Later-onset cases may also present with psychiatric symptoms leading to misdiagnosis as schizophrenia.

Approximately 30% of cases present with the AMN phenotype and usually manifests in the third to fifth decade of life.[51,54,55] Individuals affected develop progressive spastic paraplegia along with a mild-to-moderate peripheral neuropathy. Muscle stretch reflexes may be normal or reduced. Progressive dementia indicative of cerebral involvement can develop in some patients later in the course of the disease. Adrenal insufficiency is evident in approximately two-thirds of patients. Rare patients present with an adult-onset spinocerebellar ataxia or only with adrenal insufficiency.

Although these are X-linked disorders, women occasionally develop symptoms. Manifesting women carriers usually develop a myelopathy later in life (average age in late thirties) and again are often misdiagnosed with multiple sclerosis or familial spastic paraparesis.[51]

Laboratory Features

Diagnosis is made on finding that elevated very long-chain fatty acid levels (C24, C25, and C26 VLCFA) are increased in the urine.[54,56] The ratio of hexacosanoic acid to docosanoic or erucic acid (C26/C22) and tetracosanoic acid to docosanoic acid (C24:C22) are increased in both ALD and AMN. Very long chain fatty acids (VLCFA) levels can be assessed in neonates and can be used to screen for the disease shortly after birth. Because VLCFA levels are similar in ALD and AMN, these are not helpful in predicting the clinical phenotype. As many as 85% of obligate female carriers also have elevated VLCFA levels. Some, but not all, individuals have laboratory evidence of adrenal insufficiency.

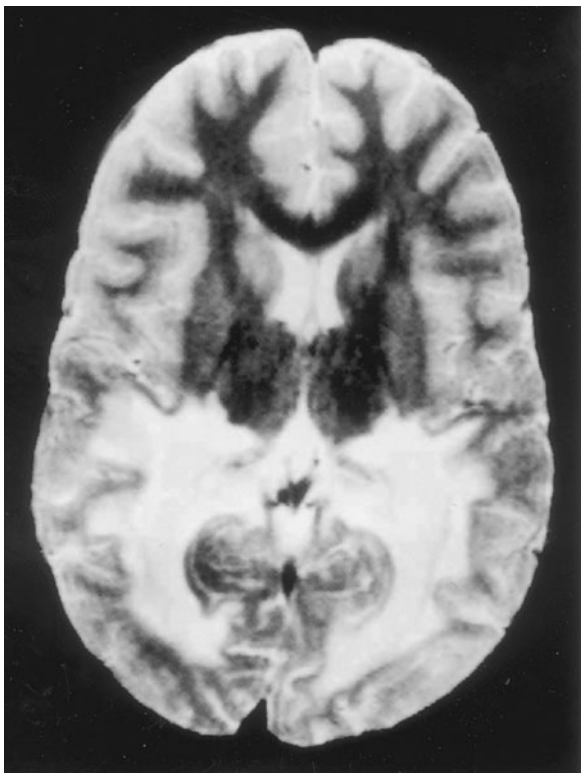

Figure 10–6. Cerebral T2-weighted MRI of an 8-year-old boy with impaired visual acuity and seizures due to adrenoleukodystrophy. (With permission from van Geel BM, Assies J, Wanders RJA, Barth PG. X linked adrenoleukodystrophy: Clinical presentation, diagnosis, and therapy. J Neurol Neurosurg Psychiatry 1997;63(1):4–14, Fig. 3, p. 6.)

MRI scans reveal confluent subcortical white matter demyelination in ALD, preferentially in the posterior parietal–occipital regions (Fig. 10–6).[53] MRI abnormalities of the cerebral white matter also develop later in the course in nearly half of patients with AMD.

NCS are usually normal in ALD. However, AMN is usually associated with a sensorimotor polyneuropathy but NCS can be normal. Typically, sensory and motor NCS reveal slightly reduced amplitudes, prolonged distal latencies, and slight slow CVs, suggesting a primary axonopathy with secondary demyelination.[48,49,52,55,57,58] Occasionally, patients fulfill electrophysiological criteria for a primary demyelination.[59] Somatosensory- and visual-evoked potentials demonstrate evidence of central slowing.[50,52]

Histopathology

Nerve biopsies demonstrate a loss of myelinated and unmyelinated nerve fibers.[389] On EM, lamellar inclusions are evident in the cytoplasm of Schwann cells (Fig. 10–7). Autopsies in ALD demonstrate demyelination and perivascular inflammation, particularly in the parietal–occipital regions.[51] The spinal cord displays bilateral, usually symmetrical, long tract degeneration, particularly of the gracile tract in a dying-back pattern.[59]

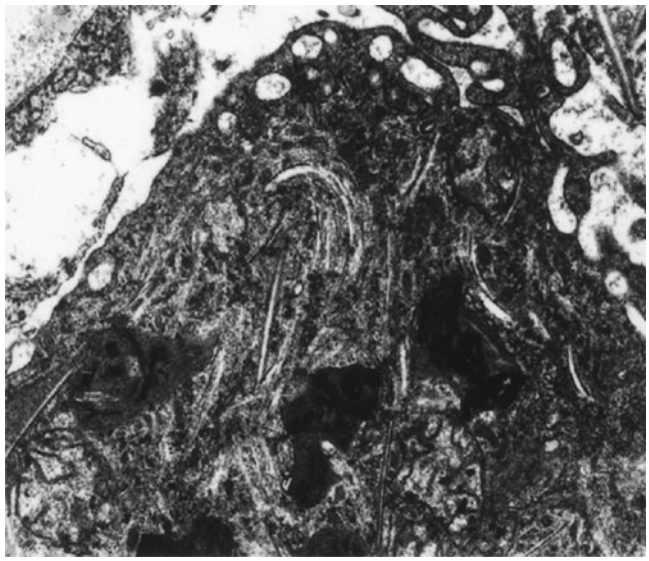

Figure 10–7. Adrenoleukodystrophy. Characteristic cellular inclusions (trilamellar membranes containing VLCFA cholesterol esters) are seen with the electron microscope in adrenal cortical cells, white matter histiocytes, Leydig cells, and Schwann cells.(With permission from www.neuropathologyweb.org/chapter10/chapter10.)

Molecular Genetics and Pathogenesis

ALD and AMN are caused by mutations in the peroxisomal transmembrane adenosine triphosphate-binding cassette (ABC) transporter gene, located on chromosome Xq28.[51,54] The ABC transporter protein is part of peroxins family of proteins, which are involved in the transport, biogenesis, and proliferation of peroxisomes.[60] There is no clear genotype–phenotype correlation associated with any specific mutation, and phenotypic heterogeneity can be found even within the family members who carry the same genetic mutation. Mutations in the gene cause impaired transport of VLCFA or VLCFA CoA synthetase into peroxisomes, thus decreasing β-oxidization of VLCFA; but how this leads to dysmyelination and axonal degeneration is not known.

Treatment

Adrenal insufficiency is managed by replacement therapy; however, there is no proven effective therapy for the neurological manifestations of ALD and AMN.[51] Diets low in VLCFAs and supplemented with Lorenzo's oil (erucic and oleic acids) reduces the levels of VLCFAs and increases the levels of C22 in serum, fibroblasts, and liver; however, such changes have not been

consistently noted in the brain.[61] Rare reports suggest clinical and MRI improvement in individual patients treated with Lorenzo's oil, but several large open-label trials of Lorenzo's oil failed to demonstrate significant efficacy.[54,62,63] Bone marrow transplantation has also been suggested in patients with early ALD or AMN.[19,54]

REFSUM DISEASE (HMSN IV)

Clinical Features

Refsum disease is a peroxisomal disorder associated with impaired α-oxidation of phytanic acid. The disease can manifest in infancy to early adulthood with the classic tetrad of (1) peripheral neuropathy, (2) retinitis pigmentosa (often the earliest symptom which manifests as night blindness), (3) cerebellar ataxia, and (4) elevated CSF protein concentration.[64–69] Patients with Refsum disease may also develop sensorineural hearing loss, cardiac conduction abnormalities, ichthyosis, and anosmia. Some or all of these clinical findings are usually manifest in the majority of patients by the end of the second decade. Infantile Refsum disease falls within the clinical spectrum of Zellweger syndrome and neonatal ALD, albeit much milder in severity.

Although not typically a presenting manifestation, most individuals who are affected develop distal numbness and paresthesia in the legs by their twenties. The distal legs become atrophic and weak and patients develop progressive foot drop. Subsequently, the proximal leg and arm muscles may become weak. Interestingly, the neuropathy can have a fluctuating course. On examination, a length-dependent loss of vibration, proprioception, and light touch is appreciated. Hypertrophic nerves may be palpated. Muscle stretch reflexes are reduced or absent throughout.

Laboratory Features

Serum phytanic acid levels are elevated, as is CSF protein concentration. Sensory NCS reveal reduced amplitudes and prolonged latencies/slow CVs.[68] Motor NCS demonstrate normal or moderately reduced amplitudes, mildly or moderately prolonged distal latencies, and mild to marked slowing of CV to <10–30 m/s.[64,66,67]

Histopathology

Nerve biopsies demonstrate a loss of myelinated nerve fibers, with remaining axons often thinly myelinated and associated with onion-bulb formation.

Molecular Genetics and Pathogenesis

Refsum disease is autosomal recessive but appears to be genetically heterogeneic.[70] Classical Refsum disease with childhood or early adult onset is caused by mutations in the gene that encodes for phytanoyl-CoA α-hydroxylase (*PAHX*) located on chromosome 10p13.[71,72] This peroxisomal enzyme helps catalyze α-oxidation of phytanic acid. The defect leads to the accumulation of phytanic acid in various organs including the central and peripheral nervous systems, leading to neuronal degeneration. Less common, mutations in the gene that encodes for peroxin 7 receptor protein (PRX 7) located on chromosome 6q22–24 are responsible for Refsum disease.[70,73,74] Mutations in PEX7 also cause rhizomelic chondrodysplasia punctata type 1, a severe peroxisomal disorder.

Treatment

Refsum disease is treated by removing phytanic precursors (phytols: fish oils, dairy products, and ruminant fats) from the diet. In addition to the noticed clinical improvement, the NCS also improve appropriate dietary restrictions as well as plasma exchange.[64–67]

TANGIER DISEASE

Clinical Features

Tangier disease is a rare autosomal-recessive disorder associated with a deficiency of high-density lipoprotein. The first reported patients came from Tangier island located in Chesapeake Bay—thus the name. Tangier disease may present as (1) an asymmetric mononeuropathy multiplex, (2) a slowly progressive symmetric polyneuropathy predominantly in the legs, or (3) a pseudosyringomyelia appearance in which there is dissociation between loss of pain/temperature and position/vibration in the arms.[75–81] Deposition of cholesterol esters within the tonsils leads to their swollen, yellowish-orange appearance. In addition, splenomegaly and lymphadenopathy may be apparent.

Laboratory Features

Serum high-density lipoprotein cholesterol levels are markedly reduced while triacylglycerol levels are increased. Motor and sensory NCS can be normal or associated with moderately reduced amplitudes, prolonged distal latencies, and slow CVs.[76–80]

Histopathology

Nerve biopsies reveal axonal degeneration with demyelination and remyelination.[75,82,83] EM demonstrates

abnormal accumulation of lipid in Schwann cells, particularly those encompassing umyelinated and small myelinated nerve.[75]

Molecular Genetics and Pathogenesis

Tangier disease is caused by mutations in the ABC transporter 1 (ABC1) gene located in chromosome 9q22–31.[84,85] The pathogenic basis of the peripheral neuropathy is unknown but may be similar to ALD/AMN, which are also caused by mutations involving the ABC transporter superfamily.

Treatment

There is no specific treatment.

CEREBROTENDINOUS XANTHOMATOSIS (CHOLESTANOLOSIS)

Clinical Features

Cerebrotendinous xanthomatosis is a rare autosomal-recessive disorder that usually presents after the second decade with progressive dementia, spasticity, ataxia, and a mild sensory neuropathy.[86–92] The name of the disorder arises because of the common occurrence of xanthomas on tendons and the skin. Cataracts are another frequent complication. Most individuals who are affected die in the fourth decade of life because of complications from premature atherosclerosis.

Laboratory Features

Serum level of cholestanol is increased. NCS are variable, depending on the presence or absence and the degree of severity of peripheral neuropathy.[86,88,89,93] Motor and sensory can be normal or reveal absent amplitudes, with slightly prolonged distal latencies, and mildly slow CVs suggestive of an axonal sensorimotor polyneuropathy.

Histopathology

Nerve biopsies reveal a loss of myelinated nerve fibers with variable degrees of demyelination and onion-bulb formation. Lipid inclusions are evident in Schwann cells.

Molecular Genetics and Pathogenesis

This disorder is caused by mutations in the sterol 27 hydroxylase gene located on chromosome 2, which results in impaired metabolism of cholestanol, the 5 α-dihydro derivative of cholesterol.[94] Cholestanol accumulates in body tissues, including peripheral nerves, thereby resulting in the associated clinical features.

Treatment

Early treatment with chenodeoxycholic acid may lead to a decrease in serum cholestanol and diminished excretion of bile alcohols in urine accompanied by clinical improvement.[87] Motor and sensory NCS improved in one patient following plasma exchange and treatment with chenodeoxycholic acid.[88]

▶ HEREDITARY ATAXIAS

The hereditary ataxias are a group of progressive neurodegenerative disorders characterized by varying degrees of degeneration of the cerebral cortex, basal ganglia, cerebellum, brainstem, corticospinal tracts, spinocerebellar tracts, motor neurons, and peripheral nerves (Table 10–1). The associated peripheral neuropathy with some of these disorders is usually overshadowed by the CNS abnormalities. However, the neuropathy can be quite prominent in Friedreich ataxia (FA) and an inherited form of vitamin E deficiency.

FRIEDREICH ATAXIA

Clinical Features

FA usually presents between 2 and 16 years of age with gait ataxia (63%), generalized clumsiness (25%), difficulty ambulating (4%), scoliosis (5%), tremor (1%) and cardiopathy (2%).[95–102] However, several genetically confirmed late-onset cases have been described.[97,103,104] FA is the most common form of autosomal-recessive ataxia. Dysarthria, optic atrophy, pigmentary retinopathy, nystagmus, reduced hearing, ataxia, pyramidal and lower motor neuron weakness, distal limb atrophy, scoliosis, and pes cavus are evident on examination. In addition, reduced vibratory sensation and proprioception associated with diminished muscle stretch reflexes but extensor plantar responses are seen.[97,103,104] Some patients develop dementia. FA is a progressive disorder and most patients are wheelchair dependent with 15 years of onset of symptoms, and there is increased mortality with the mean age of death in the mid to late thirties.

Laboratory Features

Genetic testing is available for diagnosis. MRI of the brain is usually normal, but the cervical spinal cord is often atrophic.[103,105] Electrocardiogram reveals nonspecific abnormalities (e.g., nonspecific ST and T-wave changes, low-voltage QRS complexes, deep Q-waves,

and conduction defects) in at least 30% of patients. Sensory NCS are associated with absent or reduced amplitudes.[95–97,100,101,103–106] H-reflexes are absent.[353] Motor NCS are less affected[96,98,107]; however, central motor conduction may be slow on magnetic stimulation studies.[108,109] Somatosensory-evoked potentials demonstrate reduced or absent cortical potentials and slowing of central conduction.[107,110,111]

Histopathology

Sural nerve biopsies reveal a loss of large myelinated fibers.[111] On autopsy, the posterior columns are markedly atrophied and the dorsal roots are considerably decreased in size compared to the ventral roots.

Molecular Genetics and Pathogenesis

FA is autosomal recessive, usually caused by expanding GAA trinucleotide repeat mutation within the first intron of the frataxin gene located on chromosome 9q13.[112,113] The normal gene contains 40 or fewer copies of the GAA triplet repeats, while patients with FA usually have 100 to more than 1700 repeats. Approximately 2% of cases are caused by point mutations within the frataxin gene.[114] The mutations result in low or absent levels of frataxin, mitochondria protein of unclear function. Frataxin is speculated to have a role in iron metabolism, protection against free radical toxicity, or mitochondrial DNA replication.[114]

Treatment

There is no medical treatment for FA. However, patients may benefit from speech, occupational, and physical therapy. Cardiac function needs to be monitored and treated appropriately.

VITAMIN E DEFICIENCY

Clinical Features

Vitamin E or α-tocopherol is a lipid-soluble vitamin present in the lipid bilayer of the cell membranes.[82,111,115–118] Vitamin E deficiency can arise due to (1) deficient fat absorption (e.g., cystic fibrosis, chronic cholestasis, short-bowel syndrome, and intestinal lymphangiectasia), (2) deficient fat transport (abetalipoproteinemia, hypobetalipoproteinemia, normotriglyceridemic abetalipoproteinemia, and chylomicron retention disease), or (3) secondary to mutations in α-tocopherol transfer protein.

The clinical manifestations of hereditary vitamin E deficiency and secondary deficiency are similar and resemble those seen in FA. Onset in the hereditary cases is usually between the ages of 5 and 10 years. Individuals who are affected manifest with slowly progressive ataxia, dysarthria, reduced vibratory perception and proprioception, diminished or absent muscle stretch reflexes with extensor plantar responses, and generalized weakness. Pes cavus deformities and scoliosis are common. Ophthalmoplegia, optic neuropathy, and retinitis pigmentosa are seen in acquired cases of vitamin E deficiency but are not typically present in the hereditary form.

Laboratory Features

Serum vitamin E levels are reduced. Patients deficient in vitamin E secondary to malabsorption of fat also have low serum levels of cholesterol, triglycerides, very low-density lipoproteins (VLDLs), vitamin A, and vitamin C. These levels are normal in patients with hereditary vitamin E deficiency in which there is isolated vitamin E deficiency. Sensory NCS reveal absent or low amplitudes.[111,116,117,119,120] Motor conduction studies are usually normal, although slightly prolonged distal latencies and slow NCVs may be found.[111,117] Somatosensory-evoked potentials may be unobtainable but, when recordable, demonstrate slowing of central conduction and reduced amplitudes.

Histopathology

Autopsies and nerve biopsies demonstrate a marked loss of dorsal root ganglion cells, large-diameter myelinated fibers, and degeneration of the dorsal columns and reductions in the cells of the gracile and cuneate nuclei. Vacuoles may be evident in the myelin sheath, and the Schmidt–Lanterman incisures may appear disrupted.

Molecular Genetics and Pathogenesis

Isolated vitamin E deficiency is inherited in an autosomal-recessive manner and is caused by mutations in the α-tocopherol transfer protein gene located on chromosome 8q13.[115,118] As a result, there is reduced incorporation of vitamin E into serum VLDLs.[121] Although absorption of vitamin E in the intestines and incorporation into chylomicrons are normal, recycling of vitamin E is dependent on α-tocopherol transfer protein into VLDL. Thus, vitamin E is rapidly eliminated and levels are diminished in the CNS and PNS.

Vitamin E may have antioxidant properties and may assist in modulating against glutamate excitotoxicity. The dorsal root ganglia and the posterior column nuclei have the lowest concentrations of vitamin E in the nervous system and might therefore be particularly sensitive to diminishing concentrations of vitamin E and its possible neuroprotective effects.

Treatment

Early treatment may stabilize or improve neurological function. Patients are started on vitamin E 400 mg twice a day, and the dosage is gradually increased up to 100 mg/kg/d until vitamin E levels normalize.[117]

ABETALIPOPROTEINEMIA (BASSEN–KORNZWEIG DISEASE)

Clinical Features

Abetalipoproteinemia or Bassen–Kornzweig disease is characterized by the combination of ataxia, retinitis pigmentosa, steatorrhea, and loss of sensation in the distal arms and legs.[122–125] Individuals who are affected usually present with ataxia and vision loss at night within the first two decades of life. The ataxia is progressive, leading to loss of independent ambulation by the fourth or fifth decades of life. On physical examination, patients are often short in stature and have pes cavus and hammer toes. Reduction in vibration sensation and proprioception is apparent along with sensory ataxia. Muscle stretch reflexes are reduced or absent. Mild distal muscle atrophy and weakness may be appreciated. Ophthalmoparesis may be observed in some patients.

Laboratory Features

Acanthocytes are seen on blood smear. Total serum cholesterol, low-density lipoproteins and VLDLs, and chylomicrons are reduced, as are serum concentrations of the fat-soluble vitamins A, E, and K. The electrophysiologic abnormalities are very similar to those found in FA and vitamin E deficiency.[126–128] The sensory SNAPs are absent or reveal reduced amplitudes with minimal slowing of conduction and normal or borderline distal sensory latencies. The CMAP amplitudes are normal or only slightly reduced, while distal latencies and CVs are preserved or only mildly slow. Central conduction slowing may be appreciated on somatosensory- and visual-evoked potential studies.[127,129] Brainstem auditory-evoked responses are characteristically normal, which is the only distinguishing electrophysiologic feature between this disorder and FA.

Histopathology

Nerve biopsies demonstrate axonal degeneration with a loss of large-diameter myelinated fibers as well as demyelination and remyelination on teased nerve fiber analysis. Degeneration of the posterior columns and the ventral spinocerebellar tracts has been appreciated on autopsies.

Molecular Genetics and Pathogenesis

This is an autosomal-recessive disorder associated with a deficiency of apolipoprotein-B and impaired absorption of fat-soluble vitamins from the intestinal tract. This most likely leads to decreased vitamin E, leading to the neurologic deficits in this disorder.

Treatment

Patients should be treated by replacing fat-soluble vitamins, in particular vitamin E.

▶ DISORDERS OF DEFECTIVE DNA REPAIR

ATAXIA-TELANGIECTASIA

Clinical Features

Ataxia-telangiectasia is characterized by childhood onset (usually in first 5 years of life) of cerebellar ataxia, oculocutaneous telangiectasia, oculomotor dyspraxia, and frequent sinopulmonary infections.[98,130,131] There is delay in motor milestones, but mental functioning is well preserved. Affected children develop choreoathetotic movements and dysarthric speech within the first decade. Sensory examination reveals a marked loss of proprioception and vibration sense and muscle stretch reflexes are reduced or absent. Distal motor weakness may become apparent over time.

Laboratory Features

Variable immune deficiency with reduced levels of IgA and IgG can be seen along with an increase in serum α-fetoprotein levels. The electrophysiological abnormalities are similar to those found in FA with absent or reduced amplitudes of the SNAPs, with only a mild reduction in the NCVs or prolongation in the distal sensory latencies.[98,130] Similar but less striking abnormalities can be seen on motor NCS.

Histopathology

Sural nerve biopsies reveal a loss of large myelinated nerve fibers.[99]

Molecular Genetics and Pathogenesis

The disorder is inherited in an autosomal-recessive manner and is caused by mutations in the ataxia-telangiectasia mutated (*ATM*) gene located on chromosome 11q23, which encodes for phosphatidyl inositol-3 kinase.[131,132] This enzyme is important in signal transduction, meiotic recombination, and cell-cycle regulation, and the mutations in the ATM gene result in impaired DNA repair. Cytogenetic testing reveals a

6–10-fold increase in chromosome breakage following ionizing irradiation. Further, there is increased spontaneous breakage and specific translocations involving the T-cell receptor genes on chromosome 7 and 14.

Treatment

There is no specific treatment.

COCKAYNE SYNDROME

Clinical Features

Cockayne syndrome is a rare disorder caused by defects in DNA repair and in various systemic abnormalities, including central and peripheral nervous system dysmyelination.[133–137] Most children appear normal at birth, but by the end of the first year of their life they are noted to have reduced growth rates and signs of aging. Between 4 and 10 years of age, they develop progeric facial appearance, cognitive decline, ataxia, areflexia, hearing loss, photosensitivity, pigmentary retinopathy, and dwarfism.

Laboratory Features

Motor and sensory NCS may demonstrate moderate to marked reduction in NCVs and prolonged distal latencies.[133,134,138,139]

Histopathology

Nerve biopsies reveal segmental demyelination and inclusions within Schwann cell inclusions.[140,141]

Molecular Genetics and Pathogenesis

Cockayne syndrome is an autosomal-recessive disorder associated with a defect in transcription factors that interact with RNA polymerase II. The result is impaired transcription initiation, nucleotide excision, and DNA repair.[142] The inability to properly excise and repair spontaneous DNA mutations results in accelerated signs of aging and increased risk of malignancy.

Treatment

There is no specific treatment.

▶ MISCELLANEOUS HEREDITARY NEUROPATHIES

GIANT AXONAL NEUROPATHY

Clinical Features

Giant axonal neuropathy presents in the first decade of life with progressive gait difficulty.[143–150] Children who are affected appear to have a normal birth and meet early motor milestones. However, around the age of 2 years they begin to exhibit signs of imbalance. By about 4 years of age, signs of a sensorimotor polyneuropathy and cerebellar ataxia are evident. Sensory examination reveals a decrease in all sensory modalities in a length-dependent distribution along with mild distal muscle atrophy and weakness. Muscle stretch reflexes are usually absent in the legs and reduced in the arms, while extensor plantar responses are appreciated. Truncal and limb ataxias are evident. Patients have characteristic curly or kinky hair.

Laboratory Features

NCS reveal absent or reduced amplitudes of SNAPs and CMAPs with normal or slightly prolonged distal latencies and mildly slow CVs.[149,151–153]

Histopathology

Nerve biopsies demonstrate loss of myelinated axons with segmental demyelination and, notably, giant axonal swellings (Fig. 10–8).[143–149] On electron microscopy, these axonal swellings consist of abnormal accumulations of densely packed intermediate-sized neurofilaments and are most prominent distally and in the paranodal regions. Similar giant axons occur in toxic neuropathies caused by exposure to *n*-hexane, methyl *n*-butyl ketone, acrylamide, carbon disulfide, 2,5-hexanedione, and triorthocresyl (tri-*o*-cresyl) phosphate.

Molecular Genetics and Pathogenesis

Giant axonal neuropathy is caused by mutations in the gigaxonin gene located on chromosome 16q24.[154]

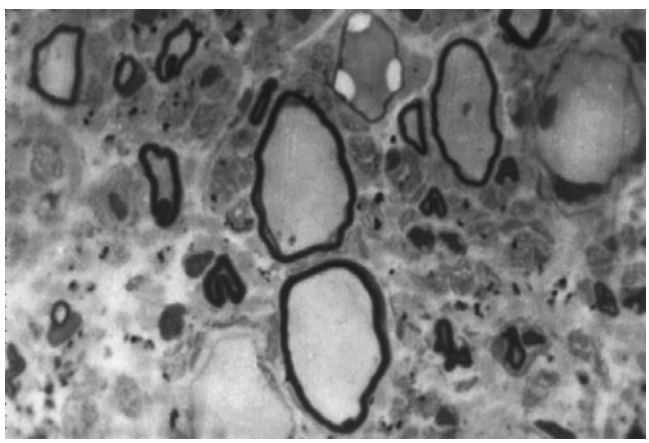

Figure 10–8. Giant axonal neuropathy. Semithin section of the sural nerve showing a giant axon filled with masses of neurofilaments. (With permission from Demir E, Bomont P, Erdem S, et al. Giant axonal neuropathy: Clinical and genetic study in six cases. J Neurol Neurosurg Psychiatry 2005;76(6):825–832, Fig. 4, p. 829.)

Gigaxonin is a cytoskeletal protein, which may be important in actin–cytoskeletal interactions.

Treatment

There is no specific treatment.

INFANTILE NEUROAXONAL DYSTROPHY

Clinical Features

Infantile neuroaxonal dystrophy presents in the first or second year of life, with progressive psychomotor regression, visual loss, generalized hypotonia, and weakness.[155–158] Those children who eventually ambulate usually lose the ability to walk independently over time due to progressive weakness, spasticity, and ataxia. Some affected children develop complex partial or generalized tonic–clonic seizures. Muscle stretch reflexes are usually reduced. Optic atrophy is apparent on fundoscopic examination.

Laboratory Features

MRI scans reveal cerebellar and cerebral atrophy, hyperintensity on T2-weighted images in the periventricular white matter and dentate nuclei, and hypointense T2 images in the globus pallidus and substantia nigra.[156] The optic chiasm is often thin. Motor and sensory NCS reveal decreased amplitudes and mild-to-moderate slowing of CV.[155–158] Visual-evoked potentials are unobtainable or have prolonged latencies.

Histopathology

Axonal swellings with spheroid bodies can be found on biopsies of peripheral nerves, muscle, skin, and conjunctiva.[155–158]

Molecular Genetics and Pathogenesis

The genetic defect associated with infantile neuroaxonal dystrophy has not been identified. A deficiency is that the lysosomal enzyme α-*N*-acetyl-galactosamide has been identified in some[158] but not all patients with infantile neuroaxonal dystrophy.[156]

Treatment

There is no specific treatment.

PORPHYRIA

Clinical Features

Porphyria is actually a group of inherited disorders caused by defects in heme biosynthesis. There are three forms of porphyria that are associated with peripheral neuropathy as well as CNS abnormalities: acute intermittent porphyria (AIP), hereditary coprophyria (HCP), and variegate porphyria (VP) (Fig. 10–9).[13,159–166] The acute neurologic manifestations are quite similar;

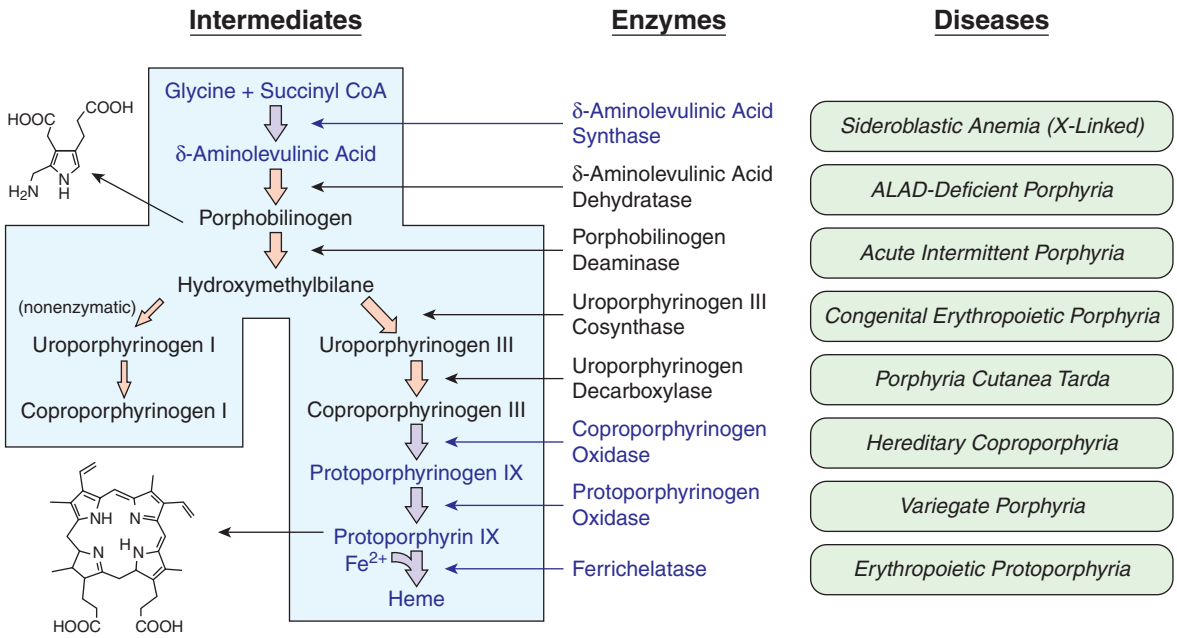

Figure 10–9. Porphyria pathway. Schematic representation of hepatic heme synthesis pathway. Defects in specific enzymes at various intermediate steps (boxes) controlling the synthesis of heme can lead to different clinical forms of porphyria. All of the noted diseases (boxes) have the potential to result in a neuropathy except porphyria cutanea tarda.

however, a photosensitive rash is seen with HCP and VP but not in AIP. Attacks of porphyria can be precipitated by certain drugs (usually those metabolized by the P450 system), hormonal changes (e.g., pregnancy and luteal phase of the menstrual cycle), and dietary restrictions.

An acute attack of porphyria is often heralded by acute abdominal pain. Subsequently, patients may develop agitation, hallucinations, or seizures. Several days later, back and leg pain followed by weakness can occur and may mimic Guillian–Barré syndrome. Motor involvement can be asymmetric, proximal, or distal and affect arms or legs preferentially. Cranial nerves can also be affected, leading to facial weakness and dysphagia. Sensory impairment may be difficult to determine if the patient is encephalopathic. Muscle stretch reflexes are often reduced. Autonomic dysfunction manifested by signs of sympathetic overactivity (e.g., pupillary dilatation, tachycardia, and hypertension) is common. Constipation, urinary retention, and incontinence can also be seen. Recovery is usually good, provided treatment is instituted rapidly to prevent excessive amounts of axonal damage.

Laboratory Features

The CSF protein can be normal or mildly elevated. Liver function tests and hematology are usually normal. Some patients are hyponatremic, relating to inappropriate secretion of antidiuretic hormone. The urine may appear brownish in color secondary to the high concentration of porphyrin metabolites. The diagnosis is made by evaluating the urine or stool for the accumulating intermediary precursors of heme (i.e., δ-aminolevulinic acid, porphobilinogen, uroporphobilinogen, coproporphyrinogen, and protoporphyrinogen).[162] The specific lowered enzyme activities can also be measured in erythrocytes and leukocytes.

Sensory NCS usually demonstrate normal NCVs and distal sensory latencies but the amplitudes may be slightly reduced, although not to the same degree as CMAPs are reduced.[161,162,164,165,167–170] Motor NCVs are only mildly reduced or normal, and distal motor latencies are normal or only slightly prolonged. The primary abnormality on NCS is the marked reduction in CMAP amplitudes. Needle EMG demonstrates primarily a reduced recruitment, fibrillation potentials, and positive sharp waves.

Histopathology

Axonal degeneration is apparent on nerve biopsies.

Molecular Genetics and Pathogenesis

The porphyrias are inherited in an autosomal-dominant fashion.[162] AIP is associated with porphobilinogen deaminase deficiency, HCP is caused by defects in coproporhyrin oxidase, and VP is associated with protoporphyrinogen oxidase (Fig. 10–9). The pathogenesis of the neuropathy is not completely understood. The biochemical alterations in heme production may effect production of energy via affects on oxidative phosphorylation in the mitochondria. The inability to detoxify various drugs in the liver may have secondary toxic effects on the nervous system. Finally, some recent studies suggest that porphyrin precursor neurotoxicity may arise due to activation of transcription factors pivotal in regulating cell survival.[171,172]

Treatment

Patients should be treated with hematin and glucose to reduce the accumulation of heme precursors. Intravenous glucose is started at a rate of 10–20 g/h. If there is no improvement within 24 hours, intravenous hematin 2–5 mg/kg/d for 3–14 days should be given. This hematin dose can be infused over a 30–60-minute period. Drugs that can precipitate the acute porphyric attack should be avoided.

ERYTHROMELALGIA

Clinical Features

Erythromelalgia is a rare disorder characterized by episodic erythema, intense burning pain, and warmth of the hands or feet.[173–176] It can occur as an inherited condition (autosomal dominant) or may be acquired. The acquired or secondary form can occurs in association with myeloproliferative diseases, neuropathies, and autoimmune diseases. Onset of symptoms may begin spontaneously at any age in the hereditary form.

Laboratory Features

NCS, quantitative sensory testing, and sudomotor testing may be normal or abnormal.[177]

Histopathological Features

Skin biopsies may reveal reduced epidermal nerve fiber density. In addition, perivascular inflammation and edema, fibrosis or arterioles, thickening of arteriolar basement membranes, and smooth muscle hyperplasia may be observed.[177]

Pathogenesis

Autosomal-dominant hereditary erythromelalgia is caused by mutations in the tetrodotoxin-sensitive sodium channel subtype Nav1.7 gene.[178–181] The Nav1.7 sodium channel is preferentially expressed in most nociceptive dorsal root ganglion neurons and in

sympathetic neurons and plays an important role in nociception and vasomotor regulation. Some mutations produced a hyperpolarized voltage dependence of activation, slower kinetics of deactivation, and impaired steady-state slow inactivation, while others do not.[182]

Treatment

This is a very-difficult-to-treat disorder. Some patients respond to lidocaine-like medications (e.g., lidoderm patches and mexilitine) and antiepileptic medication (e.g., gabapentin), but many are refractory and require opiates.[174,181,183,184]

▶ SUMMARY

These hereditary neuropathies are uncommon but need to be considered in the right clinical situation. Because of the hereditary nature of these neuropathies, some of which are quite devastating, diagnosis is important particularly for genetic counseling. With the exception of Fabry disease in which enzyme replacement therapy is available and perhaps ALD/AMN in which patients may be treated with Lorenzo's oil, most of these disorders can only be treated symptomatically.

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CHAPTER 11

Guillain–Barré Syndrome and Related Disorders

Landry described a neuropathy characterized by acute ascending paralysis in 1859. Later, Guillain, Barré, and Strohl noted the areflexia and the albuminocytological dissociation in the cerebral spinal fluid (CSF) associated with this neuropathy.[1] The contributions of Landry and Strohl have been neglected, and the neuropathy has been most commonly referred to as Guillain–Barré syndrome (GBS). In 1949, Haymaker and Kernohan detailed the histopathological features seen in 50 fatal cases of GBS. The earliest features noted were edema of the proximal nerves and the subsequent degeneration of the myelin sheaths within the first week of the illness. They did not appreciate inflammatory cells infiltrate until later in the course of the illness.[2] However, another group reported prominent perivascular inflammation in the spinal roots, dorsal root ganglia, cranial nerves, and randomly along the whole length of peripheral nerves, along with segmental demyelination adjacent to the areas of inflammation, in 19 autopsy cases of GBS.[3] Thus, the term acute inflammatory demyelinating polyradiculoneuropathy (AIDP), which is quite descriptive of the disease process, has been used synonymously with GBS.[4–7] It is now appreciated that GBS is not a single disorder but again a syndrome of several types of acute immune-mediated polyneuropathies (Table 11–1).[8,9] In addition to AIDP, there are two axonal forms of GBS: acute motor–sensory axonal neuropathy (AMSAN) and acute motor axonal neuropathy (AMAN). Further, some disorders that appear clinically different from AIDP (e.g., the Miller Fisher syndrome [MFS] and acute autonomic neuropathy) may share similar pathogenesis and can be considered a variant of GBS.

ACUTE INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY

Epidemiology and Antecedent Illness

AIDP is the most common cause of acute generalized weakness, with an annual incidence ranging from 1 to 4 per 100,000 population.[7,10,11] The neuropathy can occur at any age, with a peak age of onset of approximately 38–40 years. There may be a slight male predominance.

Approximately 60–70% of patients with AIDP have a history of a recent infection a few weeks prior to the onset of the neuropathy.[7,11] A control study of 154 patients with GBS revealed serological evidence of recent infections with *Campylobacter jejuni* (32%), cytomegalovirus (13%), Epstein–Barr virus (10%), and *Mycoplasma pneumoniae* (5%).[12] These were more frequent than that seen in the control population. Other studies have also reported that 15–45% of patients with AIDP have serologic evidence of recent *Campylobacter* enteritis.[13–20] The relationship between *C. jejuni* infection and the different variants of GBS (AIDP, AMSAN, and AMAN) has been the subject of many reports and is discussed in detail in the pathogenesis sections of these disorders. Other infectious agents associated with GBS include cytomegalovirus, Epstein–Barr virus, influenza, hepatitis A, hepatitis B, hepatitis C, and human immunodeficiency virus (HIV).[7,11,18] In HIV infection, AIDP usually occurs at the time of seroconversion or early in the course of the disease. Vaccinations, most notably to swine flu, have been associated with GBS. Further, other disorders have been linked to GBS, including other autoimmune disorders (i.e., systemic lupus erythematosus), lymphoma, organ rejection or graft vs. host disease following solid organ and bone marrow transplantation, and perhaps recent surgery.[11] Certain immunomodulating agents, such as tumor-necrosis alpha blockers, may increase the risk of developing GBS.

Clinical Features

AIDP usually presents with numbness and tingling in the feet that gradually progresses up the legs and then into the arms (Table 11–2).[7,11] Numbness and paresthesia can also involve the face. Severe, aching, prickly, or burning neuritic pain sensations in the back and limbs are present in at least half of patients. Large fiber modalities (touch, vibration, and position sense) are more severely affected than small fiber functions (pain and temperature perception). Progressive weakness typically accompanies the sensory disturbance. The severity can

TABLE 11–1. GUILLAIN–BARRE SYNDROME AND RELATED DISODERS

Acute inflammatory demyelinating polyradiculoneuropathy (AIDP)
Acute motor and sensory axonal neuropathy (AMSAN)
Acute motor axonal neuropathy (AMAN)
Other GBS variants
Miller Fisher syndrome
Idiopathic cranial polyneuropathy
Pharyngeal–cervical–brachial
Paraparetic GBS
Acute sensory neuronopathy/ganglionopathy
Acute small fiber neuropathy
Acute autonomic neuropathy

GBS, Guillain–Barré syndrome.

range from mild distal weakness to complete quadriplegia and need for mechanical ventilation. Weakness is usually first noted in the legs and ascends to the arms, trunk, head, and neck. Ropper reported that 56% had onset of weakness in the legs, 12% in the arms, and 32% simultaneously in the arms and legs.[7,11] Mild facial weakness is also often apparent in at least half of the patients during the course of the illness. Ophthalmoparesis and ptosis develop in 5–15% of patients. Occasionally, there is a descending presentation with onset in the cranial nerves, with subsequent progression to the arms and legs. The bowel and bladder are usually spared, although these may become involved in particularly severe disease states. Muscle stretch reflexes progressively diminish or become unobtainable. Autonomic instability

TABLE 11–2. DIAGNOSTIC FEATURES OF ACUTE INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY

I. Required for diagnosis
   1. Progressive weakness of variable degree from mild paresis to complete paralysis
   2. Generalized hypo- or areflexia
II. Supportive of diagnosis
   1. Clinical features
      a. Symptom progression: Motor weakness rapidly progresses initially but ceases by 4 weeks. Nadir attained by 2 weeks in 50%, 3 weeks in 80%, and 4 weeks in 90%.
      b. Demonstration of relative limb symmetry regarding paresis.
      c. Mild to moderate sensory signs.
      d. Frequent cranial nerve involvement: Facial (cranial nerve VII) 50% and typically bilateral but asymmetric; occasional involvement of cranial nerves XII, X, and occasionally III, IV, and VI as well as XI.
      e. Recovery typically begins 2–4 weeks following plateau phase.
      f. Autonomic dysfunction can include tachycardia, other arrhythmias, postural hypotension, hypertension, and other vasomotor symptoms.
      g. A preceding gastrointestinal illness (e.g., diarrhea) or upper respiratory tract infection is common.
   2. Cerebrospinal fluid features supporting diagnosis
      a. Elevated or serial elevation of CSF protein.
      b. CSF cell counts are $<$10 mononuclear cell/mm^3..
   3. Electrodiagnostic medicine findings supportive of diagnosis
      a. 80% of patients have evidence of NCV slowing/conduction block at some time during disease process.
      b. Patchy reduction in NCV attaining values less than 60% of normal.
      c. Distal motor latency increase may reach three times normal values.
      d. F-waves indicate proximal NCV slowing.
      e. About 15–20% of patients have normal NCV findings.
      f. No abnormalities on nerve conduction studies may be seen for several weeks.
III. Findings reducing possibility of diagnosis
   1. Asymmetric weakness
   2. Failure of bowel/bladder symptoms to resolve
   3. Severe bowel/bladder dysfunction at initiation of disease
   4. Greater than 50 mononuclear cells/mm^3 in CSF
   5. Well-demarcated sensory level
IV. Exclusionary criteria
   1. Diagnosis of other causes of acute neuromuscular weakness (e.g., myasthenia gravis, botulism, poliomyelitis, and toxic neuropathy).
   2. Abnormal CSF cytology suggesting carcinomatous invasion of the nerve roots

CSF, cerebral spinal fluid; NCS, nerve conduction velocity.
With permission from Amato AA, Dumitru D. Acquired Neuropathies. In Dumitru D,Amato AA, Swartz MJ (eds). Electrodiagnostic Medicine, 2nd edn. Philadelphia: Hanley & Belfus, 2002, pp. 937–1041,Table 23–1, p. 938.

is common in AIDP with hypotension or hypertension and occasionally cardiac arrhythmias.

The neuropathy usually progresses over the course of 2–4 weeks. Approximately 50% of patients reach their nadir by 2 weeks, 80% by 3 weeks, and 90% by 4 weeks.[7,11] Progression of symptoms and signs for over 8 weeks excludes GBS and suggests the diagnosis of chronic inflammatory demyelinating polyneuropathy. Subacute onset with progression of the disease over 4–8 weeks has been termed subacute inflammatory demyelinating polyneuropathy. Patients with subacute inflammatory demyelinating polyneuropathy may have a monophasic illness like AIDP or may behave like chronic inflammatory demyelinating polyneuropathy and continue to progress unless treated with immunosuppressive or immunomodulating agents. Approximately 30% of patients with AIDP develop respiratory failure. Because the immune attack of AIDP has an early predilection for the nerve roots, neck flexors and extensors and shoulder abductors, which are innervated by cervical roots close to the phrenic nerve (C3C4), correlate well with diaphragmatic strength and are thus important to closely follow. Once the disease nadir is reached, there is a plateau phase of several days to weeks followed by gradual recovery over several months. However, 50–85% of patients have some degree of residual deficits as many as 7 years after disease onset, with 5–10% of patients having disabling motor or sensory symptoms including severe fatigue.[7,11,21–23] The mortality rate is about 5%, with patients dying as a result of respiratory distress syndrome, aspiration pneumonia, pulmonary embolism, cardiac arrhythmias, and sepsis related to secondarily acquired infections.[7,11] Risk factors for a poor prognosis (slower and incomplete recovery) are age greater than 50–60 years, abrupt onset of profound weakness, the need for mechanical ventilation, and distal compound muscle action potential (CMAP) amplitudes less than 10–20% of normal.[19,24–31]

Laboratory Features

Albuminocytological disassociation with elevated CSF protein levels accompanied by no or only a few mononuclear cells is present in over 80% of patients after 2 weeks. However, within the first week of symptoms, CSF protein levels are normal in approximately one-third of patients. When CSF pleocytosis of more than 10 lymphocytes/mm^3 (particularly with cell counts greater than 50/mm^3) is found, AIDP-like neuropathies related to Lyme disease, recent HIV infection, or sarcoidosis need to be considered. Elevated liver function tests are common and may be attributed to viral hepatitis (A, B, and C), Epstein–Barr virus, or cytomegalovirus infection.

Enhancement of the nerve roots may be appreciated on magnetic resonance imaging of the spine.[32]

Antiganglioside antibodies, particularly GM1 IgG antibodies, are found in some patients and correlate with recent *C. jejuni* infection.[16,17,20,33] Serological evidence of recent antecedent *C. jejuni* infection is evident in 15–45% of patients.[7,11–17,19,20,34] Molecular mimicry between gangliosides expressed on nerve fibers and glycolipids present on *C. jejuni* may account for their association with AIDP and may play a role in the pathogenesis of the disorder.

Various electrophysiologic criteria for demyelination have been developed to aid in the diagnosis of AIDP (Table 11–3).[8] The electrophysiological hallmarks of demyelination include prolonged distal

► TABLE 11–3. ELECTRODIAGNOSTIC MEDICINE CRITERIA FORPERIPHERAL NERVE DEMYELINATION*

I. Conduction velocity reduced in two or more nerves
   1. If CMAP amplitude is >80% of lower limit of normal (LLN) then the NCV must be <80% of LLN.
   2. If CMAP amplitude <80% of LLN, then the NCV must be <70% of LLN.

II. CMAP conduction block or abnormal temporal dispersion in one or more nerves
   1. Regions to examine for these findings include
      a. Peroneal nerve between fibular head and ankle
      b. Median nerve between wrist and elbow
      c. Ulnar nerve between wrist and below elbow
   2. Partial conduction block criteria
      a. CMAP duration difference between the above noted proximal and distal sites of stimulation must be <15%, and
      b. A >50% drop in CMAP negative spike duration, or baseline-to-peak amplitude
   3. Abnormal temporal dispersion and possible conduction block
      a. CMAP duration difference between the above proximal and distal sites of stimulation is >15%, and
      b. A >20% drop in CMAP negative spike duration, or baseline-to-peak amplitude

III. Prolonged distal motor latencies (DML) in two or more nerves
   1. If CMAP amplitude is >80% of the LLN; then the DML must be >125% of the upper limit of normal (ULN).
   2. If the CMAP is <80% of the LLN, then the DML must be >150% of the ULN.

IV. Prolonged minimum F-wave latency or absent F-wave
   1. F-waves performed in two or more nerves (10–15 trials)
   2. If the CMAP amplitude is >80% of the LLN, then the F-wave latency must be >120% of the ULN.
   3. If the CMAP amplitude is <80% of the LLN, then the F-wave latency must be >150% of the ULN.

*Three of the four features must be present.
Data from Cornblath DR. Electrophysiology in Guillain–Barré syndrome. Ann Neurol 1990;27(Suppl): S17–S20.

latencies, slow conduction velocities, temporal dispersion, conduction block, and prolonged F-wave latencies.

Motor Conduction Studies

Within the first week, motor conduction studies can be normal or show only minor abnormalities. The maximum degree of motor conduction abnormality occurs within 3–8 weeks, with 80–90% of patients with AIDP having abnormalities in at least one of the motor nerve parameters (distal CMAP latency, F-wave latency, conduction velocity, and conduction block) within 5 weeks of onset.[8,24,25,35–39] F-wave studies are useful because of the early predilection for the proximal nerve segments and spinal roots in AIDP.[24,25,35,40] Prolonged or absent F-waves and H-reflexes are found in 80–90% of patients during the course of AIDP.[24,25,35,41] Albers and colleagues found that prolonged distal latencies and diminished CMAP amplitude were the earliest electrophysiological abnormalities.[35] Within 1 week of symptoms, the mean distal CMAP amplitudes were reduced to approximately 50% of normal and declined further over the next several weeks. Prolonged distal motor latencies and prolonged or absent F-waves were appreciated by the North American Guillain-Barré Syndrome Study Group, reported as the earliest abnormal features—findings that reflect the early predilection for involvement of the proximal spinal roots and distal motor never terminals in GBS.[24,25] Slowing of conduction velocities, temporal dispersion of the CMAP waveforms, and conduction block become apparent later in the course. The motor conduction abnormalities remain at their nadir for approximately 1 month and then gradually improve over the next several weeks to months, but it may take a year or more for normalization.[35] There is no correlation between the nerve conduction velocities (NCVs) or distal motor latencies and clinical severity of the neuropathy, although distal CMAP amplitudes less than 10–20% of normal are associated with a poorer prognosis.[24–29,31]

Meulstee and colleagues applied the electrophysiological criteria for demyelination designed by Albers et al.[35] Barohn et al.[42] and Asbury and Cornblath[24,25,43] to 135 patients with AIDP sequentially studied during the Dutch-GBS plasma exchange (PE) and intravenous immunoglobulin (IVIG) trials.[44] The sensitivity of the criteria for diagnosing demyelination ranged from 3–36% during the first study (performed at a median of 6 days, range 2–15 days after onset) to 13–46% during the third study (performed at a median of 34 days, range 29–49 days after onset).

Sensory Conduction Studies

Sensory studies in the arms can be affected more severely and earlier than the sural sensory nerve action potentials (SNAPs).[35] The exact explanation is multifactorial. Perhaps, entrapment sites are more prone to attack, which could account for slowing of the median SNAP across the carpal tunnel. More likely, because AIDP is a multifocal demyelinating disorder rather than a length-dependent process typical of most axonal neuropathies, the median, ulnar, or radial SNAPs may be affected prior to the sural SNAPs.

About 40–60% of patients eventually demonstrate either amplitude reduction or slow conduction velocities, with maximal abnormalities being seen after 4–6 weeks.[35,41] Reduced SNAP amplitudes can be the result of secondary axonal degeneration, conduction block, or phase cancellation related to differential demyelination and slowing of the sensory nerve fibers. Sensory conduction velocities can be slow and distal latencies prolonged.

Rarely, some persons may present with what appears to be pure sensory symptoms and signs, but usually careful evaluation reveal some motor nerve conduction abnormalities.[45,46] With a pure sensory presentation, other disorders (acute sensory neuronopathy or ganglionopathy) must be ruled out.[7]

Needle Electromyographic Examination

The earliest abnormality on electromyography (EMG) is a reduced recruitment of motor unit action potentials (MUAPs).[35] Positive sharp waves and fibrillation potentials may be appreciated 2–4 weeks after onset of weakness.[47] Myokymic discharges may be seen, especially in facial muscles.

Autonomic Testing

Autonomic instability can be assessed by looking at heart rate variability with deep breathing or Valsalva maneuvers, with about 35% of patients demonstrating an abnormality.[48] Sympathetic skin response may be absent but it has poor sensitivity.

Histopathology

Nerve biopsies are not routinely performed in cases suspected of having GBS. Nonetheless, studies have demonstrated that perivascular mononuclear cell infiltrate consisting of macrophages and lymphocytes may be seen on light microscopy.[7,49–51] There may be an initial preference for the nerve root region, areas where peripheral nerves are commonly entrapped (e.g., carpal and cubital tunnels), and the motor nerve terminals. The earliest pathophysiologic features are often appreciated at the nodes of Ranvier with loosened paranodal myelin and subsequent demyelination of the internodal segments. Monocellular infiltrates may

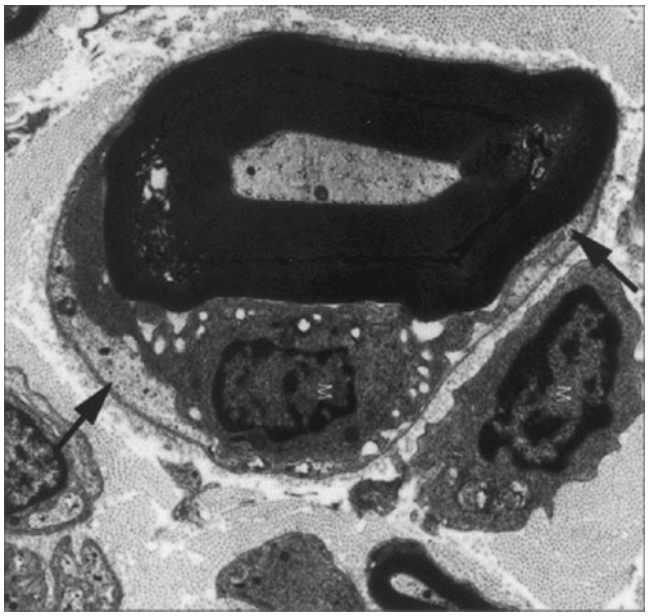

Figure 11–1. Nerve fiber from patient with AIDP. Electron micrograph shows that a macrophage (M) has invaded Schwann cell basement membrane and stripped the abaxonal Schwann cell cytoplasm (arrows). (With permission from Hughes RA, Cornblath DR. Guillain–Barre syndrome. Lancet 2005;366(9497):1653–1666, Fig. 1, p. 1567.)

be appreciated in areas of segmental demyelination (Fig. 11–1). Polymorphonuclear cells, in addition to monocytes, may be associated with axonal degeneration in severe cases. During the recovery phase, remyelination is appreciated. Myelin thickness is reduced and the number of internodes is increased compared to normal peripheral nerve.

Autopsy studies of patients in China who died early in the course of their illness have shed light on the pathology of GBS, including AIDP, AMSAN, and AMAN.[52–55] In two patients who died at 7 and 9 days after onset of the neuropathy, autopsies revealed completely demyelinated peripheral nerves accompanied by extensive lymphocytic infiltrate.[54] However, in a patient who died only 3 days after symptom onset, the peripheral nerves had only scant inflammatory infiltrate and just a few of the nerves were completely demyelinated. Markers of complement activation were demonstrated on the outermost surface of the Schwann cells, and early vesicular changes in the myelin sheaths, beginning in the outer lamellae, were appreciated on electron microscopy.

Pathogenesis

A T-cell-mediated process may play a role, given the inflammation apparent in the nerves, markers of T-cell activation (e.g., soluble interleukin-2 receptor and interferon-γ) in the serum, and the resemblance to experimental allergic neuritis.[9,56–59] The humoral arm of the immune system has been implicated by the demonstration of ganglioside antibodies in many patients and the clinical improvement following plasmapheresis.[57,58] Further, injection of serum from patients with AIDP into nerves of animal models induces complement-dependent demyelination and conduction block.[60] Buchwald et al. investigated the effect of serum from 10 patients with GBS on mouse hemidiaphragm using a macro-patch-clamp technique and observed depressed presynaptic transmitter release and, in some cases, the activation of postsynaptic channels.[61] The neuromuscular blockade was independent of complement, and there was no link to the presence (in six patients) or absence (in four patients) of antibodies to GM1 or GQ1B.

One study revealed that 56 out of 233 (23%) of GBS patients with GBS had circulating immunoglobulin G autoantibodies against proliferating, nonmyelinating human Schwann cells.[62] Immunofluorescence was localized at the distal tips (leading lamella) of the Schwann cell processes and of nerve-growth cones. Serum immunoreactivity was also observed in teased nerve fiber preparations. The observer speculated that the immune attack may be directed against nonmyelin proteins and epitopes possibly involved in Schwann cell–axon interaction.[62]

The nature of the epitope is not known but probably is a glycolipid. Molecular similarity between the myelin epitope(s) and glycolipids expressed on *Campylobacter*, *Mycoplasma*, and other infectious agents, which precede attacks of AIDP, may be the underlying trigger for the immune attack (Fig. 11–2).[54] Antibodies directed against these infectious agents may cross-react with specific antigens on the Schwann cell because of this molecular mimicry. These autoantibodies may bind to the Schwann cells and then activate the complement cascade, leading to lysis of myelin sheaths (Fig. 11–3). Inflammatory cells are subsequently recruited to complete the demyelinating process.

Treatment

PE[63–65] and IVIG[27,66] have proven effective treatments of AIDP (Table 11–4).[67,68] In the North American trial, PE reduced the time necessary to improve one clinical grade, time to walk unaided, time on a ventilator, and the percentages of patients improving after 1 and 6 months compared to the control group.[64] The French Plasmapheresis Group confirmed that PE was efficacious in GBS.[63] The exact mechanism is unclear but is likely that PE removes autoantibodies, immune complexes, complement, or other humoral factors involved in the pathogenesis of AIDP. The standard course of PE is 200–250 mL/kg of patient body weight over 10–14 days. Thus, a 70-kg patient would receive 14,000–17,500 mL (14–17.5 L) total exchange, which can be accomplished by 4–6 alternate day exchanges of 2–4 L each.

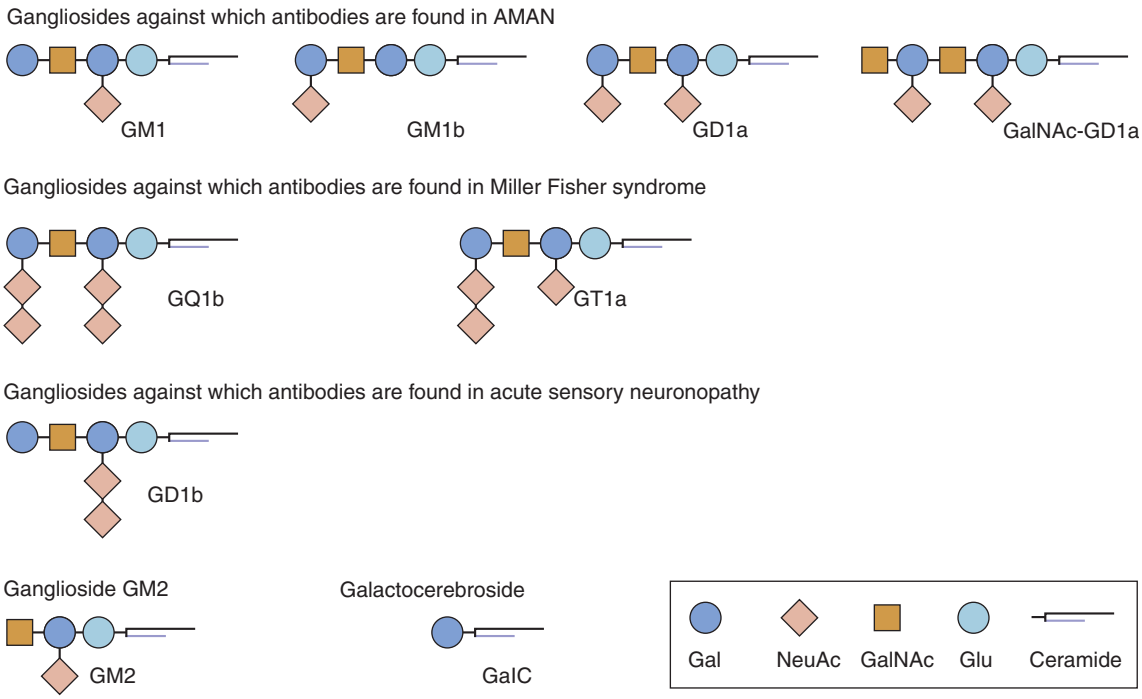

Figure 11–2. Structures of gangliosides and galactocerebroside and Guillain–Barré syndrome subtype associations. (With permission from Hughes RA, Cornblath DR. Guillain–Barre syndrome. Lancet 2005;366(9497):1653–1666, Fig. 4, p. 1659.)

IVIG has replaced PE in most centers as the treatment of choice of AIDP. IVIG was shown to be at least as effective as PE in nonambulatory adults treated within the first 2 weeks in a prospective trial (Table 11–4).[27,66,69] Importantly, there is no added benefit of IVIG following PE, and it certainly makes to sense to give IVIG and then perform PE.[27] The dose of IVIG is 2.0 g/kg body weight infused over 2–5 days. Randomized trials are needed to decide the effect of IVIG in children, in adults with mild disease, and in adults who start treatment after more than 2 weeks.[67] IVIG may inhibit the binding of ganglioside antibodies to their respective antigens, thereby preventing complement activation and subsequent pathophysiological effects.[70]

Treatment with IVIG or PE should begin within the first 7–10 days of symptoms. Improvement with PE and IVIG is often not immediate, with the mean time to improvement of one clinical grade in the various controlled, randomized PE and IVIG studies ranging from 6 days to as long as 27 days.[63,64,66] There is no evidence that PE beyond 250 mL/kg[63,71–73] or IVIG greater than 2 g/kg is of any added benefit in patients with AIDP and stable deficits. Further, as noted above, there is no indication for PE followed by IVIG or vice versa. However, as many as 10% of patients treated with either PE[63,73] or IVIG[71,72] develop a relapse following initial improvement. In patients who suffer such relapses, we give additional courses of PE or IVIG.

Unlike chronic inflammatory demyelinating polyneuropathy (CIDP), corticosteroids do not appear beneficial in the treatment of GBS, and, in fact, some patients have done worse. A small study of 25 patients treated with IVIG and intravenous methylprednisolone[74] did better than a historical control group treated with IVIG alone.[66] However, a much larger British study of 142 patients treated with methylprednisolone or placebo (approximately half the patients in each group were also treated with PE) failed to demonstrate the efficacy of corticosteroids.[75] A double-blind, placebo-controlled randomized study of IVIG plus intravenous methylprednisolone compared to IVIG plus placebo in 233 patients with GBS revealed no significant difference between treatment with methylprednisolone and IVIG versus IVIG alone.[76] Thus, there is indication for supplemental corticosteroid use in patients with GBS. Also, a small double-blind, randomized, placebo-controlled safety trial of interferon beta 1a in 19 patients with GBS also treated with IVIG revealed no added benefit of interferon beta 1a.

CHILDHOOD AIDP

Children with AIDP have clinical, laboratory, and electrophysiologic findings similar to affected adults.[8,51,68,77–80] An antecedent infection within 2 months of the attack is appreciated in approximately

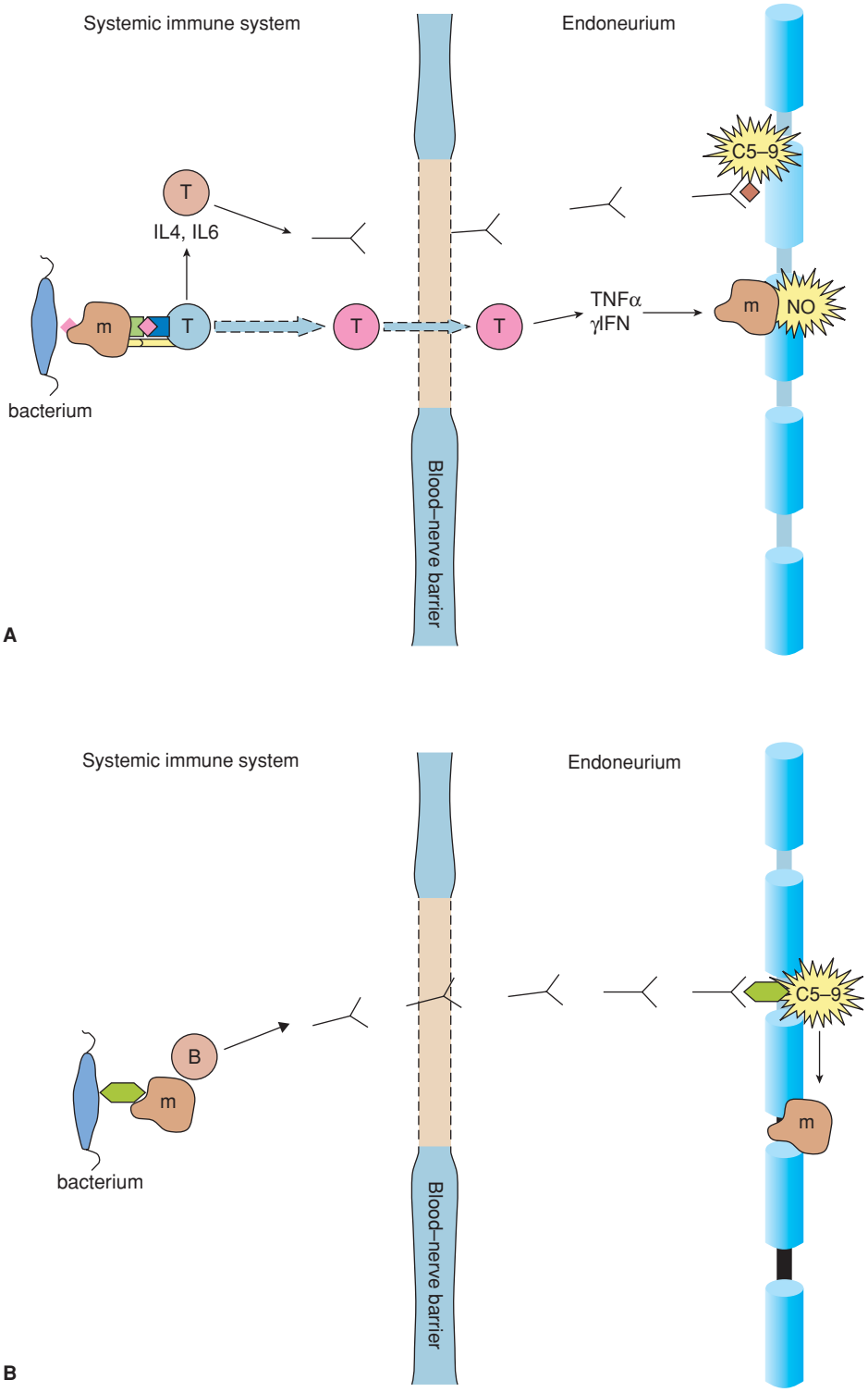

Figure 11–3. Immune mechanisms in (A) AIDP and (B) AMAN, AMSAN, and Miller MFS. (A) A bacterial protein epitope is presented by a macrophage to a T cell. The T cell is activated, penetrates the endothelium, recognizes a cross-reactive antigen, and, in the lower section, releases cytokines that activate endoneurial macrophages. These release enzymes and toxic nitric oxide (NO) radicals and so ultimately invade compact myelin. In the upper section, the activated T cell releases cytokines, which help the B cell to produce antibodies that cross a damaged blood–nerve barrier and engage unidentified cross-reactive epitopes on the abaxonal Schwann cell surface, fix complement, damage the Schwann cell, and so produce vesicular dissolution of myelin. (B) A bacterial ganglioside-like epitope stimulates B cells to induce antibodies that opsonize cross-reactive axolemmal antigens, fix complement and target macrophages to invade the periaxonal space, and block conduction or cause axonal degeneration. In Miller MFS the perisynaptic Schwann cell at the motor nerve terminal is also targeted. (With permission from Hughes RA, Cornblath DR. Guillain-Barre syndrome. Lancet 2005;366(9497):1653–1666, Fig. 3, p. 1568.)

▶ **TABLE 11–4. GUILLAIN–BARRÉ SYNDROME: PLASMAPHERESIS AND IVIG TRIALS**

	Plasmapheresis Group	Control Group	IVIG Group
North American Trial			
Number of patients	122	123	
Time to improve one clinical grade (days)	19	40	
Time to walk unaided (all patients) (days)	53	85	
Time to walk unaided (ventilator patients) (days)	97	169	
Time on ventilator (days)	9	23	
% improved at 1 month	59	39	
% improved at 6 months	97	87s	
French trial			
Number of patients	109	111	
% of patients on ventilator after study (days)	18	31	
Time to wean from ventilator (days)	70	111	
Time to walk unaided (days)	28	45	
Time in hospital	21	42	
Dutch IVIG trial			
Number of patients	73		74
% of patients improving one clinical grade after 4 weeks	34		53
Time to improve one clinical grade (days)	41		27
Time to clinical Grade 2 (days)	69		55
Ventilator dependent by week 2 (%)	42		27
Number of multiple complications	16		5
PE/Sandglobulin Trial Group			
Number of patients	121		130
Mean change in clinical grade after 4 weeks	0.9		0.8
Time to wean from ventilator (days)	29		26
Time to walk unaided (days)	49		51
Number of patients unable to walk after 48 weeks	19 (16.7%)		21 (16.5%)

*Plasma Exchange/Plasma Exchange/Sandoglobulin Guillain-Barre Syndrome Trial Group. Sandoglobulin GBS. Randomized trial of plasma exchange, intravenous immunoglobulin, Trial Group and combined treatments in Guillain–Barré syndrome. Lancet 1997;349:225–230.
*This trial also had 128 patients randomized into a treatment group, which received plasmapheresis (PE) followed by IVIG. There was no statistically significant improvement in any outcome measures in this group compared to the groups that received PE or IVIG alone.
North American Trial: Guillain-Barré Study Group. Plasmapheresis and acute Guillain–Barré syndrome. Neurology 1985;35:1096–1104.
French Trial: French Cooperative Group on Plasma Exchange in Guillain-Barré syndrome. Efficiency of plasma exchange in Guillain–Barré syndrome: Role of replacement fluids. Ann Neurol 1987;22:753–761.
Dutch IVIG Trial: van der Meche' FGA, Schmidtz PIM, the Dutch Guillain-Barré Study Group. A randomized trial comparing intravenous immunoglobulin and plasma exchange in Guillain–Barré syndrome. N Engl J Med 1992;326:1123–1129.
IVIG, intravenous immunoglobulin.
With permission from Amato AA, Dumitru D. Acquired neuropathies. In Dumitru D,Amato AA, Swartz MJ (eds). Electrodiagnostic Medicine, 2nd edn. Philadelphia: Hanley & Belfus, 2002, pp. 937–1041, Table 23–3, p. 944.

75% of children having AIDP. Most children present with back and extremity pain. Generalized weakness, respiratory failure, sensory loss (including sensory ataxia, and autonomic dysfunction can develop. Laboratory evaluation is remarkable for an elevated CSF protein. Sural nerve biopsies in children with GBS demonstrate similar histopathological abnormalities as those described in adults.[51]

The clinical and electrophysiological features as well as response to treatment are similar to what are seen in adults.[68,78–80] It is essential to look for ticks, particularly in children, as tick paralysis can mimic GBS.[9,81] Removal of the tick leads to improvement of strength and function.

AXONAL GBS: AMSAN

Clinical Features

Feasby and colleagues were the first to detail an axonal variant of GBS in 1986.[82] Initially, the existence of an axonal variant was met with early skepticism[28,83];

however, subsequent autopsy studies confirmed that AMSAN is a real disease entity.[52,53] Clinically and often by early electrodiagnostic studies, patients with AMSAN are indistinguishable from those with AIDP.[8,28,51–53,82,83–88] Usually, sensory symptoms begin in the hands or feet and later progress. Sensation to all modalities is reduced and areflexia is usually evident. Patients with AMSAN rapidly develop progressive and severe generalized weakness over only a few days, as opposed to progression over a couple of weeks in most patients with AIDP. Ophthalmoplegia, dysphagia, and respiratory muscle weakness can occur. Blood pressure instability and cardiac arrhythmias may complicate AMSAN as well. Recovery of strength and function is slow and often incomplete compared to AIDP.[87] Only a few children have been reported with AMSAN, and there is some suggestion that the prognosis is better than in adults.[82,89]

Laboratory Features

Albuminocytologic dissociation of the CSF protein is usually seen. Evidence of a recent infection with *C. jejuni* and antibodies directed against nerve gangliosides, particularly GM1 antibodies, are demonstrated in many patients with AMSAN.[53,90–92] Nerve conduction studies reveal markedly diminished amplitudes or absent CMAPs and SNAPs within 7–10 days of onset.[8,24,82,84–88,93,94] As discussed in the AIDP section, low-amplitude CMAPs are one of the earliest electrophysiological abnormalities noted in AIDP; thus, low-amplitude CMAPs do not necessarily imply axonal degeneration. Distal conduction block with or without demyelination also leads to low-amplitude distal CMAPs.[28,83] Initially, it is often impossible to distinguish AIDP from AMSAN by nerve conduction studies; however, serial nerve conduction studies may be helpful.[83] Most patients with AIDP will eventually develop other features of demyelination (e.g., significantly prolonged distal latencies and f-wave latencies, slow CVs, more proximal conduction block, or temporal dispersion). The distal latencies of the CMAPs and the nerve conduction velocities, when obtainable, should be normal or only mildly affected in AMSAN. Needle EMG demonstrates markedly abnormal reductions in recruitment. Several weeks after the presentation of major motor weakness, abundant fibrillation potentials and positive sharp waves can be detected in most muscles, especially those located in the distal regions of the limbs.[91,92,95]

Histopathology

Nerve biopsy performed early in the course of the disorder is the only way to differentiate "axonal" GBS from "pseudoaxonal" GBS because of their clinical, laboratory, and electrophysiological similarities; however, this is not indicated in clinical practice. Nerves biopsied late in the disease course of AIDP or AMSAN may show axonal degeneration, and it can be difficult to distinguish a primary axonopathy from secondary axonal degeneration. Sensory and motor nerve biopsies in several patients with inexcitable motor and sensory conduction studies revealed severe demyelination rather than primary axonal degeneration.[93,95–98] Nevertheless, some patients with inexcitable CMAPs and SNAPs have features that suggest a primary axonal insult.[52,53,82,85] Unlike AIDP, demyelination and lymphocytic infiltrates are absent or only minimally present on nerve biopsy or at autopsy in patients with AMSAN; rather, prominent axonal degeneration affecting the ventral and dorsal roots and the peripheral nerves is appreciated. As many as 80% of teased fibers reveal axonal degeneration, while demyelinating features are rare.[82,85] A marked loss of both myelinated and unmyelinated axons is evident. Griffin and colleagues reported that the autopsies of three patients with AMSAN who died early in the course of their illness demonstrated prominent axonal degeneration of the spinal roots and peripheral nerves without demyelination or significant inflammation.[53] Numerous macrophages were present in the periaxonal space of myelinated internode, as were rare intra-axonal macrophages. Similar histological abnormalities are seen in AMAN but are not typically noted in AIDP. An autopsy on another patient with AMSAN demonstrated inflammatory cell infiltrates comprising lymphocytes and macrophages in the spinal cord.

Pathogenesis

The pathogenic basis of AMSAN is unknown but is most likely due to an immune-mediated attack directed against epitopes on the axon.[9,53,59] AMSAN often follows *C. jejuni* infection and may lead to the production of the antibodies directed against various nerve gangliosides (e.g., GM1 or GM1a) (Figs. 11–2 and 11–3). These gangliosides are present on the nodal axolemma and may be the target of the immune attack due to molecular mimicry.[91,92] Early in the course or with mild disease, binding of the antibodies to neural epitopes may result in only physiological conduction block. However, complement activation on nodal and later internodal axolemma and recruitment of macrophages could result in axonal degeneration.

Treatment

There have been prospective treatment studies specifically for AMSAN; however, we treat patients with IVIG or PE.

ACUTE MOTOR AXONAL NEUROPATHY

Epidemiology

McKhann and colleagues initially described this variant in patients with seasonal outbreaks of acute flaccid paralysis in northern China.[99,100] They initially named the disorder the "Chinese paralytic syndrome," but because similar cases subsequently were described throughout the world, the term "AMAN" is more appropriate.[101,102] In northern China, AMAN is the most common variant of GBS and, although it is less frequent in other areas of the world, AMAN is still quite common. In this regard, 27 of the 147 (18%) of the patients enrolled in the Dutch GBS trial comparing IVIG to PE were later classified as having AMAN.[66,102] An antecedent illness occurs in 30–85% of patients with AMAN—most often a gastrointestinal infection.[33,51,100,102] In addition, 67–92% of patients have serologic evidence of a recent *C. jejuni* infection.[100,102]

Clinical Features

AMAN occurs in children and adults, and similar to AMSAN, it presents as an abrupt onset of generalized weakness.[8,51,80,99–101,103] The distal muscles are often more severely affected than proximal limb muscles, while cranial nerve deficits and respiratory failure requiring mechanical ventilation can be seen in up to one-third of patients.[99,100,102] Unlike AIDP and AMAN, there are no sensory signs or symptoms. However, autonomic dysfunction (e.g., cardiac arrhythmias, blood pressure fluctuations, and hyperhidrosis) may occur. Muscle stretch reflexes may be normal or absent, but of note some patients develop hyperactive reflexes during the recovery period.[37,100,101,104] The median time of recovery is similar to that seen in typical AIDP, and most affected individuals have a good recovery within 1 year, but residual distal limb weakness is common.[103] The mortality rate is less than 5%.[100] Second attacks of the illness have been described in northern Chinese patients, but the actual recurrence rate is not known.[100]

Laboratory Features

As with AIDP and AMSAN, albuminocytological dissociation in the CSF is seen and the absence of prominent CSF pleocytosis helps distinguish AMAN from poliomyelitis, which it would otherwise mimic.[99–102] Serology evidence of recent *C. jejuni* infection and GM1 and GD1a antibodies commonly detected in patients with AMAN are demonstrated in the majority of patients.[33,100,102,105]

Nerve conduction studies (NCS) reveals low-amplitude or unobtainable CMAPs with normal SNAPs.[8,99–103,106] When CMAPs are obtained, the distal latencies and conduction velocities are normal, as are F-waves when unobtainable. The decreased CMAP amplitudes may be a reflection of distal conduction block, degeneration only of the distal motor nerve terminal, or widespread axonal degeneration. Rare cases of proximal conduction block without other features of demyelination have also been reported.[37] EMG reveals fibrillation potentials and positive sharp waves and decreased recruitment of MUAPs.[99–103] Autonomic studies are relatively spared in AMAN compared to AIDP.

Histopathology

The earliest histological abnormality is lengthening of the nodal gaps. Immunocytochemistry reveals deposition of IgG and complement activation products (i.e., C3d and C5b-9) on the nodal and internodal axolemma of motor fibers rather than axonal degeneration.[54] In contrast, there is early deposition of immunoglobulin and complement on Schwann cells rather than the axons in AIDP.[54] Macrophages are recruited into the affected nodes of Ranvier and periaxonal space via complement-derived chemotropic factors.[54] The macrophages migrate through the Schwann cell basal lamina into the nodal gap where these dissect beneath the myelin sheath into the periaxonal space (Fig. 11–4). As these enter the periaxonal space, the axon retracts away from the adaxonal Schwann cell. In severe cases, the axons then begin to degenerate but the innermost myelin sheath (adaxonal lamella) appears intact. Active degeneration and severe loss of large myelinated intramuscular nerve fibers can also be demonstrated on motor point biopsy.[103] An autopsy on a patient with AMAN demonstrated inflammatory cell infiltrates comprising lymphocytes and macrophages in the spinal cord.

Pathogenesis

AMAN is most likely caused by an immune-mediated attack against an unknown epitope(s) on the nodal axolemma (Figs. 11–2 and 11–3). Axonal degeneration appears to develop predominantly in the motor nerve terminals, and only occasionally more proximally in the nerve roots.[106] Perhaps the antibodies are directed against GM1 or GD1a gangliosides that cross-react with the lipopolysaccharide membrane of *Campylobacter*.[54] The binding of antibodies to the nodal axolemma may decrease the sodium current or increase the potassium current, thereby resulting in conduction block.[107] Experimental studies demonstrate that GBS sera containing ganglioside antibodies cause neuronal cell lysis by targeting specific cell surface gangliosides and, secondly, that this cell lysis is complement dependent. The GD1a cell membrane pool appeared to be more susceptible to ganglioside antibody-mediated injury than the GM1 pool. Of

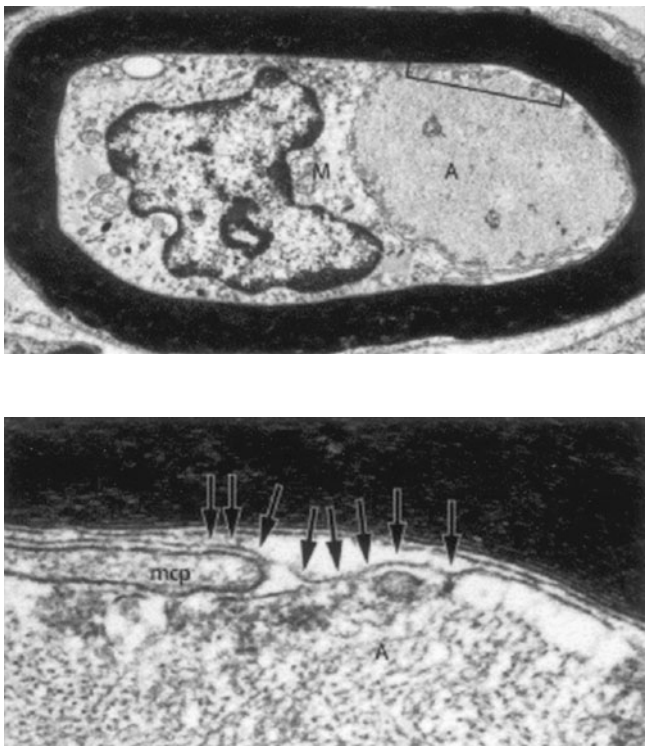

Figure 11–4. Nerve fiber from patient with AMAN. Lower panel is enlargement of box in upper panel. Electron micrograph shows macrophage (M) that has invaded the periaxonal space and axolemma (arrows) surrounding the axon (A). mcp, macrophage process. (With permission from Griffin JW, Li CY, Macko C, et al. Early nodal changes in the acute motor axonal neuropathy pattern of the Guillain–Barré syndrome. J Neurocytol 1996;25:33–51, Fig. 8, p. 44.)

note, IVIG significantly decreased this complement-dependent cytotoxicity.

Treatment

There have not been any treatment trials devoted to AMAN, although 27 of the 147 (18%) of the patients enrolled in the Dutch GBS trial comparing IVIG to PE were later classified as having AMAN.[66,102] Subgroup analysis of the AMAN group suggested that the IVIG-treated patients may recover faster than PE-treated patients. However, there was no significant difference in outcome, regardless of treatment (IVIG, PE, or PE followed by IVIG) between AIDP and AMAN, in a subgroup analysis of 369 patients.[33]

OTHER GBS VARIANTS

Besides AMSAN and AMAN, there are several other variants of GBS including the MFS (comprised of ataxia, areflexia, and ophthalmoplegia), idiopathic cranial polyneuropathy, pharyngeal–cervical–brachial weakness with or without ophthalmoparesis, and paraparetic weakness.[108–110] These disorders may represent oligosymptomatic or forme fruste of AIDP. Of these possible GBS variants, the MFS is best characterized. Other disorders that might be considered variants of GBS include acute sensory ganglionopathies and acute autonomic neuropathies.

MILLER FISHER SYNDROME

Clinical Features

MFS is characterized by ataxia, areflexia, and ophthalmoplegia in 1956.[7,68,111] There is a spectrum between MFS and Bickerstaff encephalitis, which is associated with ataxia, ophthalmoplegia, and abnormalities in consciousness.[112,113] The mean age of onset of MFS is in the early forties, but it can occur in children. There is a 2:1 male predominance. As with other forms of GBS, an antecedent infection is common, occurring in over two-thirds of the cases. Double vision is usually the earliest symptom (39%), followed by unsteadiness and incoordination due to a sensory ataxia (21%). Asymmetric oculomotor weakness may be seen, but this often progresses to complete ophthalmoplegia. Ptosis also occurs but pupillary involvement is uncommon. Other cranial nerves are also affected with facial weakness evident in 57%, dysphagia in 40%, and dysarthria in 13% patients. Approximately 50% of the patients complain of paresthesias of the face and distal limbs during the course, and areflexia is evident on examination in over 80%. Mild proximal limb weakness may develop in approximately one-third of cases, and some patients progress to develop severe generalized weakness similar to typical AIDP.[111,114–116] Recovery usually begins within about 2 weeks following the onset of symptoms, and a full return of function is usually seen within 3–5 months.

Laboratory Features

CSF protein is usually elevated without significant pleocytosis.[7,111] Serological evidence of recent infection by *C. jejuni* and ganglioside antibodies, in particular anti-GQ1b, are evident in many patients (Fig. 11–2).[117,118] A large study of 123 patients with MFS demonstrated CSF albuminocytological dissociation in 59% of patients during the first 3 weeks of illness, while serum GQ1b IgG antibodies were positive in 85%. While the incidence of CSF albuminocytological dissociation increased from the first to second weeks, GQ1b IgG antibodies peaked in the first week. GQ1b IgG antibodies are also seen in Bickerstaff encephalitis.

NCS reveals reduced amplitudes of SNAPs out of proportion to any prolongation of the distal latencies or slowing of sensory conduction velocities.[8,119–123] CMAPs in the arms and legs are

usually normal. However, mild-to-moderate reduction of facial CMAPs amplitudes is evident in over 50% of patients with MFS.[120] A loss or mild delay of R1 and R2 responses may be appreciated on blink reflex testing.[115,120,124]

Histopathology

Nerve biopsy and autopsy data are limited and need to be viewed cautiously, as some of the cases began with ophthalmoplegia, ataxia, and areflexia but later evolved to severe quadriparesis characteristic of more typical AIDP.[125] The brainstem appeared normal or revealed only secondary chromatolysis of the oculomotor, trochlear, or abducens nuclei. Demyelination and mild inflammatory infiltrates were noted along the course of these cranial nerves and in the sensory ganglia of peripheral nerves.

Pathogenesis

The pathogenic basis for the disorder is not known, although it is likely autoimmune, with preferential early attack directed against the sensory ganglia and oculomotor fibers.[7,111] Recent antecedent infections (e.g., *C. jejuni*) suggest that autoantibodies directed against these infectious agents cross-react with neuronal epitopes (e.g., GQ1b) (Figs. 11–2 and 11–3). In this regard, oculomotor fibers and the sensory ganglion are enriched in GQ1b and antibodies directed against this protein are detected in most patients with MFS. Immunohistochemistry studies reveal that GQ1b antibodies stain sensory neurons in the dorsal root as well as cerebellar nuclei. In mice infused with serum from patients with MFS, the GQ1b antibodies also bind to neuromuscular junctions and, in a complement-dependent process, this resulted in massive quantal release of acetylcholine from nerve terminals and eventually blocked neuromuscular transmission.[126] The similarities between MFS and Bickerstaff encephalitis suggests that these disorders fall along a spectrum and there may be central nervous system (CNS) as well as peripheral nervous system (PNS) involvement in MFS.[112]

Treatment

There are no controlled treatment trials of patients with MFS. A large retrospective study of 92 patients with MFS (28 treated with IVIG, 23 treated with PE, and 41 who did not receive treatment) suggested that IVIG might have slightly hastened the improvement of the ophthalmoplegia and ataxia, while PE was of no benefit.[127] The reason for the lack of significant improvement was that the natural history of MFS is of good recovery. Nonetheless, in absence of any controlled trials, we treat patients with IVIG.[113] In this regard, IVIG inhibits the binding of GQ1b antibodies to GQ1b, thereby preventing complement activation and subsequent pathophysiological effects in ex vivo mouse models, suggesting that it might be beneficial.[70]

IDIOPATHIC SENSORY NEURONOPATHY/GANGLIONOPATHY

Background

This disorder is believed to be caused by an autoimmune attack directed against the dorsal root ganglia. The differential diagnosis of sensory neuronopathy includes a paraneoplastic syndrome, which is typically associated with anti-Hu antibodies, and a sensory ganglionitis related to Sjögren syndrome. Certain medications or toxins, infectious agents, and other systemic disorders are also associated with a sensory neuronopathy. Despite extensive evaluation, many cases of sensory neuronopathy have no clear etiology, the so-called idiopathic sensory neuronopathy. The acute cases may represent a variant of GBS, although the onset can be insidiously progressive as well.

Clinical Features

Idiopathic sensory neuronopathy is a rare disorder that usually presents in adulthood (mean age of onset 49 years, with range 18–81 years) and has a slight female predominance.[8,128–131] Symptoms can develop over a few hours or evolve more insidiously over several months or years, and the course can be monophasic with a stable or remitting deficit, chronic progressive, or chronic relapsing. Unlike typical GBS, only a few patients report a recent antecedent infection. The presenting complaint is numbness and tingling face, trunk, or limbs, which can be painful. Symptoms begin asymmetrically and in the upper limbs in nearly half of the patients, suggesting a ganglionopathy as opposed to a length-dependent process. Usually, the sensory symptoms become generalized, but they can remain asymmetric. Patients also describe clumsiness of the hands and gait instability.

On examination, marked reduction in vibration and proprioception are found, while pain and temperature sensations are less affected. Manual muscle testing is usually normal. Some muscle groups may appear weak, but this is usually secondary to impaired modulation of motor activity due to the proprioceptive defect. Most patients have sensory ataxia, which can be readily demonstrated by having the patient perform the finger–nose–finger test with their eyes open and then closed. Patients may have only mild dysmetria with their eyes open, but when their eyes are closed, they consistently miss their nose and the examiner's stationed finger. Pseudoathetoid movements of the extremities may also be

appreciated. Patients exhibit a positive Romberg sign and, not surprisingly, describe more gait instability in the dark. Muscle stretch reflexes are decreased or absent, while plantar reflexes are flexor.

A detailed history and examination are essential to exclude a toxin-induced neuronopathy, paraneoplastic syndrome, or disorder related to a connective tissue disease (i.e., Sjögren's syndrome). Importantly, the sensory neuronopathy can precede the onset of malignancy or SICCA symptoms (i.e., dry eyes and mouth); therefore, these disorder should always be kept in mind. Pertinent laboratory and malignancy workup should be ordered. We refer patients to ophthalmology for Rose Bengal stain and a Schirmer's test. A lip or parotid gland biopsy is obtained in all suspected patients. Subacute sensory neuronopathy has also been associated with recent Epstein–Barr virus infection.[132]

Laboratory Features

The CSF protein is normal or only slightly elevated in most patients. However, the CSF protein can be markedly elevated (reportedly as high as 300 mg/dL) when examined within a few days in cases with a hyperacute onset. Only rare patients exhibit CSF pleocytosis. MRI scan can reveal gadolinium enhancement of the posterior spinal roots or increased signal abnormalities on T-2-weighted images in the posterior columns of the spinal cord.[133] Some patients have a monoclonal gammopathy (IgM, IgG, or IgA). Ganglioside antibodies, particularly GD1b antibodies, have been demonstrated in some cases of idiopathic sensory neuronopathy associated with IgM monoclonal gammopathy.[134]

Antineuronal nuclear antibodies (e.g., anti-Hu antibodies) should be assayed in all individuals with sensory neuronopathy to evaluate for a paraneoplastic syndrome. Likewise, antinuclear, SS-A, and SS-B antibodies should be ordered to look for evidence of Sjögren syndrome, which can also present with a sensory neuronopathy.

The classic NCS finding or low-amplitude SNAPs is absent.[129,130,133] When SNAPs are obtainable, the distal sensory latencies and nerve conduction velocities are normal or only mildly abnormal. In contrast, motor nerve conduction studies either are normal or reveal only mild abnormalities. In addition, H-reflexes and blink reflexes may typically be unobtainable.[135] An abnormal blink reflex favors a nonparaneoplastic etiology for a sensory neuronopathy but does not exclude an underlying malignancy.[136] The masseter reflex or jaw jerk is abnormal in patients with sensory neuropathy but is usually preserved in patients with sensory neuronopathy.[135] The masseter reflex is unique amongst the stretch reflexes in that the cell bodies of the afferent limb lie in the mesencephalic nucleus within the CNS. This differs from the sensory cell bodies innervating the limbs, which reside in the dorsal root ganglia of the PNS. The afferent cell bodies lie in the Gasserian ganglia that are outside the CNS, which explains why the blink reflex can be impaired in sensory ganglionopathies.

Histopathology

Sensory nerve biopsies may reveal a preferential loss of large myelinated fibers compared to small myelinated fibers or similar loss of both large- and small-diameter nerve fibers. Mild perivascular inflammation may be seen, but prominent endoneurial infiltrate is not appreciated. There is no evidence of segmental demyelination.

An autopsy performed 5 weeks after onset of idiopathic sensory neuronopathy in one man revealed widespread inflammation involving sensory and autonomic ganglia, with loss of associated neurons and Wallerian degeneration of the posterior nerve roots and dorsal columns being evident.[128] The motor neurons and roots appeared normal. Immunohistochemical analysis suggested a CD8+ T-cell-mediated cytotoxic attack against the ganglion neurons.

Pathogenesis

Autoimmune sensory neuronopathies are caused by an autoimmune attack directed against the dorsal root ganglia. Serum from affected patients immunostains dorsal root ganglia cells in culture and inhibits neurite.[137] The neuronal epitope is unknown, but the ganglioside GD1b has been hypothesized to be the target antigen.[134] GD1b localizes to neurons in the dorsal root ganglia, and antibodies directed against this ganglioside have been detected in some patients with idiopathic sensory neuronopathy.[128] Further, rabbits immunized with purified GD1b develop ataxic sensory neuropathy, with loss of the cell bodies in the dorsal root ganglia and axonal degeneration of the dorsal column of the spinal cord without demyelination or an inflammatory infiltrate.

Treatment

Various modes of immunotherapy have been tried, including corticosteroids, PE, and IVIG.[128,133] However, there have been no prospective, double-blinded, placebo-controlled trials. Occasionally, patients appear to improve with therapy; however, some improve spontaneously and many stabilize without treatment. In our experience, most patients have not experienced a dramatic improvement following treatment. Perhaps, this is because once the cell body of the sensory neuron is destroyed, it will not regenerate. However, in patients seen in the acute setting or those who have a chronic

progressive deficit, a trial of immunotherapy may be warranted.

ACUTE SMALL FIBER SENSORY NEUROPATHY

Clinical Features

Small fiber neuropathies typically present insidious with slowly progressive burning pain and paresthesia in the legs, which may later involve the arms (see Chapter 20). Most are idiopathic in nature, but diabetes mellitus, amyloidosis, Sjogrens' syndrome, and hereditary sensory and autonomic neuropathy need to be excluded. Rarely, patients present acutely with symptoms suggestive of a small fiber neuropathy that may or may not be length-dependent.[138,139] An antecedent infection is common. Neurological examination disclosed normal muscle strength, length-dependent or non-length dependent sensory loss for pain and temperature, normal proprioception, and vibration senses with normal or brisk muscle stretch reflexes. However, non-length dependent sensory loss and burning sensation can also be seen[139] The burning dysesthesia usually disappear within 4 months; however, the numbness and objective sensory loss tended to persist longer.

Laboratory Features

CSF examination may reveal albuminocytological dissociation. Motor and sensory conduction studies that primarily assess large fiber function are normal. Autonomic testing may be abnormal.

Histopathology

No nerve biopsy data have been reported in these. However, skin biopsies in some patients have shown reduced nerve fiber density, which in most cases was worse in the thigh compared to calf.[34]

Pathogenesis

The acute clinical presentation often following an infection and CSF findings suggests that this is a rare variant of GBS.

Treatment

A trial of IVIG would seem warranted in patients who present in the acute phase of the illness.

AUTOIMMUNE AUTONOMIC NEUROPATHY

Clinical Features

Young et al. were the first to report a detailed clinical, laboratory, and histological description of a patient with acute pandysautonomia.[140,141] Subsequently, there have been a number of small reports of idiopathic autonomic neuropathy.[8,142–157] Many of these cases are presumed to have an autoimmune basis. This is a heterogenic neuropathy in terms of onset, the type of autonomic deficits, the presence or absence of somatic involvement, and the degree of recovery. A Mayo Clinic series of 27 cases of idiopathic autonomic neuropathy followed for a mean of 32 months found that approximately 20% of patients had selective cholinergic dysfunction, while 80% had various degrees of widespread sympathetic and parasympathetic dysfunction.[153] The most common symptom is orthostatic dizziness or lightheadedness occurring in about 80% of patients. Gastrointestinal involvement is present in over 70%, with patients complaining of nausea, vomiting, diarrhea, constipation, ileus, or postprandial bloating. Heat intolerance and poor sweating are also present in the majority of patients. Blurred vision, dry eyes and mouth, urinary retention or incontinence, and impotence are common. Numbness, tingling, and dysesthesia of the distal extremities are evident in about 30% of patients, but muscle strength is normal. Most patients have a monopathic course with progression, followed by a plateau and slow recovery or a stable deficit.[153] Although some patients exhibit a complete recovery,[141,155] it tends to be incomplete in most.[153]

Laboratory Features

The CSF often reveals slightly elevated protein without pleocytosis.[153] Supine plasma norepinephrine levels are not different, but standing levels are significantly reduced, when compared to normal controls.[153] In a large study, patients with idiopathic autonomic neuropathy 18/106 (18%) had high levels of ganglionic acetylcholine receptor (AChR) autoantibodies.[157,158] The seropositive group had a significant overrepresentation of abnormal pupillary responses, sicca complex, and lower gastrointestinal tract dysautonomia. A subacute mode of onset was more common in the seropositive group. Rabbits immunized with a neuronal AChR alpha3 subunit fusion protein produce ganglionic AChR antibodies and develop autonomic failure.[159] Immunohistochemical staining of superior cervical ganglia and myenteric plexus neurons reveals intact presynaptic nerve terminals and postsynaptic neurons containing cytoplasmic nAChR, but lacking surface AChR.

Routine motor and sensory nerve conduction studies and EMG are usually unremarkable.[153] Quantitative sensory testing may reveal abnormalities in thermal thresholds.[147] Autonomic testing can be helpful.[160,161] Orthostatic hypotension and reduced variability of the heart rate on deep breathing are evident in over 60% of affected individuals.[153] An abnormal response to

Valsalva maneuver (i.e., exaggerated fall in blood pressure during early phase II of the response, absent recovery of systolic and diastolic blood pressure during late phase II, or reduced or absent overshoot of systolic and diastolic pressures during phase IV) has been demonstrated in over 40% of patients. Sympathetic skin response may be absent.[144,162] Abnormal quantitative sudomotor axon reflex test scores are seen in 85% of patients.[153] Most patients have abnormal thermoregulatory sweat tests, with areas of anhidrosis in 12–97% of the body. Gastrointestinal studies may reveal hypomotility anywhere from the esophagus to the rectum.

Histopathology

Nerve biopsies reveal reduced density of mainly small-diameter myelinated nerve fibers, along with stacks of empty Schwann cell profiles and collagen pockets.[141,145,150,153,162] Scant epineurial perivascular inflammation may be seen.

Pathogenesis

The disorder is suspected to be the result of an autoimmune attack directed against peripheral autonomic fibers or the ganglia. A subset of patients may have antibodies directed against calcium channels, which are present on presynaptic autonomic nerve terminals.

Treatment

PE, prednisone, IVIG, and other immunosuppressive agents have been tried with variable success.[146,152,153] The most important aspect of management is supportive therapy for orthostatic hypotension and bowel and bladder symptoms.[160,161] Fluodrocortisone is effective at increasing plasma volume but is administered only in the morning or in the morning and at lunch to avoid nocturnal hypertension. We begin treatment at 0.1 mg/d and increase by 0.1 mg every 3–4 days until the blood pressure is controlled. Midodrine, a peripheral α1 adrenergic agonist, is also effective and can be used in combination with fluodrocortisone. Midodrine is started at 2.5 mg/d and can gradually be increased to 40 mg/d in divided doses (every 2–4 hours) as necessary.[163] Gastrointestinal hypomotility can be treated with metaclopramide, cisapride, or erythromycin. Bulking agents, laxatives, and enemas may be need in patients with constipation. Urology should be consulted in patients with neurogenic bladders. Patient may require cholinergic agonists (e.g., bethanechol), intermittent self-catheterization, or other modes of therapy.

▶ SUMMARY

GBS is an acquired immune-mediated neuropathy. It most commonly presents in the Western hemisphere as an acute inflammatory demyelinating polyneuropathy (AIDP) in which the immune attack is directed against myelin in peripheral nerves. Occasionally, the immune attack is directed against the axons of motor and sensory nerves (AMSAN) or just axons of motor nerves (AMAN). These axonal variants of GBS are more common in Asia but do occur worldwide. Other immune-mediated neuropathies such as MFS, acute autonomic neuropathy, acute sensory neuronopathies, and acute small fiber neuropathies may also fall into the spectrum of GBS. The natural history of most of these neuropathies is for gradual spontaneous improvement, but treatment with IVIG or PE may facilitate improvement.

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CHAPTER 12

Chronic Inflammatory Demyelinating Polyneuropathy and Related Neuropathies

The chronic inflammatory demyelinating polyneuropathies are a group of disorders that share some similar clinical, electrophysiological, and histological features but in most instances represent distinct neuropathies with different pathogenic bases, prognoses, and response to various therapies (Table 12–1). Within this category are included classical chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), distal acquired demyelinating sensorimotor (DADS) neuropathy, multifocal acquired demyelinating sensory and motor (MADSAM) neuropathy, multifocal motor neuropathy (MMN), and multifocal acquired motor axonopathy (MAMA).

▶ CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY

CLINICAL FEATURES

CIDP is an immune-mediated neuropathy characterized by a relapsing or progressive course.[1–12] The diagnostic approach requires detailed clinical examination, combined with supportive laboratory and electrodiagnostic abnormalities and occasionally a nerve biopsy (Fig. 12–1). Various research criteria for CIDP have been developed but none have been universally accepted (Tables 12–2 and 12–3).[1,9,13–15] CIDP may account for 10–33% of initially undiagnosed peripheral neuropathies in large tertiary referral centers.[1,4,16] By definition, symptoms and signs of the neuropathy must be progressive for at least 2 months, which distinguishes CIDP from Guillain–Barre syndrome (GBS) or the most common form of GBS, namely acute acquired inflammatory demyelinating neuropathy (AIDP).[1,13] Differentiating AIDP from CIDP can be difficult early on, as it is not always possible to determine in the first few weeks how many patients will continue to progress over 2 months and how many will reach a plateau. Further, some patients have a subacute onset over 4–8 weeks, a variant some have called subacute demyelinating polyneuropathy.[17–20] The subsequent natural history of these subacute cases can be that of AIDP (spontaneous remission) or CIDP (chronic relapses or progression) requiring treatment. Dyck et al. describe four courses of progression in patients with CIDP: (1) chronic monophasic (15%), (2) chronic relapsing (fluctuations of weakness or improvement over weeks or months) (34%), (3) stepwise progressive (34%), and (4) steady progressive (15%).[21] As one can see this is similar to multiple sclerosis, an immune-mediated demyelinating disorder affecting the central nervous system (CNS).

CIDP usually presents in adults (peak incidence at about 40–60 years of age) but it can manifest in children.[1,3,5,6,21,22] The relapsing form often presents earlier, usually in the twenties.[1,23] There is a slightly increased prevalence in men. Pregnancy can be associated with relapses or exacerbations of the neuropathy.[24] Infections may precede 20–30% of CIDP relapses or exacerbations.[3,25]

Most patients manifest with progressive, symmetric proximal, and distal weakness of the arms and legs.[1,3,6,22,26] The diagnostic criteria proposed by Barohn et al. require symmetric, proximal, and distal weakness; however, the American Academy of Neuropathy (AAN) and Inflammatory Neuropathy Course and Treatment (INCAT) group criteria are looser clinically and do not require either proximal or symmetric weakness (Tables 12–2 and 12–3).[13,14] Early in the course of the illness, only distal extremity numbness and weakness may be apparent; thus, these patients have a DADS phenotype.[27] However, if weakness remains distal, other diagnoses need to be considered (e.g., hereditary demyelinating neuropathy and paraprotein-related DADS neuropathy). Although most patients (at least 80%) have both motor and sensory involvement, a few patients may have pure motor (10%) or pure sensory (5–10%) symptoms and signs.[1,21,28,29] Subjective numbness in the extremities is present in 68–80% of patients, while painful paresthesias occur in 15–50%.[3,21,28] As one would expect, sensory examination is abnormal in most

TABLE 12–1. COMPARISON OF THE CHRONIC ACQUIRED IMMUNE-MEDIATED DEMYELINATING POLYNEUROPATHIES

	CIDP	DADS	MADSAM	MMN
Clinical Features				
Weakness	Symmetric proximal and distal weakness	None or only mild symmetric distal weakness	Asymmetric, distal > proximal, arms > legs	Asymmetric, distal > proximal, arms > legs
Sensory loss	Yes; symmetric	Yes; distal and symmetric	Yes; asymmetric	No
Reflexes	Symmetrically reduced or absent	Symmetrically reduced or absent	Asymmetrically reduced or absent	Asymmetrically reduced or absent
Electrophysiology				
CMAPs	Demyelinating features including CB	Demyelinating features excluding CB	Demyelinating features including CB	Demyelinating features including CB
SNAPs	Abnormal	Abnormal	Abnormal	Normal
Laboratory Findings				
CSF protein	Usually elevated	Usually elevated	Usually elevated	Usually normal
Monoclonal protein	Occasionally present, usually IgG or IgA	IgM usually present (most anti-MAG)	Rarely present	Rarely present
GM1 antibodies	Rarely present	Rarely present	Rarely present	Frequently present
Sensory nerve biopsies	Demyelinating/ remyelinating features are common	Demyelinating/ remyelinating features are common, with IgM deposition evident in paranodal regions	Demyelinating/ remyelinating features are common	Demyelinating/ remyelinating features are scant, if present
Treatment Response				
Prednisone	Yes	Poor	Yes	No
Plasma exchange	Yes	Poor	Not adequately studied	No
IVIG	Yes	Poor	Yes	Yes
Cyclophosphamide	Yes	Poor	Not adequately studied	Yes

CIDP, chronic inflammatory demyelinating polyneuropathy; DADS, distal acquired demyelinating symmetrical; MADSAM, multifocal acquired demyelinating sensory and motor; MMN, multifocal motor neuropathy; CMAPs, compound motor action potentials; SNAPs, sensory nerve action potentials; CB, conduction block; CSF, cerebrospinal fluid; MAG, myelin-associated glycoprotein; IVIG, intravenous immunoglobulin.
With permission from Saperstein DS, Katz JS, Amato AA, Barohn RJ. The spectrum of the acquired chronic demyelinating polyneuropathies. Muscle Nerve 2001;24:311–324, Table 4, p. 213.

patients, particularly large-fiber modalities (vibration and touch).[1,3,21,22,28] Some patients exhibit sensory ataxia and gait imbalance. Most patients with CIDP are areflexic or at least hyporeflexic. Symptomatic autonomic neuropathy (e.g., orthostatic hypotension, incontinence, and impotence) can occur but is uncommon.[21,30,31]

Rare patients may have only sensory symptoms and signs, a so-called "chronic sensory demyelinating neuropathy."[32–34] However, in most such cases, nerve conduction studies (NCS) reveal slowing of the motor nerves as well. It is not unusual for CIDP to present with sensory symptoms and then later develop motor abnormalities.[35] In our experience, patients with a demyelinating neuropathy who have sensory signs out of proportion to muscle weakness often have an IgM monoclonal gammopathy with or without antibodies directed against myelin-associated glycoprotein (MAG). Whenever a pure sensory neuropathy is present, consideration should be given to other diseases as well, such as Sjögren syndrome or a paraneoplastic neuronopathy, which are associated with sensory ganglionitis.[36] However, there are indeed rare cases of demyelination that appears to be focused on the sensory roots (chronic demyelinating sensory polyradiculopathy), which likely falls into end of the spectrum of CIDP.[37] This is distinguished from sensory ganglionopathies and anti-MAG neuropathies by the clinical absence or reduction of muscle stretch reflexes but normal routine sensory SNAPs. On the other hand, H-reflexes and somatosensory-evoked potentials are

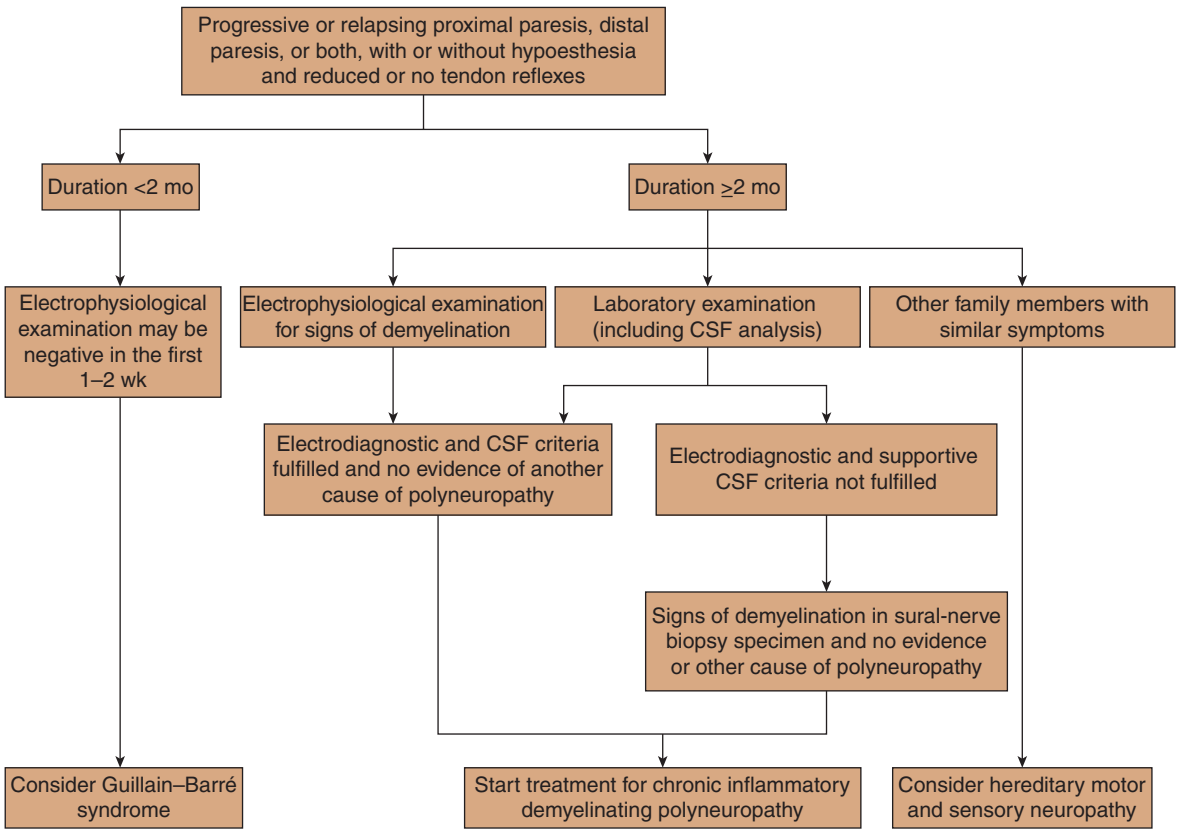


Figure 12–1. Diagnostic approach. Algorithm of diagnostic procedures. If a patient presents with a history of symptoms suggestive of chronic inflammatory demyelinating polyneuropathy of 2 months' duration or more, we perform nerve-conduction studies for signs of demyelination—including partial conduction block, reduced motor-nerve CV, prolonged distal latency of the motor nerve, and the absence of F waves or a prolonged F-wave latency—to differentiate between predominantly demyelinating and axonal disease of peripheral nerves. We also use laboratory tests—including cell-count and protein studies of cerebrospinal fluid (CSF)—to evaluate supportive criteria and to rule out other causes. If these causes have been ruled out and electrodiagnostic and supportive CSF criteria are fulfilled, patients may begin long-term immunomodulating/ immunosuppressive therapy. A sural nerve is helpful if diagnosis is not clear. (With permission from Koller. N Engl J Med 2005;352(13):1343–1356, Fig. 2, p. 1349.)

abnormal, indicating proximal demyelination of the sensory roots.

Cranial neuropathies can lead to mild facial weakness, ophthalmoparesis, dysarthria, dysphagia, hearing loss, or vertigo.[1,3,21,22,38,39] A rare presentation is neck extensor weakness leading to dropped head syndrome.[40] Papilledema may be seen in a few patients, particularly those with a CIDP-line neuropathy related to POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes). Respiratory insufficiency secondary to intercostal muscle and diaphragm is rare in idiopathic CIDP, and development should also make one consider POEMS.[21,22,41] As POEMS is frequently associated with an osteosclerotic myeloma, a skeletal survey and scans for focal plasmacytomas or lymphoma should be performed.

As many as 3% of patients with CIDP develop evidence of central nervous system (CNS) demyelination clinically, electrophysiologically (evoked potential studies), or by magnetic resonance imaging (MRI) scans.[42–48] Attacks of CNS demyelination can precede or follow the onset of CIDP or may be entirely asymptomatic lesions. It is unclear if these patients have multiple sclerosis or a distinct immunologic disorder of the CNS. Several medical conditions, particularly other autoimmune disease, HIV infections, and immunoproliferative disorders/malignancies, are associated with CIDP or a CIDP-like neuropathy (Table 12–4).[1,13,36,49–55] Rarely, patients with diabetes mellitus develop a CIDP-like neuropathy with symmetric proximal and distal extremity weakness, elevated CSF protein, and demyelinating features on the NCS and nerve biopsies.[56–60] These patients may have an unusual form of diabetic neuropathy, incidental

▶ TABLE 12–2. AMERICAN ACADEMY OF NEUROLOGY RESEARCH CRITERIA FOR DIAGNOSIS OF CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY (CIDP)

I. Clinical
  A. Mandatory
    1. Progressive or relapsing motor and sensory, rarely only motor or sensory, dysfunction of more than one limb of a peripheral nerve nature, developing over at least 2 months
    2. Hypo or areflexia. This will usually involve all four limbs
  B. Supportive
    1. Large-fiber sensory loss predominates over small-fiber sensory loss
  C. Exclusion
    1. Mutilation of hands or feet, retinitis pigmentosa, ichthyosis, appropriate history of drug or toxic exposure known to cause a similar peripheral neuropathy, or family history of a genetically based peripheral neuropathy
    2. Sensory level
    3. Unequivocal sphincter disturbance

II. Physiologic studies
  A. Mandatory
    Nerve conduction studies including studies of proximal nerve segments in which the predominant process is demyelination
    Must have three of four:
    1. Reduction in conduction velocity (CV) in two or more motor nerves:
      a. <80% of lower limit of normal (LLN) if amplitude >80% of LLN
      b. <70% of LLN if amplitude <80% of LLN
    2. Partial conduction block or abnormal temporal dispersion in one or more motor nerves: peroneal nerve between ankle and below fibular head, median nerve between wrist and elbow, or ulnar nerve between wrist and below elbow

      Criteria suggestive of partial conduction block: <15% change in duration between proximal and distal sites and >20% drop in negative-peak (−p) area or peak-to-peak (p–p) amplitude between proximal and distal sites

      Criteria for abnormal temporal dispersion and possible conduction block: >15% change in duration between proximal and distal sites and >20% drop in -p area or p–p amplitude between proximal and distal sites. These criteria are only suggestive of partial conduction block, as these are derived from studies of normal individuals. Additional studies, such as stimulation across short segments or recordings of individual motor unit potentials, are required for confirmation
    3. Prolonged distal latencies in two or more nerves:
      a. >125% of upper limit of normal (ULN) if amplitude >80% of LLN
      b. >150% of ULN if amplitude <80% of LLN
    4. Absent F waves or prolonged minimum F-wave latencies (10–15 trials) in two or more nerves:
      a. >120% of ULN if amplitude >80% of LLN
      b. >150% of ULN if amplitude <80% of LLN
  B. Supportive
    1. Reduction in sensory CV <80% of LLN
    2. Absent H reflexes

III. Pathologic features
  A. Mandatory
    1. Nerve biopsy showing unequivocal evidence of demyelination and remyelination
    2. Demyelination by either electron microscopy (>5 fibers) or teased fiber studies (>12% of 50 teased fibers, minimum of four internodes each, demonstrating demyelination/remyelination)
  B. Supportive
    1. Subperineurial or endoneurial edema
    2. Mononuclear cell infiltration
    3. “Onion-bulb” formation
    4. Prominent variation in the degree of demyelination between fascicles
  C. Exclusion
    1. Vasculitis, neurofilamentous swollen axons, amyloid deposits, or intracytoplasmic inclusions in Schwann cells or macrophages, indicating adrenoleukodystrophy, metachromatic leukodystrophy, globoid cell leukodystrophy, or other evidence of specific pathology

IV. CSF studies
  A. Mandatory
    1. Cell count <10/mm^3 if HIV seronegative or <50/mm^3 if HIV seropositive
    2. Negative VDRL
  B. Supportive
    1. Elevated protein

Diagnostic categories for research purposes: DEFINITE: Clinical A and C, Physiology A, Pathology A and C, and CSF A. PROBABLE: Clinical A and C, Physiology A, and CSF A. POSSIBLE: Clinical A and C and Physiology A.
Laboratory studies: Depending on the results of the laboratory tests, those patients meeting the criteria above will be classified into the groups listed below.
The following studies are suggested: CBC, ESR, SMA 6/12, CK, ANA, thyroid functions, serum and urine immunoglobulin studies (to include either immunofixation electrophoresis or immunoelectrophoresis), and HIV and hepatitis serology. The list of laboratory studies is not comprehensive. For instance, in certain clinical circumstances other studies may be indicated, such as phytanic acid, long-chain fatty acids, porphyrins, urine heavy metals, and alpha-lipoprotein.
CSF, cerebrospinal fluid.
With permission from Cornblath DR, Asbury AK, Albers JW, et al: Research criteria for diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP). Neurology 1991;41:617–618.

▶ **TABLE 12–3. COMPARISON OF DIAGNOSTIC CRITERIA FOR CIDP**

	Barohn et al. (1988)	AAN Ad Hoc Subcommittee (1991)	Saperstein et al. (2001)	INCAT (2001)	European Federation of Neurological Societies (2006)
Mandatory clinical features					
Weakness	Symmetrical; proximal and distal	Involving one or more limbs	Symmetrical; proximal and distal	Involving one or more limbs	Typical: symmetrical; proximal and distal Atypical: DADS, MADSAM, pure motor, and pure sensory
Reflexes	Areflexia or hyporeflexia	Areflexia or hyporeflexia	Areflexia or hyporeflexia	Areflexia or hyporeflexia	Areflexia or hyporeflexia
Time course	At least 2 months	At least 2 months	At least 2 months	At least 2 months	At least 2 months
Exclusionary features	• Pure sensory neuropathy, mutilation of hands or feet, retinitis pigmentosa, ichthyosis, orange tonsils, and history of exposure to drugs or toxins known to cause peripheral neuropathy • Low serum cholesterol levels, abnormal porphyrin metabolites, fasting glucose $\geq$7.7 mmol/L, low serum B12 levels, hypothyroidism, heavy metal intoxication, and CSF WBC $>50/mm^3$ • EDX features of neuromuscular transmission defect, myopathy, or anterior horn cell disease	• Mutilation of hands or feet, retinitis pigmentosa, ichthyosis, history of drug or toxin exposure known to cause a similar peripheral neuropathy, or family history of a genetically based neuropathy • Sensory level • Unequivocal sphincter disturbance	• Clinical features of a hereditary neuropathy or exposure to drugs or toxins known to cause peripheral neuropathy • Laboratory or nerve biopsy evidence of a potential etiology other than CIDP • EDX features of neuromuscular transmission defect, myopathy, or anterior horn cell disease	Exclusion of systemic diseases that may cause neuropathy, including paraproteinemia	• Clinical features of a hereditary neuropathy • Diphtheria • Multifocal motor neuropathy • Sphincter disturbance • Myelin-associated glycoprotein antibodies

(*continued*)

► **TABLE 12–3. (CONTINUED)**

	Barohn et al. (1988)	AAN Ad Hoc Subcommittee (1991)	Saperstein et al. (2001)	INCAT (2001)	European Federation of Neurological Societies (2006)
Laboratory features					
Electrodiagnostic studies (EDX)		Three out of four criteria must be met	Two out of four criteria must be met	One of the following must be met: 1. CB or TD in at least two nerves with abnormal CV, DL, or abnormal F waves or 2. In absence of CB/TD, there is abnormal CV, DL, or F waves in at least three nerves or 3. If there is abnormal CV, DL, or F waves in only two nerves, demyelinated nerve fibers must be present on nerve biopsy	One of the following must be met for definite diagnosis
Conduction block	No specific criteria	>20% drop in negative peak area or peak-to-peak amplitude, with a <15% change in duration between proximal and distal sites (must be present in ≥1 motor nerves)	>50% drop in negative peak area or peak-to-peak amplitude, with a <30% change in duration between proximal and distal sites	>15% idrop in negative peak area or peak-to-peak amplitude with <15% change in duration	CB of at least 50% if distal CMAP is at least 20% of LLN in two nerves or in one nerve plus one other nerve with feature of demyelination
Temporal dispersion	No specific criteria	>15% increase in duration	>30% increase in duration	>15% increase in duration	>30% increase in duration in two nerves
Distal CMAP dispersion	No specific criteria	No specific criteria	No specific criteria	No specific criteria	Distal CMAP duration >9 ms plus one of the following other feature of demyelination must be met

Conduction velocity	Reduced <70% of LLN	• Reduced <80% of LLN if CMAP amplitude >80% of LLN • Reduced <70% of LLN if CMAP amplitude <80% of LLN (must be abnormal in ≥2 motor nerves)	Same as for AAN criteria	Reduced CV as per AAN criteria	At least 30% slowing of CV below LLN in two nerves
Distal latency	No specific criteria	• Prolonged >125% of ULN if CMAP amplitude >80% of LLN • Prolonged >150% of ULN if CMAP amplitude <80% of LLN (must be abnormal in ≥2 motor nerves)	Same as for AAN criteria	Prolonged distal latency as per AAN criteria	At least 50% prolongation of DL above ULN in two nerves
F wave latency	No specific criteria	• Absent or prolonged >125% of ULN if CMAP amplitude >80% of LLN • Prolonged >150% of ULN if CMAP amplitude <80% of LLN (must be abnormal in ≥2 motor nerves)	Same as for AAN criteria	Prolonged F waves as per AAN criteria	At least 20% increase in F wave above ULN (at least 50% increase if distal CMAP amplitude is <80 LLN) Absent F wave if distal CMAP amplitude is >20% of the LLN
Cerebrospinal fluid (CSF) studies	CSF protein >45 mg/dL	Mandatory: cell count <10/mm^3 if HIV (−) Or <50/mm^3 of HIV (+) Negative VDRL Supportive: elevated protein	CSF protein >45 mg/dL Cell count <10/mm^3 if HIV (−) Or <50/mm^3 of HIV (+)	CSF cell count <10/mm^3 (CSF examination is encouraged but not mandatory)	Elevated CSF protein and cell count <10/mm^3
Nerve biopsy features	Predominant features of demyelination that include segmental demyelination, remyelination, onion-bulb formation, and inflammation	Unequivocal evidence of demyelination and remyelination	Predominant features of demyelination that include segmental demyelination, remyelination, and onion-bulb formation	Evidence of demyelination on nerve biopsy is required based on EDX criteria above	Evidence of demyelination/remyelination on nerve biopsy with >5 fibers on EM or 6/60 teased fibers

(*continued*)

▶ **TABLE 12–3. (CONTINUED)**

	Barohn et al. (1988)	AAN Ad Hoc Subcommittee (1991)	Saperstein et al. (2001)	INCAT (2001)	European Federation of Neurological Societies (2006)
Requirements for diagnostic categories					
Definite	Clinical, EDX, CSF, and biopsy	Clinical, EDX, CSF[†], and nerve biopsy	Clinical, EDX, and CSF nerve (biopsy supportive but not mandatory)	Clinical and EDX (criteria 1 or 2) (CSF and nerve biopsy not necessary) or Clinical, EDX (criteria 3), and nerve biopsy (nerve biopsy not necessary)	Clinical plus definite EDX criteria or Probable EDX criteria plus one laboratory-supportive criterion (CSF, nerve biopsy, MRI of roots, plexus or nerves showing thickening or enhancement, or clinical improvement with immunotherapy) Or Possible EDX criteria plus two laboratory-supportive criteria
Probable	Clinical and two out of three laboratory criteria (EDX, CSF, or biopsy)	Clinical, EDX, and nerve biopsy	Clinical, EDX, and nerve biopsy or Clinical, CSF, and nerve biopsy		Clinical and NCS showing CB $<50\%$ but $>30\%$ if distal CMAP is at least 20% of LLN in two nerves (excluding the posterior tibial) or in one nerve plus one other nerve with feature of demyelination
Possible	Clinical and one out of three laboratory criteria (EDX, CSF, or biopsy)	Clinical and EDX	Clinical and one out of three laboratory criteria (EDX, CSF, or nerve biopsy)		Clinical plus any one of the above EDX criteria found in only one nerve

[†]The AAN criteria require only an elevated cell count to consider CSF abnormal (elevated protein is not a mandatory feature).
CIDP, chronic inflammatory demyelinating polyneuropathy; AAN, American Academy of Neurology; EDX, electrodiagnostic studies; LLN, lower limit of normal; CMAP, compound motor action potential; ULN, upper limit of normal; CSF, cerebrospinal fluid; INCAT, Inflammatory Neuropathy Cause and Treatment group.

TABLE 12–4. MEDICAL CONDITIONS ASSOCIATED WITH CHRONIC ACQUIRED IMMUNE-MEDIATED DEMYELINATING POLYNEUROPATHY

HIV infection
Inflammatory bowel disease
Systemic lupus erythematosus
Diabetes mellitus
Monoclonal gammopathy of uncertain significance (MGUS)
Paraneoplastic
POEMS syndrome
Lymphoma
Castleman disease
Waldenstrom macroglobulinemia (usually associated with DADS phenotype)
Small cell carcinoma of the lung
Carcinoma of the pancreas
Carcinoma of the colon
Cholangiocarcinoma
Melanoma
Bone marrow and solid organ transplantations (often in setting of graft-vs.-host disease or rejection)
Neurotoxicity

occurrence of CIDP, or perhaps a predisposition toward developing CIDP due to their diabetes. A toxic-induced neuropathy resembling CIDP has been associated with certain medications such as cyclosporine, tacrolimus, and tumor necrosis alpha blockers.[36,49,61,62] It is likely that CIDPs in such cases are not caused by a direct toxic effect; rather, these medications alter the immune status of treated individuals and may predispose them to CIDP.

LABORATORY FEATURES

Most patients (80–95%) have an elevated cerebral spinal fluid (CSF) protein (>45 mg/dL) with a mean of 135 mg/dL and levels over 1200 mg/dL.[1,5,6,21,22,28,63] Very high CSF protein levels should make one think of CIDP-like neuropathy in the setting of POEMS syndrome. Similar to GBS, the CSF cell count is usually normal, although up to 10% of patients have greater than five lymphocytes/mm^3. Elevated CSF cell counts should lead to the consideration of HIV infection, sarcoidosis, Lyme disease, and lymphomatous or leukemic infiltration of nerve roots. Oligoclonal bands may be demonstrated in the CSF in approximately 65% of patients.[64,65]

A monoclonal gammopathy (IgA, IgG, or IgM) is present in up to 25% of patients with CIDP.[1,25,27,28,60,66] Unlike GBS, only a small number of patients have autoantibodies directed against myelin proteins (e.g., GM_1 ganglioside, P_0, and P_2).[67] The strongest evidence incriminates P_0, to which antibodies have been found in 20% of cases.[8,9,68] Antitubulin antibodies were reported in one study of CIDP[69] but was not seen in others.[70,71]

Hypertrophy and enhancement of the nerve roots and peripheral nerves may be appreciated with MRI.[72,73] Rarely, a myelopathy can develop secondary to the markedly enlarged nerve roots compressing the spinal cord.

Multiple nerves should be evaluated on NCS because of the multifocal nature of the disease process; some nerves can have normal conduction studies, while other nerves are abnormal. Various electrophysiological criteria for demyelination have been devised (Tables 12–2 and 12–3).[1,8,9,13,14,74–76] However, we reinforce that these are research criteria and are not meant to necessarily "rule in" or "rule out" CIDP. Less than two-thirds of patients with CIDP fulfill electrophysiological criteria for demyelination, regardless of what criteria are used.[77]

MOTOR CONDUCTION STUDIES

Motor conductions studies evaluating compound muscle action potential (CMAP) amplitudes, distal latencies, conduction velocities (CV), and F-wave latencies as well as looking for evidence of temporal dispersion or conduction block are the most useful electrodiagnostic tools for CIDP.[1,3,5,22,44,78] The most commonly used guidelines for demyelination include reduction of motor nerve CV to less than 70% of the lower limit of normal; distal motor latencies are typically prolonged 125–150% of the upper limit of normal, prolonged (>125% or 150% of the upper limit of normal), or unobtainable F waves.[1,13,14,48,76,79–81]In addition, one may see conduction block or temporal dispersion of the CMAP waveform between distal and proximal sites of stimulation. Dispersion of the distal CMAP waveform ≥9 milliseconds has a sensitivity of 0.78 for CIDP and specificity of 0.94 vs. axonal polyneuropathies or motor neuron disease but does not help distinguish CIDP from forms of CMT.[82–84] Adding distal CMAP duration criteria to other commonly accepted criteria enhanced their sensitivity with little sacrifice of specificity.

As patients' strength and function improve, repeat NCS may show increase in the CMAP amplitudes and CVs along with reduced conduction block.[22,85–91] Clinical improvement is primarily the result of resolving conduction block, although some may be attributed to collateral sprouting and regeneration of axons.

SENSORY NCS

Most patients with CIDP have low-amplitude or unobtainable sensory nerve action potentials (SNAPs) in both the upper and the lower extremities.[1,3,5,22,33,79,91,92] Obtainable SNAPs may have prolonged distal latencies and slow CVs. However, the "slowing" is usually not as severe as that demonstrated in motor nerves. In a study of

18 patients using the near-nerve technique, sensory conduction slowing was only moderately slow in proportion to the degree of amplitude loss.[93] A helpful feature when present is abnormal median, ulnar, or radial SNAPs when the sural SNAPs are normal. This pattern of abnormality suggests a non-length-dependent process (most axonal neuropathies are length dependent). When these electrodiagnostic abnormalities are worse in the arms than in the legs, one needs to consider a demyelination neuropathy or sensory ganglionopathy.

EVOKED POTENTIAL STUDIES

Rare patients have abnormal visual-evoked, brainstem auditory-evoked, and somatosensory-evoked potentials suggestive of superimposed central demyelination.[45,48]

AUTONOMIC STUDIES

Although most patients are not symptomatic, evidence of subclinical autonomic neuropathy is not uncommon.[30,31] The tilt tests followed by the 30/15 heart rate ratio are most frequently abnormal autonomic studies.

NEEDLE ELECTROMYOGRAPHY

Insertional and spontaneous activity are often normal on needle electromyography (EMG). However, fibrillation potentials may be seen due to secondary axonal loss. Occasionally, myokymic discharges may be seen related to cross talk between demyelinated nerve fibers. The earliest abnormality one might see on EMG is reduced recruitment (fast-firing) motor unit action potentials (MUAPs) that otherwise appear morphologically normal.

ELECTROPHYSIOLOGIC CRITERIA FOR DIAGNOSIS

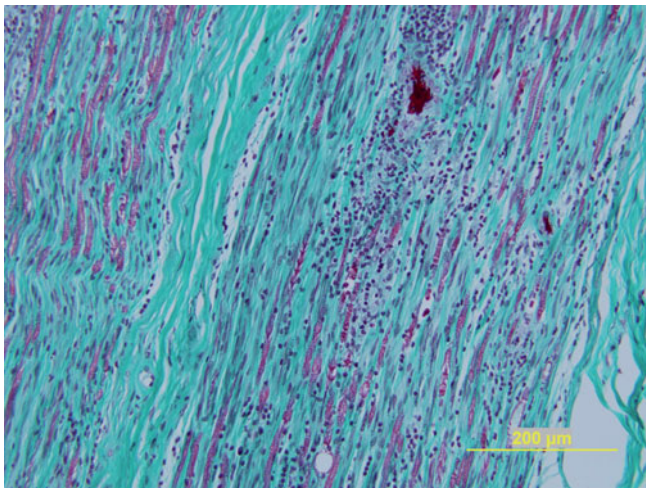
As previously noted, various electrophysiologic criteria have been proposed for the diagnosis of CIDP (Tables 12–2 and 12–3). Investigators from Paris proposed other electrophysiologic criteria, which they believe captured 90% of the patients with CIDP.[74] Adding dispersion of the distal CMAP to standard electrophysiologic parameters increases the sensitivity of existing criteria.[54] Bromberg compared the electrophysiologic criteria proposed by Albers and Kelly,[76] Barohn et al.,[1] and the AAN[13] and found no statistically significant difference in the sensitivity (range 48–64%) in 70 of their patients who fulfilled clinical criteria for CIDP.[77] A smaller study comparing diagnostic sensitivity in 15 patients with CIDP reported that the patients fulfilled criteria as follows: AAN criteria 40%, Saperstein et al. criteria 47%, Nicolas et al. 53% (Paris group)INCAT 60%, and Thaisetthawtkul et al. 70% (Rochester group).[94] At this time, the INCAT criteria probably have the best track record for use in clinical research studies. Regardless of which "research" criteria are used, many patients with CIDP do not fulfill electrophysiologic criteria for the diagnosis; this should not dissuade the clinician from treating these patients if the clinical features (progressive, symmetric proximal, and distal numbness and weakness) and laboratory features (e.g., increased CSF protein) are compatible with the diagnosis.

HISTOPATHOLOGY

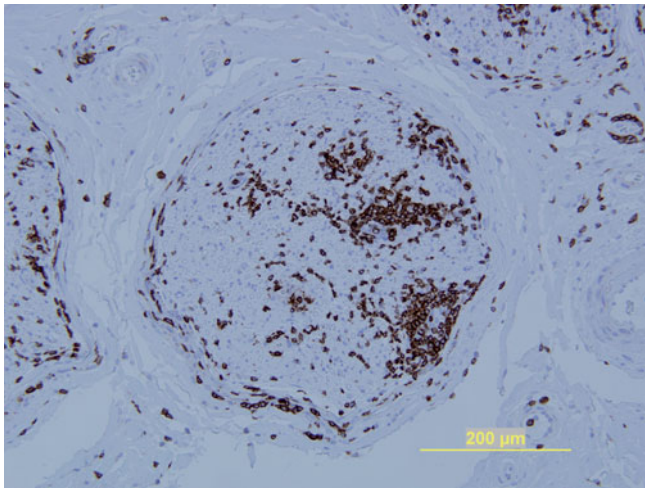
Nerve biopsies may reveal segmental demyelination and remyelination but due to the multifocal process these are not always evident (Fig. 12).[1,21,43,95–97] Chronic demyelination and remyelination result in proliferation of surrounding Schwann cell processes forming the so-called "onion bulbs (see Chapter 3, Fig. 3-26)." However, these onion bulbs are not as prominent as those observed in Charcot–Marie–Tooth disease. Schwann cell proliferation can lead to a hypertrophic appearance of the nerve. The number of myelinated fibers is usually reduced. Teased nerve fibers analysis demonstrates segmental demyelination and/or remyelination in 23–46%, axonal degeneration in 21–42%, mixed demyelinating and axonal features in 12.5%, and normal findings in 18–43.5% of teased nerve fibers.[1,21]

Endoneurial and perineurial edema may also be appreciated on biopsy. Inflammatory cell infiltrate may be evident in the epineurium, perineurium, or endoneurium and was usually perivascular but is often quite subtle or absent on sural nerve biopsies (Fig. 12–2A).[1,21] Inflammatory cells are better appreciated with immunostaining for lymphocytes (Fig. 12–2B).[98,99] The inflammatory component comprises of macrophages, CD3+-activated T cells (mainly CD8+ but also CD4+ cells lymphocytes), and dendritic cells.[99] Of note, a similar frequency of inflammatory cell infiltrate within nerves is seen in a variety of neuropathies, raising concern regarding the pathogenic role of these cells.[98] The matrix metalloproteinases MMP-2 and MMP-9 (gelatinase A and B) are overexpressed in the peripheral nerves in patients with CIDP.[100] These enzymes that are secreted by T cells are capable of digesting basement membrane proteins, thereby facilitating the infiltration of inflammatory cells into peripheral nerves.

Nerve biopsy is not essential for the diagnosis of CIDP; however, if there remains a question of the diagnosis, nerve biopsy remains a useful diagnostic tool.[97,101] Biopsies are particularly useful when lymphomatous infiltration, amyloidosis, or sarcoidosis are considered, as these disorders can mimic CIDP.



A



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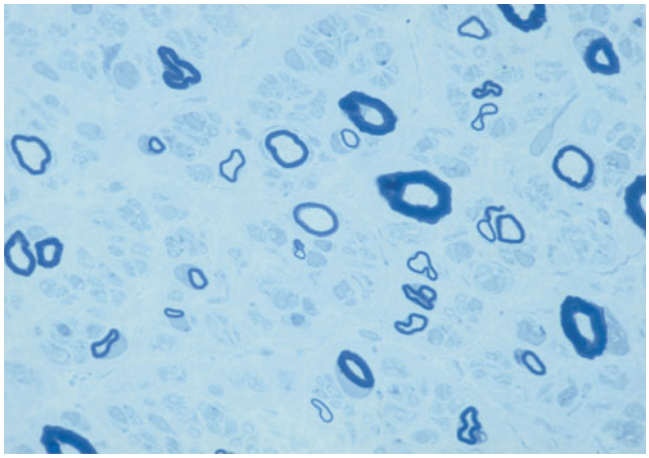

C

Figure 12–2. CIDP. Nerve biopsy reveals endoneurial inflammatory cell infiltration (A, paraffin section, modified Gomori-trichrome). Immunostaining demonstrates that many of these cells are CD3-positive T cells (B). Semithin sections reveal scattered thinly myelinated nerve fibers (C).

On electron microscopy (EM), macrophages may be appreciated penetrating the basement membrane and displacing of the Schwann cell cytoplasm, lysing the superficial myelin lamellae, penetrating along intraperiod lines, and engulfing the disrupted myelin by endocytosis. Subsequently, Schwann cells are recruited to remyelinate the demyelinated internodes. The demyelinated axons diminish in diameter as much as 50% but latter regain some of their diameter following remyelination. The proliferation of Schwann cell processes and basement membrane following relapses of demyelination and remyelination can lead to onion-bulb formations seen on biopsy (see Chapter 3, Fig. 3-26).

PATHOGENESIS

CIDP is an autoimmune disorder, but the antigen(s) to which the immune attack is targeted and specific roles of the humoral and cellular system played in the pathogenesis of CIDP are not known (Fig. 12–3). Failure of regulatory T-cell mechanism is thought to underlie persistent or recurrent disease, differentiating CIDP from the acute inflammatory demyelinating polyneuropathy form of GBS.[8,9] The sometimes rapid improvement following plasma exchange (PE) or intravenous immunoglobulin (IVIG) and the demonstration of immunoglobulin and complement on peripheral nerve tissues suggest a role of the humoral arm of the immune system.[22,102] Perhaps, some antibodies are directed against neuronal elements (e.g., ion channels), resulting in conduction block and subsequent demyelination.

Physiologically, paranodal and internodal demyelinations impair the propagation of the action potential down the nerve.[103] Demyelination of a nerve segment produces an increased transverse capacitance and reduced resistance in the area. This causes a leakage of current and increases the time required for the longitudinal current to reach the next node of Ranvier. If the current leakage is too excessive, there may not be enough current to depolarize the next node of Ranvier, which is necessary to continue propagating the action potential. It is this block of conduction, not just the slowing of velocity, which is responsible for motor weakness.

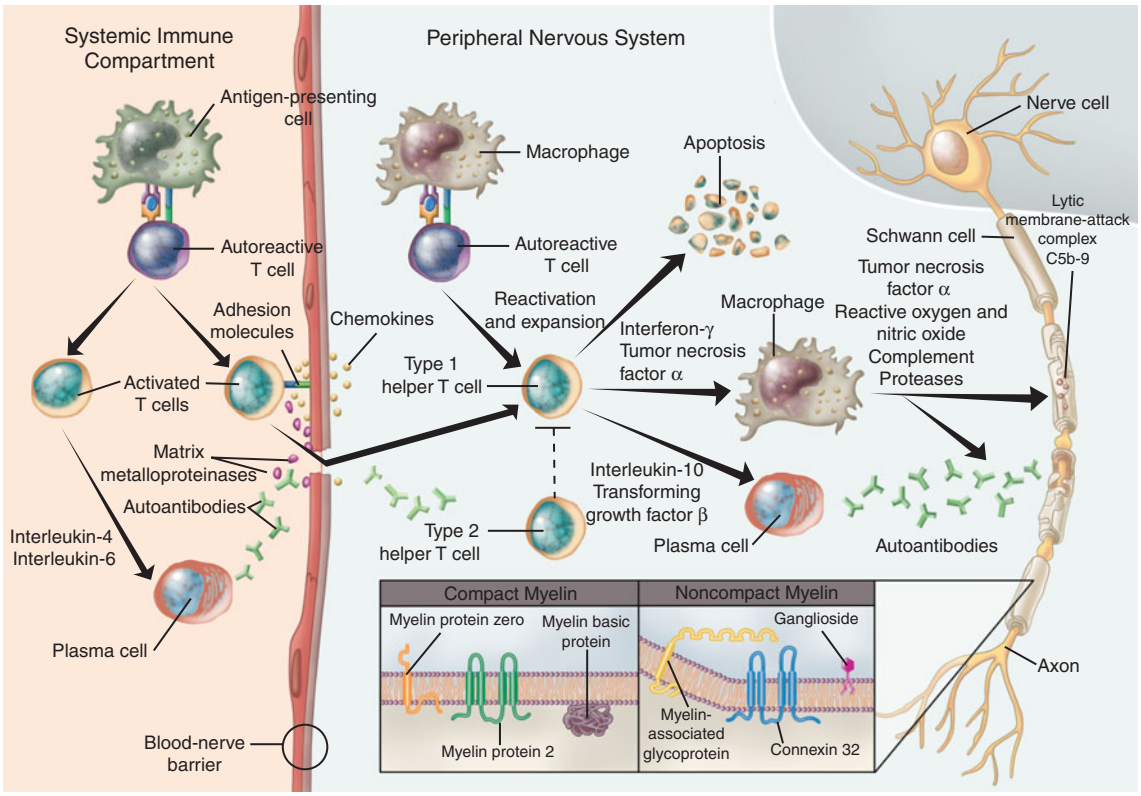

Figure 12–3. Immunopathogenesis of chronic inflammatory demyelinating neuropathy. A schematic illustration of the basic principles of the cellular and humoral immune responses shows that autoreactive T cells recognize a specific autoantigen in the context of major histocompatibility complex class II and costimulatory molecules on the surface of antigen-presenting cells (macrophages) in the systemic immune compartment. An infection might trigger this event through molecular mimicry, a cross-reaction toward epitopes shared between the microbial agent and nerve antigens. These activated T lymphocytes can cross the blood–nerve barrier in a process involving cellular adhesion molecules, matrix metalloproteinases, and chemokines. Within the peripheral nervous system, T cells activate macrophages that enhance phagocytic activity, the production of cytokines, and the release of toxic mediators, including nitric oxide, reactive oxygen intermediates, matrix metalloproteinases, and proinflammatory cytokines including tumor necrosis factor (alpha) and interferon-(gamma). Autoantibodies crossing the blood–nerve barrier or locally produced by plasma cells contribute to demyelination and axonal damage. Autoantibodies can mediate demyelination by antibody-dependent cellular cytotoxicity, potentially block epitopes that are functionally relevant for nerve conduction, and activate the complement system by the classic pathway, yielding proinflammatory mediators and the lytic membrane-attack complex C5b-9. Termination of the inflammatory response occurs through the induction of T-cell apoptosis and the release of anti-inflammatory cytokines, including interleukin-10 and transforming growth factor (beta). The myelin sheath (inset) is composed of various proteins, such as myelin protein zero, which account for more than 50% of the total membrane protein in human peripheral nervous system myelin, myelin protein 2, myelin basic protein, myelin-associated glycoprotein, connexin 32, and gangliosides and related glycolipids. These molecules have been identified as target antigens for antibody responses with varying frequencies in patients with this disease. (With permission from Koller. N Engl J Med 2005;352(13): 1343–1356, Fig. 3, p. 1350.)

TREATMENT

Corticosteroids, PE, and IVIG have been demonstrated to be beneficial in randomized control trials in patients with CIDP (Table 12–5).[14] No significant difference in efficacy between IVIG and PE was seen in one prospective trial.[87] A clinical trial of IVIG vs. prednisolone for 6 weeks demonstrated no significant difference between these two treatments in the short term.[14] However, some patients may respond to one therapy when they were refractory to another form of treatment. IVIG has become the treatment of choice because of the fewer

TABLE 12–5. IMMUNOMODULATING THERAPY FOR CHRONIC ACQUIRED DEMYELINATING POLYNEUROPATHIES

Therapy	Neuropathy Used for	Route	Dose	Side Effects	Monitor
Prednisone	CIDP and MADSAM	p.o.	100 mg/d for 2–4 weeks, then 100 mg every other day; single a.m. dose	Hypertension, fluid and weight gain, hyperglycemia, hypokalemia, cataracts, glaucoma, gastric irritation, and osteoporosis	Weight, blood pressure, serum glucose/potassium, and ophthalmologic examination
Methylprednisone	CIDP and MADSAM	i.v.	1 g in 100 mL/normal saline over 1–2 h, three to six doses, daily or every other day	Arrhythmia, flushing, dysgeusia, anxiety, insomnia, fluid and weight gain, hyperglycemia, and hypokalemia	Heart rate, blood pressure, and serum glucose/potassium
Azathioprine	CIDP, ? MADSAM	p.o.	2–3 mg/kg/d; single a.m. dose	Flu-like illness, hepatotoxicity, leukopenia, macrocytosis, and neoplasia	Monthly blood count and liver enzymes
Cyclophosphamide	CIDP, MMN, ? MADSAM	p.o.	1.5–2 mg/kg/d; single a.m. dose	Leukopenia, hemorrhagic cystitis, alopecia, infections, and neoplasia	Monthly blood count and urinalysis
		i.v.	0.5–3 g/m^2 (max 85 mg/kg)	Same as p.o. (although more severe) and nausea/vomiting	Daily to weekly blood count and urinalysis
Cyclosporine	CIDP, ? MADSAM	p.o.	3–6 mg/kg/d; b.i.d.	Nephrotoxicity, hypertension, hepatotoxicity, hirsutism, tremor, and gum hyperplasia	Blood pressure, weekly or monthly cyclosporine level, creatinine/BUN, and liver enzymes
Rituximab	MMN, ? DADS	i.v.	375 mg/m^2 weekly $\times$ 4 weeks or 750 mg/ m^2 (up to 1 g) $\times$ 2 weeks; usually the course will need to be repeated in 6 to 12 months	Infusion-related symptom complex (e.g. hypotension, rash, chills, urticaria, angioedema, and bronchospasm), asthenia, headaches, nausea vomiting, dizziness, and infection	Periodic blood counts Avoid live vaccines
Intravenous immunoglobulin (IVIG)	CIDP, MMN, and MADSAM	i.v.	0.4 g/kg/d over 5 days, or 1 g/kg/d over 2 days; then 0.4 g/kg single doses every 4–8 weeks as needed	Hypotension, arrhythmia, diaphoresis, flushing, nephrotoxicity, headache, aseptic meningitis, and anaphylaxis	Heart rate, blood pressure, and creatinine/BUN
Plasmapheresis	CIDP, ? MADSAM	i.v.	Remove total of 200–250 cc/kg plasma over 7–14 days; may require periodic exchanges	Hypotension, arrhythmia, electrolyte imbalance, anemia, and coagulation disorders	Heart rate, blood pressure, blood count, electrolytes, PT/PTT, and volume removed and replaced

p.o., oral; i.v., intravenous; CIDP, chronic inflammatory demyelinating polyneuropathy; MMN, multifocal motor neuropathy; MADSAM, multifocal acquired demyelinating sensory and motor neuropathy; PT, prothrombin time; PTT, partial thromboplastin time; BUN, blood urea nitrogen.

long-term side effects than seen with corticosteroids. In our experience, more than 90% of patients improve with therapy; however, at least 50% demonstrate a subsequent relapse within the next 4 years and less than 30% achieve remission off medication.[1] Of importance, patients treated early are more likely to respond, underscoring the need for early diagnosis and treatment.

CORTICOSTEROIDS

Anecdotal cases and small series have long shown that corticosteroids can be beneficial,[1,5,22,26,78,81] and these observations were supported in a randomized control trial of oral prednisone in patients with CIDP.[23] Intermittent high-dose intravenous corticosteroids may be useful in CIDP and perhaps associated with fewer side effects.[104,105] When we treat CIDP with corticosteroids, prednisone is initiated at a dose of 1.5 mg/kg (up to 100 mg) per day for 2–4 weeks, then we switch to alternate day treatment (e.g., 100 mg qod).[1,4] Patients remain on this dose of prednisone until their strength is normalized or there is a clear plateau in clinical improvement, which usually takes 4–6 months. Subsequently, we slowly taper the prednisone by 5 mg every 2–3 weeks until they are on 20 mg every other day. At that point, the prednisone reduced no faster than 2.5 mg every week. Using this method of treatment, the time of initial improvement ranges from several days to 5 months (mean 1.9 months) and the time to maximum improvement averaged 6.6 months, and significant improvement in strength and function is appreciated in 95% of patients after 1 year of treatment.[1]

Side effects of corticosteroid treatment include osteoporosis, glucose intolerance, hypertension, cataract formation, aseptic necrosis of the hip, weight gain, hypokalemia, and type 2 muscle fiber atrophy. We prescribe calcium 1000–1500 mg/d and vitamin D 400–800 IU/d for osteoporosis prophylaxis. In addition, in postmenopausal women, we recommend a bisphosphonate for prophylaxis and treatment of osteoporosis. We obtain baseline bone density studies and repeat the study at least yearly while patients are under prednisone treatment. If a male or premenopausal female patient has or develops osteoporosis, we also start a bisphosphonate. Baseline and periodic fasting blood glucose and serum electrolytes are monitored when patients are initially started on prednisone to look for evidence of glucose intolerance and hypokalemia. Patients are instructed on a low-sodium, low-carbohydrate diet to avoid excessive weight gain, hypertension, and diabetes mellitus. Physical therapy and an exercise program are beneficial as well in reducing these side effects.

PLASMA EXCHANGE

PE is not used as much for treatment of CIDP since IVIG was demonstrated to be beneficial. Yet it still is an effective therapy in patients who are refractory or have contraindications to IVIG and/or corticosteroids. Efficacy of PE was demonstrated in prospective, randomized, double-blinded, placebo-controlled trials using sham PE.[86,89] However, the response to PE is transient, usually lasting only a few weeks, and therefore repeated courses of PE must be given intermittently or the addition of immunosuppressive agents is required. We have used PE, approximately 200–250 mL/kg body weight over five to six exchanges over a 2-week period, usually in combination with prednisone, in patients with severe generalized weakness, because the response to PE may be quicker than that of using prednisone alone. Maintenance exchanges are necessary if the patients are not started on another immunosuppressive or immunomodulating agent. Patients may require PE every 1–2 weeks, and the duration between exchanges gradually increased. We use PE alone in patients whom we wish to avoid long-term prednisone (e.g., patients with poorly controlled diabetes mellitus or HIV infection) or in whom IVIG is contraindicated (e.g., patients with renal insufficiency and severe atherosclerotic cardiovascular disease). A trial of PE may be useful in patients who we are not sure have CIDP because of an underlying condition making the diagnosis difficult (e.g., patients with diabetes and superimposed neuropathy with demyelinating features).[56] Because the response to PE is generally faster than the response to prednisone, one can often determine earlier whether or not such patients could have an immune-responsive neuropathy.

INTRAVENOUS IMMUNOGLOBULIN

IVIG has been demonstrated to be effective in treatment of CIDP in controlled clinical trials.[90,106–108] Further, an observer-blinded, prospective, randomized trial found no clear difference in efficacy between IVIG and PE.[87] The INCAT group demonstrated essentially no significant difference in the short term between IVIG and prednisolone for 6 weeks.[14] The predominant mechanisms by which IVIG exerts its action on these neuropathies appear to be a combined effect on complement inactivation, neutralization of idiotypic antibodies, cytokine inhibition, and saturation of Fc receptors on endoneurial macrophages.[109]

IVIG is now considered the treatment of choice in CIDP by most experts. However, because the effect is transient, repeat courses of IVIG are necessary. The treatment regimen needs to be individualized. We initiate

IVIG at a dose of 2 g/kg body weight over 2–5 days monthly for at least 3 months. Subsequent dosing is dependent on clinical response. We then try to spread the interval between courses or reduce the dosage of each course (e.g., down to 1 g/qd) as tolerated. Some patients need more frequent dosing (i.e., every 2 weeks), while others can go a couple of months between infusions. IVIG maintenance treatment can have a beneficial long-term effect on muscle strength and disability but may not prevent a slight decrease in muscle strength.[110] Follow-up electrophysiological findings imply that IVIG treatment may favorably influence the mechanisms of remyelination or reinnervation but that axon loss cannot necessarily be prevented.[110] In patients who become refractory to IVIG, courses of PE may restore responsiveness to IVIG.[111]

IVIG is generally well tolerated. It is important to ascertain if patients are IgA deficient prior to treatment with IVIG, as these individuals may have IgE anti-IgA antibodies or a congenital deficiency. The patients may develop anaphylaxis to IVIG preparations that contain some IgA.[112] In addition, IVIG must be used cautiously in patients with diabetes and avoided in those with renal insufficiency because it can lead to acute tubular necrosis and renal failure in such cases.[113] The most common adverse effects are headaches, diffuse myalgias, and flu-like symptoms. A few patients actually have aseptic meningitis. Rarely thrombotic events occur (e.g., stroke and myocardial infarction), perhaps related to hyperviscosity. In addition, neutropenia is common, but this is rarely clinically significant.

▶ OTHER TREATMENT OPTIONS

AZATHIOPRINE

Small anecdotal reports suggest a beneficial effect of azathioprine at doses of 100–300 mg/d in CIDP.[114–117] A prospective, randomized, but nonblinded 9-month study of 27 patients with CIDP failed to demonstrate a benefit of azathioprine (2 mg/kg/d) when added to prednisone.[118] However, the dose of azathioprine may have been too small (we go up to 3 mg/kg/d) and the duration of this study too short to see a beneficial effect. It can sometimes take longer than 9 months before any benefit is noted from azathioprine in other immunological disorders.

We do not initiate treatment with azathioprine alone but will add it in patients who have been resistant to prednisone taper in combination with IVIG to spread out the dosing interval. We begin azathioprine at a dose of 50 mg/d and gradually increase over a couple months to a total dose of 3 mg/kg/d. Approximately 12% of patients receiving azathioprine develop fever, abdominal pain, nausea, and vomiting, requiring discontinuation of the drug.[119] Other side effects include bone marrow suppression, hepatotoxicity, risks of infection, and future malignancy. We monitor CBC and LFTs monthly while adjusting the dose and then periodically thereafter.

CYCLOSPORINE

Cyclosporine may also be effective in some patients with CIDP, even in those refractory to other modes of therapy, including prednisone, PE, IVIG, and cyclophosphamide.[72,120–122] The major side effects of cyclosporine include nephrotoxicity, hypertension, tremor, gingival hyperplasia, hirsuitism, and increased risk of infection and future malignancies—mainly skin cancer and lymphoma. We administer cyclosporine at a dose of 4–6 mg/kg orally per day, initially aiming for a trough level between 150 and 200 mg/dL. Electrolytes and renal function need to be monitored closely.

METHOTREXATE

Recently, a small study reported improvement for seven of 10 patients, with otherwise treatment-resistant CIDP, in the following treatment with methotrexate.[123] Methotrexate can be given orally, starting at a dose of 7.5 mg per week and increased as tolerated to 20 mg weekly. Higher doses require parenteral administration. CBC and LFTs need to be monitored closely. We start patients on folate to help avoid anemia.

CYCLOPHOSPHAMIDE

A few anecdotal reports and small series suggest that both oral or monthly pulses of intravenous cyclophosphamide can be beneficial in patients with CIDP.[3,5,124–127] We use cyclophosphamide as a last resort because of its major side effects, which include hemorrhagic cystitis, bone marrow suppression, increased risk of infection and future malignancy, teratogenicity, alopecia, nausea, and vomiting. Monthly pulsed intravenous cyclophosphamide is associated with less risks of hemorrhagic cystitis. It is important to frequently monitor CBCs and urinalysis in patients treated with cyclophosphamide.

ALPHA-INTERFERONS

There are a few reports of patients with CIDP benefiting from α-interferon.[128,129] However, a double-blind, placebo-controlled, cross-over study of interferon

β-1a in 10 patients with CIDP failed to demonstrate any benefit.[130]

MYCOPHENOLATE MOFETIL

Mycophenolate mofetil is an immunomodulating agent that selectively inhibits the proliferation of T and B lymphocytes by blocking the rate-limiting enzyme in the de novo synthesis of guanosine nucleotides. A few small studies have suggested that mycophenolate mofetil may benefit patients with CIDP.[131,132] Other reports have been less favorable.[133] In our experience, mycophenolate mofetil is generally ineffective, but modest benefit is obtained in approximately 20% of CIDP patients by stabilizing their condition and allowing reduction of steroid or IVIG therapy.[134]

TOTAL LYMPHOID IRRADIATION

Total lymphoid irradiation was reported to be effective in three of four patients unresponsive to prednisone or cyclophosphamide.[135]

CIDP IN CHILDREN

CIDP can begin in childhood and the clinical, laboratory, and electrophysiological features are similar to those affected in adulthood.[39,78,128,129,136–146] As with adult-onset CIDP, these improve with standard forms of treatment, although prospective control trials of childhood CIDP range have not been performed.

DADS NEUROPATHY

We feel that it is helpful to classify patients with acquired demyelinating polyneuropathies, particularly patients with a monoclonal gammopathy of undetermined significance, by their pattern of weakness (i.e., whether the patients have no weakness/only mild distal weakness or if they demonstrate both proximal and distal weakness). In a study of 53 consecutive patients with an acquired demyelinating neuropathy, 23 patients had proximal and distal arm and leg weakness, which we define as necessary criteria for the diagnosis of CIDP.[27] Only four patients with CIDP (22%) had a monoclonal gammopathy (mainly IgG). The remaining, 30 patients had only distal symptoms (eight pure sensory loss and 12 distal sensory loss plus ankle dorsiflexor and foot intrinsic weakness). The term "DADS neuropathy" was applied to these later patients (Table 12–1). Monoclonal proteins were detected in 20 of 30 cases of DADS neuropathy (18 IgM and two IgG). MAG antibodies were found in 67% of patients with IgM-DADS neuropathy. The patients with IgM-DADS neuropathy were older (mean age 62 years) than patients with idiopathic-DADS neuropathy (no associated monoclonal protein) or CIDP (defined clinically by symmetric proximal and distal weakness). No significant electrophysiological differences between IgM-DADS, idiopathic-DADS, and CIDP patients were appreciated. Most importantly, in regards to treatment, patients with IgM-DADS neuropathy demonstrated a poor response to immunotherapy, while patients with idiopathic DADS and CIDP (with or without an associated monoclonal protein) usually improved with therapy. Others have had similar experience that classification by presence or absence of proximal weakness separates patients with chronic acquired symmetric demyelinating polyneuropathy into groups (CIDP vs. MADSAM) that are different in clinical course, disability, and treatment response.[147] Yet in other series, patients with DADS responded just as favorably to treatment as patients with proximal and distal weakness.[10]

▶ MULTIFOCAL MOTOR NEUROPATHY

CLINICAL FEATURES

MMN is an immune-mediated demyelinating neuropathy characterized clinically by asymmetrical weakness and atrophy, typically in the distribution of individual peripheral nerves (Table 12–1).[63,110,148–162] Not uncommonly MMN is misdiagnosed as amyotrophic lateral sclerosis (ALS). However, in MMN the weakness is in the distribution of individual peripheral nerves in MMN as opposed to ALS, in which weakness is in distribution of myotomes. The incidence of MMN is much less than that of ALS.[149] There is a male predominance with a male-to-female ratio of approximately 3:1, with an age of onset of symptoms usually ranging from the second to the eighth decade of life (most occur in the fifth decade of life). Rarely, childhood onsets are encountered.[163] Focal muscle weakness accompanied by cramps and fasciculations usually is first noted in the distal arms. However, weakness can develop initially in the legs. Most patients present with intrinsic hand weakness, wrist drop, or foot drop. The onset is usually insidious, and the weakness typically progresses over the course of several years to involve other limbs. As with CIDP, MMN can complicate treatment with tumor necrosis factor alpha blockers, probably through modulation of the immune system.[164,165]

On clinical examination, weakness is apparent in the distribution of peripheral nerves (mononeuropathy multiplex pattern) as opposed to myotomal distribution

of weakness seen in motor neuron disease. Early in the course there is no noticeable atrophy in weak muscles and occasionally the affected muscle groups are hypertrophied. The hypertrophy may result from frequent myokymia of the involved muscle. Over time atrophy can develop. Rarely, MMN can affect cranial nerves.[166,167] Although some patients may describe mild sensory symptoms, objective sensory loss should lead to the consideration of MADSAM neuropathy.

Muscle stretch reflexes are highly variable in that unaffected muscles can be normal, whereas weak and atrophic muscles are usually associated with depressed or absent reflexes. Unequivocal corticospinal tract signs (i.e., clonus, spasticity, and extensor plantar responses) are not seen.

As inherent in its name, MMN implies involvement of two or more motor nerves. However, MMN usually starts as a mononeuropathy. Such cases of monofocal motor neuropathy may represent the early presentation of MMN and should be treated as such.[168]

LABORATORY FEATURES

CSF protein is usually normal in patients with MMN, which can help differentiate the neuropathy from CIDP and MADSAM. Anywhere from 22 to 84% of patients with MMN have IgM serum antibodies directed against gangliosides, mainly GM_1 but also asialo-GM_1 and GM_2; however, the importance of these antibodies in terms of pathogenesis is still not clear.[158,159,169–173] The characteristic electrophysiological hallmark of MMN is persistent conduction block in motor nerves in segments not usually associated with compression or entrapment.[148,153,155–161,174,175] There are no universally accepted criteria for defining definitive conduction block,[176] although consensus criteria by some experts in the field have been published, depending on the specific nerve and site.[161] A reduction in the distal CMAP amplitude can be seen in chronic lesions due to secondary axonal loss.

Although motor conduction block has been considered the electrodiagnostic hallmark of MMN, other features of demyelination (i.e., prolonged distal latencies, temporal dispersion, slow CVs, and prolonged or absent F waves) are typically present on motor NCS.[151,154,177–179] We feel that conduction block need not be present for the diagnosis, if other features of demyelination are present.[154,178,180,181] Importantly, there should be no sensory conduction abnormalities including across the region where conduction block can be demonstrated in motor fibers. Electrophysiological evidence of demyelination is found more often in the nerves of the arms and is distributed randomly over lower arm, upper arm, and shoulder segments.[154,182] Approximately one-third of electrophysiological abnormalities are found in nerves innervating non-weakened muscles.[182]

Needle EMG demonstrates decreased recruitment in weak muscles.[148,154,166,171] Fibrillation potentials and positive sharp waves can be seen in long-standing neuropathy due to secondary axonal loss. Fasciculation potentials, complex repetitive discharges, and myokymic discharges occasionally are observed.

HISTOPATHOLOGY

Sensory nerve biopsies in MMN are usually normal, although slight reduction of myelinated fibers or axonal degeneration has been appreciated.[155,156,159,183,184] Mild perivascular inflammation may also be seen.[63,185]

PATHOGENESIS

Although initially considered to be a variant of CIDP, most authorities now regard MMN as a distinct neuropathy (Table 12–3).[151,156,157,171,175,186–189] Because sensory nerves are spared, the autoimmune attack is likely directed against an antigen relatively specific for the motor nerve. Although ganglioside antibodies are common, the pathogenic role for these antibodies is not known. Reduction of antibody titers has correlated with clinical improvement following immunotherapy in some patients[158,159] but not in others.[152,190] Further, there has been no association between the presence or absence of ganglioside antibodies and response to immunotherapy in some series.[154,173,183,191] Sera from patients with MMN injected into rat sciatic or tibial nerves in vivo and in vitro was shown to induce conduction block in some studies,[182,192–194] but this has not been demonstrated in other studies.[195] Not all patients with MMN have detectable ganglioside antibodies, so, at best, these antibodies can now only be considered a marker of the disease.[149]

Of note, anti-GM1 sera raised from immunized rabbits cause abnormal sodium and potassium currents in isolated rat myelinated motor nerve fibers.[196] The immune attack may be directed against an ion channel or at least affects the ion channel leading to conduction block. The prolonged attack subsequently may cause demyelination.

TREATMENT

Unlike CIDP and MADSAM, patients with MMN generally do not respond to corticosteroids or PE (Table 12–5).[63,153,155,156,159,166,190,197–199] Fortunately, the MMN is typically responsive to IVIG as demonstrated in small

case reports [152,154,166,181,191,200–202] and a double-blinded, placebo-controlled trial.[203] We initiate treatment with IVIG 2 g/kg over 2–5 days with subsequent maintenance courses as necessary. Improvement is usually noted within a few days or first few weeks of treatment. Most patients need repeated infusions every 2–4 weeks. Not everyone with MMN responds to IVIG, particularly those with long-standing disease prior to starting treatment and a later age of onset and patients who have significant muscle atrophy.[183,191] We give three monthly courses of IVIG before concluding that a patient has failed treatment.

Rituximab has recently been used to treat immune-mediated neuropathies including MMN.[87,171,204,205] Rituximab is a monoclonal antibody that binds to the CD20 antigen on normal and malignant B lymphocytes, destroying these cells. It is approved to treat B-cell lymphoma and reduces peripheral B-lymphocyte counts by 90% within 3 days. Rituximab can be given at 375 mg/m^2 weekly for 1 month or 750 mg/m^2 (up to 1.0 gram) and repeated after one or two weeks. Further, patients periodic maintenance courses.[206] However, not all patients improve and some continue to decline with rituximab.[205] Randomized control trials are necessary to confirm the efficacy of rituximab.

Intravenous cyclophosphamide was the first therapy noted to be useful in MMN, although no double-blinded, placebo-controlled trials have been performed.[153,155,156,159,171,173] An initial dosage of intravenous cyclophosphamide has been as high as 3 g/m^2 given over an 8-day period with subsequent reduction for maintenance. However, this high dose of intravenous cyclophosphamide (3 g/m^2) is associated with alopecia, nausea and vomiting, hemorrhagic cystitis, and significant bone marrow suppression. We reserve cyclophosphamide for patients who fail IVIG and rituximab. Sometimes cyclophosphamide given in combination with IVIG may prolong the interval between IVIG infusions.[207] When given, we start off with intravenous pulse of cyclophosphamide to 0.5 g/m^2 in order to avoid severe side effects and gradually increase to 0.75 g/m^2 if tolerated and then to 1 g/m^2. We also treat patients with Mesna and keep them well hydrated in order to avoid hemorrhagic cystitis. Nausea can be managed with ondansetron or granisetron.

▶ MULTIFOCAL MOTOR ACQUIRED MOTOR AXONOPATHY

Rare patients have the clinical phenotype of MMN but have only axonal features on electrodiagnostic studies.[181,208,209] The term "MAMA" has been used to describe these patients.[208] Unlike patients with MMN, most patients with MAMA lack GM1 antibodies. Some individuals with MAMA improve with prednisone or IVIG. It is felt that this rare subgroup of patients is distinct from typical MMN and other established motor neuron disorders (e.g., ALS). The implication is that if a patient has the clinical appearance of MMN with weakness in the distribution of individual nerves rather than myotomes and no upper motor neuron abnormalities, then it is worthwhile treating them with immunomodulating therapy, regardless of the presence or absence of serum GM1 antibodies or NCS demonstrating conduction block or other features of demyelination.

▶ MADSAM (LEWIS–SUMNER SYNDROME)

CLINICAL FEATURES

Lewis and colleagues described the first cases of patients with multifocal demyelinating neuropathy with persistent conduction block.[210] The term MADSAM neuropathy is used to describe such patients to distinguish the neuropathy from MMN.[75] The signs and symptoms in MADSAM neuropathy patients are those of mononeuropathy multiplex (Table 12–1).[6,10,75,211–218] As with MMN, there is a male predominance, an average age of onset is in the early fifties, and it usually initially involves the arms. However, the legs can also be initially involved and often do become affected over time. Motor and sensory symptoms are in the distribution of discrete peripheral nerves. Some patients describe pain and paresthesias. Cranial neuropathies have been reported, including optic neuritis, oculomotor, trigeminal, and facial nerve palsies. Muscle stretch reflexes can be normal or reduced depending on the nerves affected.

LABORATORY FEATURES

CSF protein levels are usually elevated (mean level of around 70 mg/dL) and the serum lacks GM_1 antibodies in contrast to that seen in MMN (Table 12–3).[6,75,211–217] NCS in MADSAM neuropathy demonstrates conduction block, temporal dispersion, prolonged distal latencies, prolonged F waves, and slow CVs in one or more motor nerves.[6,75,211–217] In contrast to MMN, the sensory nerve action potentials are usually absent or small in amplitude in affected segments of involved nerves. EMG reveals decreased recruitment of motor unit action potentials in affected muscles. With long-standing weakness, fibrillation potentials can also be seen in muscles.

HISTOPATHOLOGY

Sensory nerve biopsies demonstrate many thinly myelinated nerve fibers, subperineurial and endoneurial edema, mild onion-bulb formations, and occasional inflammatory cell infiltrates.[6,75,212–217] Inflammatory cells are often perivascular.[6,215] Asymmetric loss of large myelinated nerve fibers between and within fascicles may be appreciated.[75,212,214]

PATHOGENESIS

We feel MADSAM falls into the spectrum of CIDP and likely has a similar pathogenesis.[75,211] MADSAM neuropathy and CIDP are similar with respect to CSF and sensory nerve biopsy findings, as well as in response to corticosteroids but is distinct from MMN (Table 12–3). The cause is unknown.

TREATMENT

Most patients with MADSAM neuropathy improve with IVIG treatment (Table 12–5).[6,75,211–217] Also, in contrast to MMN but similar to CIDP, most patients with MADSAM neuropathy respond to treatment with corticosteroids.[6,75,211,214–217]

▶ CHRONIC IMMUNE SENSORY POLYRADICULOPATHY

CLINICAL FEATURES

This rare entity may represent a restricted form of CIDP.[32,37,219,220] Patients present with an insidious onset of progressive numbness and paresthesia of the extremities and sensory ataxia. Symptoms and signs may be asymmetric. On examination, large-fiber sensory functions are profoundly affected. Muscle stretch reflexes are reduced or absent. In contrast, muscle strength is preserved. The differential diagnosis includes a paraneoplastic sensory neuronopathy/ganglionopathy (e.g., anti-Hu syndrome) or sensory ganglionopathy associated with Sjogren's syndrome.

LABORATORY FEATURES

As in more classic CIDP, CSF protein is usually elevated but cell count in the CSF is normal. Serology is negative for GM1, GD1b, GQ1b, antinuclear, anti-Ro, and anti-La antibodies. Routine motor and sensory NCS are normal as is EMG of the extremities.[32,37,219,220] However, H-reflexes should be abnormal. Further, abnormal somatosensory-evoked potentials are usually evident with prolonged N13 (cervical) or N9–N13 interpeak latencies, reflecting slowing of conduction in the proximal segments of the nerves. MRI may reveal thickening and enhancement of nerve roots (Fig. 12–4).[37,219]

HISTOPATHOLOGY

Biopsies of lumbar sensory rootlets has revealed a decreased density of large myelinating fibers, demyelinated axons, endoneurial edema, and onion-bulb formation (Fig. 12–5).[37]

PATHOGENESIS

This most likely represents a rare variant of CIDP.

TREATMENT

Patients may respond to corticosteroids or IVIG similar to CIDP.

▶ IDIOPATHIC PERINEURITIS

CLINICAL FEATURES

Perineuritis is a nonspecific histological abnormality characterized by inflammation and thickening of the perineurium, which may be found in neuropathies associated with diabetes mellitus, connective tissue diseases, ulcerative colitis, vasculitis (including cryoglobulinemia), lymphoma, and other malignancies.[221–226] However, perineuritis can occur without a systemic disorder.[221,227] The clinical presentation associated is variable.[137,225,227] Some patients develop sensory loss, dysesthesias, hyperpathia, and weakness in the distribution of multiple individual nerves, while others manifest with generalized symmetric motor and sensory loss indistinguishable from AIDP or CIDP. Migrating areas of sensory loss have also been described. The course of the neuropathy can be remitting and relapsing. Hypesthesia and hyperpathia are often appreciated on examination and a positive Tinel's sign may be present over involved nerves. Large-fiber sensory functions are typically less affected than small-fiber modalities. Muscle strength is usually preserved, but cases with generalized weakness, suggestive of GBS or CIDP, have been reported.[196,225]

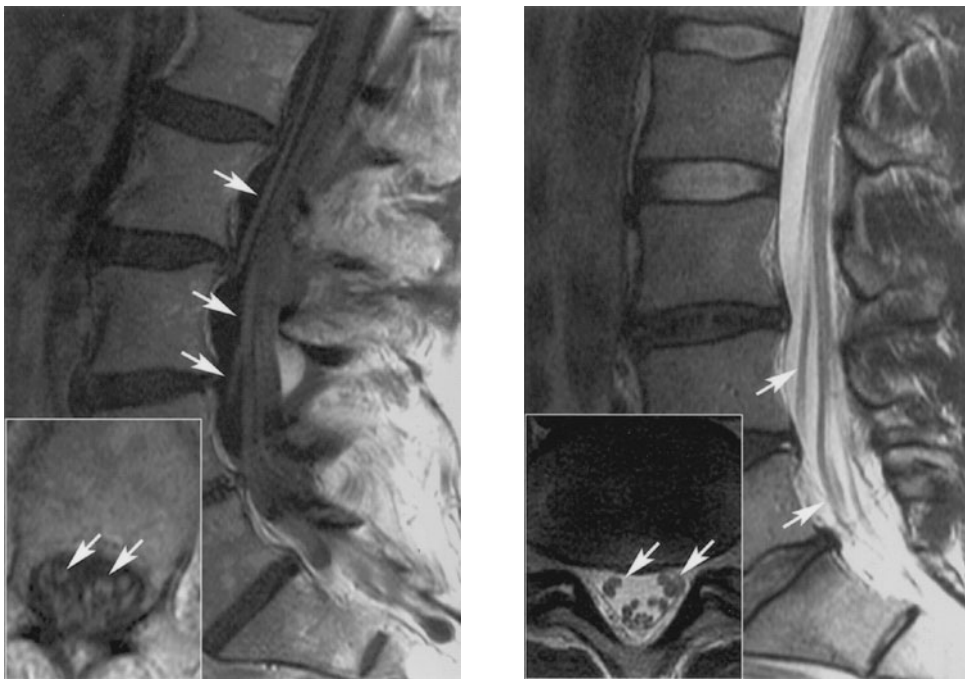

Figure 12–4. Sagittal and transverse (inserts) MR images of the cauda equina from two patients with chronic immune sensory polyradiculopathy (CISP). Both patients had enlarged nerve roots (arrows) and subsequently underwent dorsal root biopsies. The image on the left (T1 postgadolinium image) shows nerve root enhancement, whereas the image on the right (T2 image) shows thickened lumbar nerve roots. (With Permission from Sinnreich M, Klein CJ. Daube JR, Engelstad J, Spinner RJ, Dyck PJB. Chronic immune sensory polyneuropathy. A possibly treatable sensory ataxia. Neurology 2004;63:1662–1669, Fig. 1, p. 1664.)

Muscle stretch reflexes are often normal in patients with pure sensory symptoms.

LABORATORY FEATURES

CSF, ANA, ESR, liver function tests, serum protein electrophoresis, and vasculitic profile are usually normal.[221,227] The presence of an abnormal laboratory workup should lead to the consideration of an underlying systemic disorder such as vasculitis. NCS demonstrated multifocal or generalized reduction in SNAP amplitudes or absent SNAPs.[221,227] Motor NCS and EMG are normal unless patients have mononeuropathy multiplex or radiculoplexopathy with motor and sensory involvement.[224,225]

HISTOPATHOLOGY

Nerve biopsies reveal the prominent thickening and fibrosis of the perineurium along with lymphocytes and macrophages infiltrate.[221,225,227] Mild perivascular inflammation may be evident. There is a loss of myelinated nerve fibers due to axonal degeneration.

PATHOGENESIS

The pathogenic basis for the disorder is unknown but likely autoimmune in nature. Perineuritis may cause its damage via ischemia, impairment of nutrient or toxin flow to and from nerve fibers in the endoneurium, or by direct humoral or cellular autoimmune attack against the nerve fibers.

TREATMENT

Response to immunotherapy is variable and difficult to ascertain because the natural history of the neuropathy may be one of remissions and relapses. We have tried prednisone and IVIG in such idiopathic cases with variable success in patients with mainly sensory disturbances.

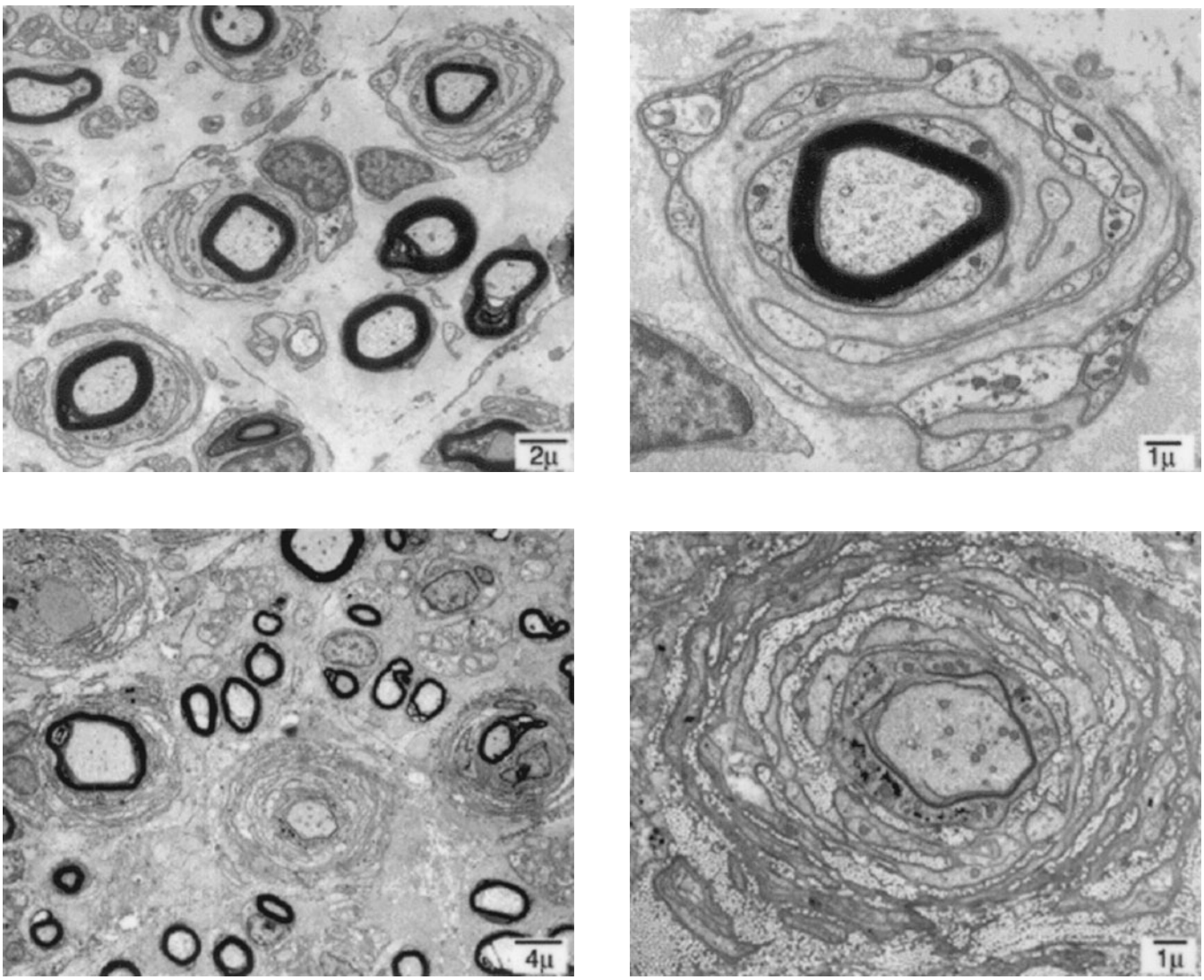

Figure 12–5. Electron micrographs from lumbar dorsal rootlet biopsies of patients with chronic immune sensory polyradiculopathy (CISP) reveal evidence of chronic demyelination and abortive repair. The left column (taken at low power) shows frequent onion-bulb formations associated with thinly myelinated and demyelinated profiles. The right column demonstrates two of these onion bulbs at higher power; the one on the bottom right shows an axon with only a few layers of myelin lamellae. Onion bulbs like these were very common in these two biopsies. (With permission from Sinnreich M, Klein CJ, Daube JR, Engelstad J, Spinner RJ, Dyck PJB. Chronic immune sensory polyneuropathy. A possibly treatable sensory ataxia. Neurology 2004;63:1662–1669, Fig. 6, p. 1667.)

▶ SUMMARY

The chronic inflammatory demyelinating polyneuropathies include CIDP, DADS, MADSAM, MMN, and MAMA. These neuropathies are distinguished on the basis of the clinical, laboratory, and electrodiagnostic features. It is important to recognize these neuropathies and distinguish them from hereditary neuropathies (Charcot–Marie–Tooth disease) in the case of CIDP and from ALS in the case of MADSAM and MMN, because these neuropathies are often responsive to treatment with immunotherapy.

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CHAPTER 13

Vasculitic Neuropathies

Vasculitis is an immune-mediated disorder directed against blood vessels, which results in ischemia to end organs supplied by the affected blood vessels.[1–5] The vasculitides can be classified based on the caliber of vessel involved (i.e., small, medium, or large vessel), whether the vasculitis is primary (e.g., polyarteritis nodosa [PAN] and Churg–Strauss syndrome [CSS]) or secondary to other systemic disorders (e.g., connective tissue disease, malignancy, infection, or drug reaction), and if the vasculitis is systemic or isolated to the peripheral nervous system (PNS) (Table 13–1).[2,3] Vasculitis is much more common in adults but can develop in children.[6]

CLINICAL FEATURES

PNS vasculitis can present as (1) a mononeuropathy or multiple mononeuropathies, (2) overlapping mononeuropathies, or (3) distal symmetric polyneuropathies (Fig. 13–1).[3] In this first pattern, patients may present with just a mononeuropathy but usually multiple nerves eventually become affected, giving a distinct asymmetric pattern of involvement in the distribution of individual nerves. With the second pattern, different nerves on both sides of the body are affected but to varying degrees, leading to a generalized, yet asymmetric, pattern of involvement. Finally, with gradual progression, somewhat uniform and generalized involvement of peripheral nerves results in what looks like a distal symmetric polyneuropathy. Approximately 6–70% of patients present with mononeuropathy or multiple mononeuropathies (mononeuropathy multiplex pattern), while 30–40% of patients present as a distal symmetric polyneuropathy.[7] There is a large differential diagnosis of patients with a mononeuropathy multiplex (Table 13–2).[8] For this reason, multiple mononeuropathies or mononeuropathy multiplex is preferable to mononeuritis multiplex because the latter term implies a histologically defined disorder rather than a clinically defined syndrome. Patients usually complain of burning or tingling pain in the distribution of the affected nerve(s). On examination, weakness and sensory loss are evident as well. Rare patients have purely sensory symptoms and signs.[9] Muscle stretch reflexes may be normal or diminished, depending on whether or not the nerve innervating the muscle is clinically affected.

LABORATORY FINDINGS

Most patients have elevated erythrocyte sedimentation rate (ESR).[2,10] Some vasculitides are associated with antineutrophil cytoplasmic antibodies (ANCAs), antinuclear antibodies (ANAs), cryoglobulins, rheumatoid factor, C-reactive protein, leukocytosis, and anemia. Ultrasound of affected nerves may appear enlarged and hypoechoic.[11]

Motor and sensory nerve conduction studies demonstrate unobtainable potentials or reduced amplitudes.[3,7,8,12–15] In particular, it is important to look for side-to-side asymmetries in amplitudes that reflect the multifocal nature of the pathology. Distal latencies are normal or slightly prolonged, while conduction velocities are normal or only mildly reduced. Conduction block or pseudoconduction block may be demonstrated in some affected nerves.[16–19] The needle electromyography (EMG) reveals denervation changes in affected muscle groups. Again, the EMG abnormalities are often also asymmetric.

HISTOPATHOLOGY

The sural, superficial peroneal (sensory branch), and superficial radial sensory nerves are the most common nerves that are biopsied.[1,4,5,20] We usually biopsy the superficial peroneal nerve if involved and by nerve conduction studies (NCS), because the peroneus brevis muscle can also be biopsied from the same incision site and the diagnostic yield is increased when the nerve and muscle both are biopsied (Fig. 13–2).[5,20] We like to see transmural inflammatory cell infiltration and necrosis of the vessel wall to diagnose vasculitis on histopathological grounds (Fig. 13–3).[1,4,7,14,21–23] Immunocytochemistry may reveal immunoglobulin (IgM and/or IgG), complement, and membrane attack complement deposition on blood vessels. A common finding is asymmetrical nerve fiber loss between and within individual nerve fascicles and axonal degeneration. Nerve biopsies also demonstrate immunostaining for the receptor for advanced glycosylation end products, nuclear factor-kappaB, and interleukin-6 in mononuclear cells, epineurial and endoneurial vessels, and the perineurium.[24] The Receptor for advanced glycosylation end products, nuclear factor-kappaB, and interleukin-6 are expressed by CD4(+), CD8(+), and CD68(+) cells invading the nerves. These data suggest that the receptor

▶ TABLE 13–1. VASCULITIDES ASSOCIATED WITH PERIPHERAL NEUROPATHY

Primary vasculitis
Large vessel vasculitis
Giant cell (temporal) arteritis
Medium and small vessel vasculitis
Polyarteritis nodosa
Churg–Straus syndrome
Wegener granulomatosis
Microscopic polyangiitis
Nonsystemic/isolated peripheral nerve vasculitis
Secondary vasculitis
Vasculitis associated with connective tissue diseases
Vasculitis associated with malignancies
Vasculitis associated with infections
Vasculitis associated with cryoglobulinemia
Vasculitis associated with hypersensitivity reaction (leukocytoclastic angiitis)— uncommonly associated with a peripheral neuropathy

for advanced glycosylation end products pathway plays a critical proinflammatory role in vasculitic neuropathy. Matrix metalloproteinases (e.g., MMP-9) are upregulated as well and may play an important role as means for inflammatory cell invasion.[25] Skin biopsies have also demonstrated reduced epidermal nerve fiber density in some cases of vasculitic neuropathy.[26]

▶ PRIMARY SYSTEMIC VASCULITIC DISORDERS AFFECTING LARGE- AND MEDIUM-SIZED VESSELS

GIANT CELL VASCULITIS

Temporal arteritis and Takayasu arteritis are the two forms of giant cell arteritis, but peripheral neuropathy only occurs in the setting of temporal arteritis.[10,27] Giant cell arteritis affects medium- and large-size vessels, particularly the aortic arch and the internal and external carotid arteries and the vertebral arteries. Patients may present with headaches, jaw and tongue claudication, generalized myalgias, vision loss secondary to ischemic optic neuropathy, or stroke. Approximately 14% of patients develop multiple mononeuropathies, radiculopathies, plexopathies, or a generalized sensorimotor peripheral neuropathy.[10] The temporal artery is often

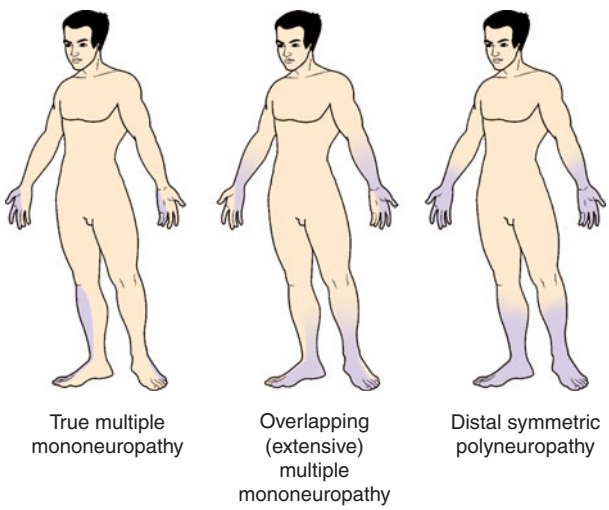


Figure 13–1. Patterns of involvement in vasculitic neuropathy. Vasculitis can present as (1) a mononeuropathy or multiple mononeuropathies, (2) called overlapping mononeuropathies, or (3) distal symmetric polyneuropathies.

▶ TABLE 13–2. MONONEUROPATHY MULTIPLEX: DIFFERENTIAL DIAGNOSIS

Isolated peripheral nerve vasculitis
Polyarteritis nodosa
Wegener's granulomatosis
Churg–Strauss syndrome
Microscopic polyangiitis
Connective tissue disorders associated with vasculitic neuropathies (e.g., SLE, RA, and MCTD)
Nonsystemic vasculitis neuropathy
Remote effect of cancer
Other immune-medicated neuropathies
Multifocal acquired demyelinating sensory and motor neuropathy (MADSAM or asymmetric chronic inflammatory demyelinating polyneuropathy [CIDP])
Multifocal motor neuropathy
Sensory perineuritis
Infectious neuropathies
Leprosy
Herpes zoster
Lyme disease
HIV
CMV
Hepatitis B and C
Compression neuropathy
Primary compression neuropathies (e.g., traumatically induced)
Secondary compression neuropathies (e.g., superimposed on generalized peripheral nerve disease; e.g., diabetes mellitus and carpal/cubital tunnel syndrome)
Hereditary liability to pressure neuropathy
Granulomatous infiltration
Sarcoid
Lymphomatoid granulomatosis
Other disorders
Diabetes mellitus
Amyloidosis
Neoplastic infiltration
Atherosclerotic vascular disease
Drug induced (e.g., amphetamine and sulfonamides)
Lumbosacral plexus neuropathy
Brachial plexus neuropathy

HIV, human immunodeficiency virus; CMV, cytomegalovirus; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; MCTD, mixed connective tissue disease.
Modified with permission from Amato AA, Dumitru D. Acquired neuropathies. In Dumitru D, Amato AA, Swartz MJ (eds). Electrodiagnostic Medicine, 2nd edn. Philadelphia: Hanley & Belfus, 2002, pp. 937–1041, Table 23–7, p. 9640.

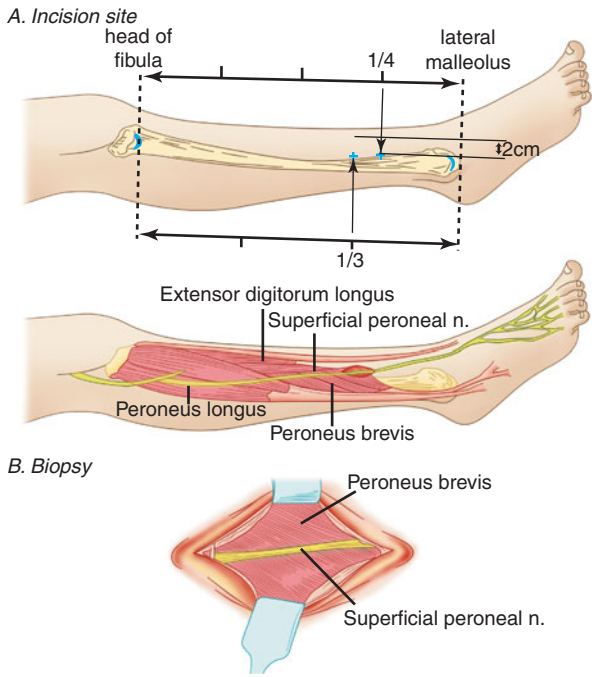


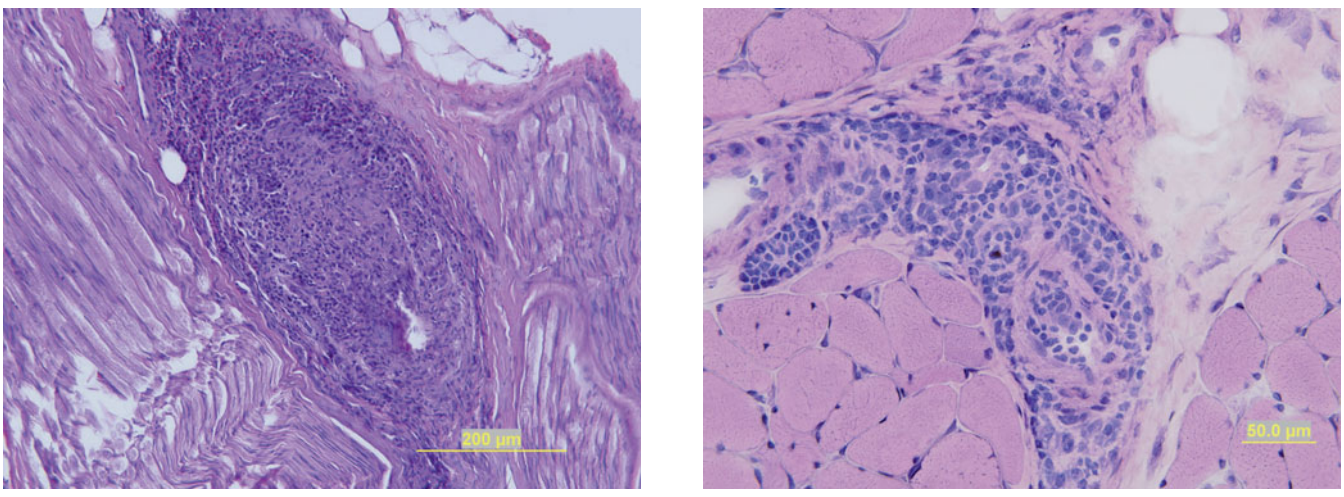
Figure 13–2. Superficial peroneal nerve and peroneus brevis muscle biopsy. The superficial peroneal nerve can usually be biopsied at a site between one-third and one-fourth the distance between the lateral aspect of the ankle and the fibular head and about 1.5–2 cm anterior to the fibula. After the nerve is biopsied, the underlying peroneus brevis muscle can be biopsied. This combination increases the yield of finding vasculitis and can be made through one incision. (Modified with permission from Mendell JR, Erdem S, Agamonolis DR. Peripheral nerve and skin biopsies. In Mendell JR, Kissel JT, Cornblath DR (eds). Diagnosis and Management of Peripheral Nerve Disorders. New York: Oxford University Press, 2001, Fig. 7–2, p. 92.)

tender and a palpable cord can be felt. Ultrasound of the arteries may reveal thickening. Temporal artery biopsies reveal inflammatory infiltrate with giant cell in only two-thirds of suspected cases. Patients generally respond quite well to the treatment with corticosteroids.

▶ PRIMARY SYSTEMIC VASCULITIC DISORDERS AFFECTING MEDIUM- AND SMALL-SIZED VESSELS

POLYARTERITIS NODOSA

PAN, the most common of the necrotizing vasculitides, is a systemic disorder involving small- and medium-caliber arteries in multiple organs.[1,2,4,28] PAN has an incidence ranging from two to nine per million and usually presents between 40 and 60 years of age. The most common pattern of nerve involvement is multiple mononeuropathies. The sciatic nerve or its peroneal or tibial branches are the most frequently involved nerves. Cranial neuropathies and central nervous system (CNS) involvement are rare, occurring in <2% of patients.[2] Other organ systems affected include the liver, kidneys, gastrointestinal and associated complications of liver or renal failure, abdominal pain, and gastrointestinal bleeding. Notably, the lungs are generally spared. Myalgias and arthralgias occur in 30–70% of patients. Vasculitis involving the skin results in petechiae, livido reticularis, subcutaneous nodules, and distal gangrene.[28] Orchitis is also a common complication. Constitutional symptoms include weight loss, fever, and loss of appetite.



A B

Figure 13–3. Vasculitis. Superficial peroneal nerve biopsy demonstrates transmural inflammatory cell infiltrate with near obliteration of the lumen (A). The peroneus brevis muscle biopsy also demonstrates vasculitis (B). Paraffin sections stained with hematoxylin and eosin (H&E).

Elevated ESR is seen in the majority of patients.[2] One-third of cases are associated with hepatitis B antigenemia,[2,28] but PAN can also complicate hepatitis C virus (HCV) and human immunodeficiency virus (HIV) infections.[2,29] Abdominal angiograms can reveal a vasculitic aneurysm, a useful finding in patients with nondiagnostic biopsies.

Median-sized arteries are usually affected; however, smaller-sized vessels can be involved in PAN.[2,4] Nerve biopsies may demonstrate transmural infiltration of CD8+ T cells, macrophages, and polymorphonuclear along with fibrinoid necrosis of the vessel wall. IgM, IgG, complement, and membrane attack complex deposition may be appreciated on blood vessels. Unlike CSS, granulomas and eosinophilic infiltration are not seen on nerve biopsies in PAN. The pathogenic mechanism of PAN is unknown, although a T-cell-dependent, endothelial cell-mediated process is postulated with secondary complement-mediated vascular damage.[4]

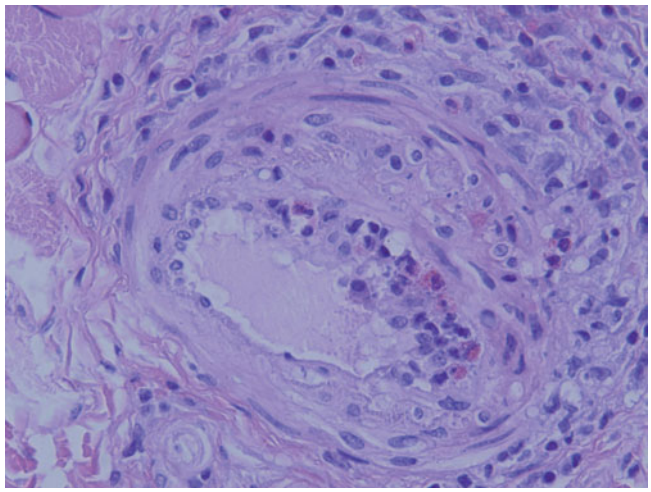


Figure 13–4. Churg–Strauss Syndrome. Nerve biopsy demonstrates transmural infiltration of vessel wall that includes eosinophils and obliteration of the lumen. Paraffin section stained with H&E.

CSS (ALLERGIC ANGIITIS/ GRANULOMATOSIS)

CSS manifests with signs and symptoms similar to PAN except that respiratory involvement is common in CSS.[1,2,30–34] The incidence is of CSS in about one-third that of PAN, but the frequency of neurological complications is about the same. In this regard, multiple mononeuropathies develop in as many as 75% of individuals who are affected.[2] People with CSS typically present with allergic rhinitis, nasal polyposis, sinusitis, and late-onset asthma (after the age of 35 years). Symptoms and signs of systemic vasculitis occur at an average of 3 years after the onset of asthma. Anywhere from 16% to 49% of patients with CSS develop a necrotizing glomerulonephritis as opposed to an ischemic nephropathy that can complicate PAN. Several cases of CSS have been reported in patients treated with leukotriene antagonists after weaning corticosteroids.[35]

Routine laboratory workup reveals eosinophilia, leukocytosis, elevated ESR, C-reactive protein, rheumatoid factor, and serum IgG and IgE levels. One should be suspicious of the diagnosis of CSS in any patient with a neuropathy and peripheral eosinophilia. Approximately two-thirds of individuals who are affected also have positive antineutrophil antibodies (ANCAs), primarily myeloperoxidase or p-ANCA, because of its perinuclear staining pattern.[2] Chest X-rays reveal that pulmonary infiltrates are present in nearly half of the patients.

Nerve biopsies may demonstrate necrotizing vasculitis with CD8+ cytotoxic T lymphocytes, CD4+ cells, and to a lesser extent eosinophilic infiltrates (Fig. 13–4).[2,32,36] In addition, intravascular and extravascular granulomas are occasionally found in and around affected blood vessels.

WEGENER GRANULOMATOSIS

Wegener granulomatosis is characterized by necrotizing vasculitis and granulomas involving the upper and lower respiratory tract and kidneys (glomerulonephritis).[1,4,37–44] Early respiratory symptoms (e.g., nasal discharge, cough, hemoptysis, and dyspnea) can help distinguish this from other vasculitides. In a large prospective study of 128 patients with Wegener's granulomatosis, 64 patients (50%) developed CNS or PNS involvement.[37] Peripheral neuropathy occurred in 56 patients and in nine cases the CNS was involved. Thirty-one patients had a distal symmetrical polyneuropathy, while 25 had multiple mononeuropathies. Neuropathy is more common in patients with severe renal involvement.[41] Cranial neuropathies, particularly the second, sixth, and seventh nerves, develop in approximately 5–10% of cases as a result of extension of the nasal or paranasal granulomas rather than vasculitis.[37,43]

The majority of individuals who are affected have ANCAs directed against proteinase-3 in their sera, and this test has a specificity of 98% and sensitivity of 95%.[41] The histological appearance of the vasculitis is similar to PAN, with involvement of medium- and small-sized blood vessels. In addition, granulomatous infiltration of the respiratory tract and necrotizing glomerulonephritis are also seen. The absence of peripheral eosinophilia, eosinophilic infiltrates on biopsy, and asthma help distinguish Wegener's granulomatosis from CSS.

MICROSCOPIC POLYANGIITIS

Microscopic polyangiitis (MPA) clinically resembles PAN and CSS, except that diffuse alveolar damage and interstitial fibrosis develop due to involvement of pulmonary capillaries.[1,2,4,32,33,45] The incidence of MPA is about one-third that of PAN. The average age of onset of 50 years and polyneuropathy complicates MPA in 14–36% of cases.[2,4,45]

Laboratory evaluation is remarkable for renal insufficiency, hematuria, and p-ANCAs in most patients. C-ANCAs can also occasionally be detected. As suggested by the name, MPA affects small arterioles, venules, and capillaries.[2,4] In contrast to PAN, there are few or no immune deposits on the blood vessels. Kidney biopsies reveal focal segmental thrombosis and necrotizing glomerulonephritis.

BEHÇET SYNDROME

This disorder is characterized by recurrent oral and genital ulcerations, inflammation of the eye, arthritis, thrombophlebitis, skin lesions, and vasculitic lesions of these organs involving the small- to medium-size arteries.[46–49] The CNS complications (brainstem strokes, meningoencephalitis, and psychosis) are more common than peripheral neuropathy.

▶ SECONDARY SYSTEMIC VASCULITIDES

VASCULITIS ASSOCIATED WITH CONNECTIVE TISSUE DISEASE

Neuropathies are not uncommon in people with connective tissue diseases, although necrotizing vasculitis as the cause is infrequent (see Chapter 14 regarding "Neuropathies Associated with Systemic Disease"). That said, secondary vasculitis can complicate rheumatoid arthritis but may also complicate systemic lupus erythematosus and Sjogren syndrome and, less frequently, systemic sclerosis.[13,50,51] The clinical, histological, and electrophysiological features are similar to PAN.

INFECTION-RELATED VASCULITIS

Vasculitic neuropathy can arise as a complication of a variety of infections.[29,52,53] The most common infectious agents associated with vasculitic neuropathy are HIV, hepatitis B and C, cytomegalovirus, Epstein–Barr viruses, and herpes varicella zoster (Discussed in Chapter 15, "Neuropathies Associated with Infections"). Multiple mononeuropathies related to HIV or cytomegalovirus infection occurs in up to 3% of patients with acquired immune deficiency syndrome (AIDS).[54] As previously discussed, hepatitis B and C infections are associated with PAN, a medium-sized systemic vasculitis, as well as a small vessel vasculitis associated with cryoglobulinemia. Vasculitic neuropathy may also complicate Lyme disease.

MALIGNANCY-RELATED VASCULITIS

Rarely, cancers have been associated with vasculitic neuropathy. Small cell lung cancer and lymphoma are the most commonly implicated malignancies, but leukemia, other myelodysplastic syndromes, and carcinomas of the kidneys, bile duct, prostate, and stomach have also been described.[55–63] However, most of the reported cases were not associated with a necrotizing vasculitis, rather only nonspecific transmural or perivascular inflammation of small blood vessels without necrosis was seen on biopsy. In this regard, several of the cases with "vasculitic" neuropathy associated with lung cancer and anti-Hu antibodies were reported as having vasculitis, although this disorder is not a true vasculitis (see Chapter 17 regarding "Neuropathies Associated with Malignancies").[55] Multiple mononeuropathies or generalized neuropathy associated with lymphomas are often paraneoplastic in etiology or due to lymphomatous infiltration of the nerves. However, rare cases of vasculitic neuropathy have been reported in the setting of lymphoma.[61]

DRUG-INDUCED HYPERSENSITIVITY VASCULITIS

Hypersensitivity vasculitis is often secondary to drug reactions and is a self-limited process as opposed to the systemic necrotizing vasculitides.[4] Skin manifestations (e.g., petechiae) predominate the clinical picture of hypersensitivity vasculitis, while neuropathy is rare. Drugs of abuse (e.g., amphetamine, cocaine, and opioids) can cause vasculitis of the CNS or PNS.[64,65] The pathogenesis most likely relates to a complement-mediated leukocytoclastic reaction.

VASCULITIS SECONDARY TO ESSENTIAL MIXED CRYOGLOBULINEMIA

Cryoglobulins are circulating immune complexes, consisting of immunoglobulins directed against polyclonal immunoglobulins. These complexes precipitate out of solution when exposed to a cool temperature but dissolve back into solution when rewarmed, thus the name cryoglobulin. There are actually three types of

cryoglobulins. Type I cryoglobulins are monoclonal immunoglobulins, usually the IgM, directed against polyclonal IgG. These are most commonly seen in individuals with plasma cell dyscrasias. Type II cryoglobulins are composed of a combination of monoclonal IgM and polyclonal immunoglobulins directed against polyclonal IgG. Type III cryoglobulins are a mixture of polyclonal IgM, IgG, and IgA directed against polyclonal IgG. Type II and III cryoglobulins are seen in patients with the so-called mixed cryoglobulinemia and typically occur in the setting of disorders, connective tissue diseases, and hepatitis B and C. Essential mixed cryoglobulinemia is the term used when mixed cryoglobulinemia is found without a systemic disorder other than viral hepatitis. Most patients with essential mixed cryoglobulinemia are associated with hepatitis C antigenemia. Peripheral neuropathy develops in 25–90% of patients with cryoglobulinemia of any type.[16,66–73] The neuropathy may manifest as a painful, distal, symmetric sensory or sensorimotor polyneuropathy; as a mononeuropathy multiplex pattern; or rarely as a pure small fiber neuropathy.[16]

The lack of local HCV replication in nerve biopsies suggest that that HCV-mixed cryoglobulinemia-associated neuropathy results from virus-triggered immune-mediated mechanisms rather than direct nerve infection and in situ replication.[71,74] The neuropathy may arise due to ischemia from hyperviscosity or due to vasculitis related to immune complex deposition in small epineurial blood vessels. Nerve conduction studies are similar to PAN. Conduction block was appreciated on motor NCS in one report.[16]

▶ NONSYSTEMIC VASCULITIS

NONSYSTEMIC OR ISOLATED PNS VASCULITIS

In nearly 60% of all vasculitic neuropathies the vasculitis is restricted to peripheral nerves.[1,3,6,7,20,23,75–78] This so-called nonsystemic vasculitis or isolated PNS vasculitis is usually seen in adults, but children can also be affected.[6] The clinical, electrophysiological, and histopathological features of isolated PNS vasculitis are quite similar to PAN, except that there is no significant involvement of other organ systems. Individuals who are affected may present with multiple mononeuropathies or a generalized symmetric sensorimotor polyneuropathy. Laboratory testing may demonstrate elevated ESR or positive ANA titers. Vasculitis may be apparent on muscle biopsies,[5] but the peripheral nerves are predominantly affected. The diagnostic yield of finding vasculitis is increased by biopsying both muscle and nerve.

The vasculitis typically involves small- and medium-sized arteries of the epineurium and perineurium, and immune complex deposition on these blood vessels may be appreciated on biopsy. MMPs, in particular MMP-2 and MMP-9 (gelatinase A and B), are upregulated in the peripheral nerves in patients with nonsystemic vasculitis.[79] T cells are the predominant source of MMP-2 and MMP-9, although stromal cells of the perineurium and endoneurium may also secrete MMP. These enzymes digest the subendothelial basement membrane and thus facilitate inflammatory cells penetrate the blood–nerve barrier.

The prognosis for isolated PNS vasculitis is much better than that for systemic vasculitic disorders. Although some patients may be managed with corticosteroids alone, the combination of corticosteroid and cyclophosphamide appears to be more useful in inducing remission and improving disability.[20]

▶ TREATMENT OF VASCULITIC NEUROPATHY

There is a lack of randomized trials of corticosteroids and other immunosuppressive agent therapies in vasculitic neuropathy.[1,80] However, the mainstay of initial treatment of systemic vasculitis is the combination of corticosteroids and cyclophosphamide.[2,4,32,81–83] Since the use of corticosteroids to treat systemic vasculitis began in the 1950s, the 5-year survival rate increased from 10% to 55% by the mid-to-late 1970s.[2] The addition of cyclophosphamide to corticosteroids further increased the 5-year survival rate to over 80%.[2,83] Hypersensitivity vasculitis and sometimes isolated PNS vasculitis may be treated with only prednisone. However, a large retrospective series suggested that the combination of corticosteroids and cyclophosphamide was more effective than corticosteroids alone.[20]

We begin treatment with methylprednisolone (1 g intravenously every day for 3 days), then switch to oral prednisone 1.5 mg/kg/d (up to 100 mg/d) as a single dose in the morning. After 2–4 weeks, we switch to alternate-day prednisone (i.e., 100 mg every other day). However, if a patient is diabetic, we treat with daily corticosteroids (e.g., prednisone 50 mg daily) so as not to have wide fluctuations in blood glucose. Patients are concurrently started on calcium and vitamin D supplementation and sometimes on a bisphosphonate to prevent and treat steroid-induced osteoporosis.

In addition, oral or intravenous cyclophosphamide is started. Oral cyclophosphamide at a dose of 1.0–2.0 mg/kg is a more potent suppressor of the immune system but is associated with more adverse side effects (e.g., hemorrhagic cystitis) than intravenous doses. Thus, we usually treat patients with monthly intravenous pulses of cyclophosphamide at a dose of 500–1000 mg/m^2 of body surface area. We premedicate patients with sodium 2-mercaptoethane sulfonate to reduce the incidence of bladder toxicity and with antiemetics to diminish

nausea. Hydration is essential to minimize bladder toxicity. Following intravenous pulses of cyclophosphamide, the leukocyte count drops. The nadir of the leukopenia occurs between 7 and 18 days, during which time the risk of infection is greatest. We check complete blood counts and urinalysis prior to each treatment. Urinalysis is obtained every 3–6 months after treatment because of the risk of future bladder cancer.

If patients do not respond to pulsed cyclophosphamide, oral dosing should be tried prior to concluding that the patient failed cyclophosphamide treatment. High-dose corticosteroids and cyclophosphamide are continued until the patient begins to improve or at least the deficit stabilizes. This usually occurs within 4–6 months. Subsequently, we discontinue the cyclophosphamide and start methotrexate (7.5 mg per week). The methotrexate dose is gradually increased as necessary. Also at the same time we begin to taper the prednisone by 5 mg every 2–3 weeks. The use of cyclophosphamide and glucocorticoids for induction and methotrexate for maintaining remission appears to be an effective and well-tolerated therapeutic regiment in patients with active Wegener's granulomatosis and is a reasonable approach in other vasculitic neuropathies.[84] Patients with CSS often require continued low doses of prednisone in order to control their asthma. Relapses are uncommon in PAN, MPA, and isolated PNS vasculitis but occur in as many as 50% of cases of Wegener's granulomatosis.[2,41] Thus, life-long immunosuppressive therapy is required in many patients.

There is less experience with other immunotherapies in the treatment of vasculitis. Methotrexate (0.15–0.3 mg/kg/week) in combination with corticosteroids can be effective in Wegener's granulomatosis.[44,84] Azathioprine, cyclosporine, tacrolimus, chlorambucil, and intravenous immunoglobulin have been tried in refractory cases with variable success.[81,85–87]

PAN associated with hepatitis B or C infection deserves special comment. Conventional treatment with high-dose corticosteroids and cyclophosphamide may allow the virus to persist and replicate, thus increasing the risk of liver failure. Further, methotrexate can directly cause hepatotoxicity. Some authorities advocate corticosteroids only for the first few weeks of treatment to manage life-threatening manifestations of systemic vasculitis and then switch over to maintenance therapy with plasma exchange and antiviral agents such as vidarabine or α-interferon.[2] The 7-year survival rate using this regimen in patients with hepatitis B-related PAN was 83%, while the HBeAG/HBeAB conversion rate was 51%, and total viral clearance was seen in 24%—all of which represent a significant improvement from that seen with corticosteroids with or without cyclophosphamide or plasma exchange.[88]

In patients with mixed cryoglobulinemia, due to hepatitis C infection, treatment with α-interferon (3 million units three times a week) may be effective.[12,56,70,89–94] As in PAN associated with hepatitis B or C, a short course of corticosteroids may be required to control the initial manifestations of the systemic vasculitis followed by plasma exchange and α-interferon. Small series suggest that rituximab may be beneficial in cryoglobulinemic vasculitis, although it probably should not be used in cases related to hepatitis infection.[95,96]

▶ SUMMARY

There are a number of causes of systemic vasculitis that can affect peripheral nerves, and many times the vasculitis may be isolated to the peripheral nerves. Individuals who are affected may manifest with mononeuropathy, multiple mononeuropathies, and overlapping mononeuropathies, or even as a generalized symmetric sensorimotor polyneuropathy. It is important to take a detailed medical history for disorders that may be associated with vasculitis (e.g., connective tissue diseases, viral hepatitis, and late-onset asthma). Useful laboratory tests include assessment for eosinophilia, antinuclear antibodies, p-ANCA, c-ANCA, ESR, rheumatoid factor, cryoglobulins, hepatitis serology, and urinalysis. We like to have histological confirmation of vasculitis before initiating what can turn out to be long-term immunosuppressive therapy. The diagnostic yield of a combined superficial peroneal nerve and peroneus brevis muscle biopsy, when clinically affected, is high. Most patients improve with combination of high-dose corticosteroids and cyclophosphamide.

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CHAPTER 14

Neuropathies Associated with Systemic Disease

Neuropathies are associated with a number of systemic disorders (Table 14–1). Neuropathies related to vasculitis, infection, cancer, and medications are discussed in other chapters. The neuropathies discussed in this chapter may be directly related to the systemic disorder or may be indirectly related (e.g., nutritional deficiency due to malabsorption in gastrointestinal disease).

▶ NEUROPATHIES ASSOCIATED WITH CONNECTIVE TISSUE DISEASES

SJÖGREN SYNDROME

Clinical Features

Sjögren syndrome is characterized by the sicca complex: xerophthalmia (dry eyes), xerostomia (dry mouth), and dryness of other mucous membranes. It is more common in women and typically presents in middle adult life. Sjögren syndrome can be complicated by central nervous system (CNS) and peripheral nervous system involvement. The CNS manifestations can mimic transverse myelitis or multiple sclerosis. Peripheral neuropathy occurs in 10–22% of patients with Sjögren syndrome.[1–12] Further, peripheral neuropathy can be the presenting feature of Sjögren syndrome and develop in patients without the typical sicca symptoms.

The most common form of peripheral neuropathy is a length-dependent axonal sensorimotor neuropathy characterized by numbness and tingling in the distal portions of the limbs.[1,2,6,7,9–11] Mild distal muscle weakness may also be seen. A pure small fiber neuropathy characterized by burning discomfort and tingling is also common.[13,14] Signs of an autonomic nervous system dysfunction involving the cardiovascular system are often evident.[15,16] Necrotizing vasculitis may be responsible for as many as one-third of the cases of neuropathy associated with Sjögren syndrome.[8] Vasculitis should be suspected in patients with asymmetric, multiple mononeuropathy pattern of involvement. Cranial neuropathies, particularly involving the trigeminal nerve, can also be seen.[17]

Sjögren syndrome is also associated with sensory neuronopathy/ganglionopathy.[1–3,7,10,18–20] Patients with sensory ganglionopathies develop progressive numbness and tingling of the limbs, trunk, and face in a non-length-dependent manner. Symptoms can involve the arms more than the legs, and involvement can be quite asymmetric or even unilateral. The onset can be acute or insidious. Sensory examination demonstrates severe vibratory and proprioceptive loss leading to sensory ataxia. Romberg sign is noted in patients with lower limb involvement. The lack of proprioception may lead to pseudoathetotic posturing of affected arms and legs. There can also be diminished sensation in the face. Signs of autonomic neuropathy may be appreciated: Adie's pupils, anhidrosis, fixed tachycardia, and orthostatic hypotension. Muscle stretch reflexes are often reduced or absent. Muscle strength is usually normal.

Laboratory Features

Patients with neuropathy due to Sjögren syndrome may have antinuclear antibodies (ANA), SS-A/Ro, and SS-B/La antibodies in the serum, but most do not.[7] Cerebral spinal fluid is usually normal. Schirmer's test and Rose-Bengal stain are useful for diagnosing keratoconjuctivitis. The diagnosis can be confirmed by parotid gland or lip biopsies demonstrating a lymphocytic invasion of salivary glands. Salivary gland biopsies can demonstrate histopathological features of Sjogren syndrome even in patients without complaints of dry mouth.[7]

Nerve conduction studies (NCS) in patients with the distal sensorimotor polyneuropathy demonstrate absent or reduced amplitudes of sensory nerve action potentials (SNAPs) with normal or only mildly slow conduction velocities.[1,2,6] Motor conduction studies are less affected but may show slightly reduced amplitudes. Abnormal blink reflexes and cutaneous masseter inhibitory reflexes may be appreciated in patients with trigeminal neuropathy.[17]

NCS in patients with sensory neuronopathy/ganglionopathy demonstrate absent or reduced amplitudes of the SNAPs in a non-length-dependent manner such that these may be abnormal in the arms

TABLE 14–1. NEUROPATHIES ASSOCIATED WITH SYSTEMIC DISORDERS

Connective tissue disease
Sjogren syndrome or sicca complex
Rheumatoid arthritis
Systemic lupus erythematosus
Scleroderma
Mixed connective tissue disease
Sarcoidosis
Celiac disease
Inflammatory bowel disease
Ulcerative colitis
Crohn disease
Primary biliary sclerosis
Hypereosinophilic syndrome
Uremia
Liver disease
Whipple disease
Gout
Critical illness polyneuropathy
Amyloidosis
Acquired
Familial
Vasculitis
Isolated peripheral nerve vasculitis
Vasculitis associated with systemic disease
Wegener granulomatosis
Churg–Strauss syndrome
Microscopic polyangiitis
Infection
HIV
HTLV1
CMV
EBV
Lyme
Syphilis
Cancer
Direct tumor infiltration of nerves
Paraneoplastic

while normal in the legs.[1–3,5,18–20] In addition, there may be asymmetric involvement. Motor conduction studies and electromyography (EMG) are usually normal. If the trigeminal nerve is affected, blink reflexes are also abnormal.[21] An important clinical and electrophysiological feature that can help distinguish length-dependent sensory neuropathy from a sensory neuronopathy/ganglionopathy is the preservation of the masseter reflex or jaw jerk in the latter.[22] The masseter reflex is unique amongst the stretch reflexes in that the cell bodies of the afferent limb lie in the mesencephalic nucleus within the CNS as opposed to the dorsal root ganglia where the sensory cell bodies innervating the extremities lie. The Gasserian ganglia, which is responsible for conveying sensory nerves responsible for facial sensation and the blink reflex, also reside outside the CNS.

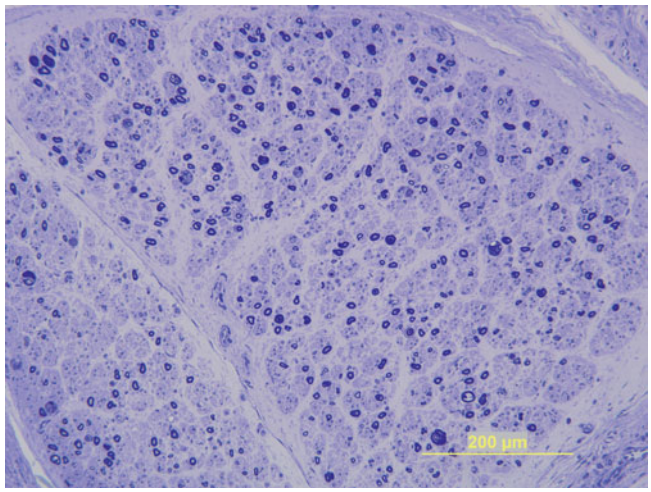


Figure 14–1. Sjogren syndrome. Sural nerve biopsy demonstrates a moderate reduction of large and small myelinated nerve fibers and evidence of axonal degeneration. Plastic section stained with toluidine blue.

Histopathology

Peripheral nerve biopsies in patients with the more common sensorimotor polyneuropathy demonstrates axonal degeneration and some degree of secondary segmental demyelination (Fig. 14–1).[1,2,6] Nonspecific perivascular inflammation involving perineurial or endoneurial blood vessels is occasionally seen. Rarely, necrotizing vasculitis is appreciated.

Biopsy of sensory nerves in patients with sensory neuronopathy/ganglionopathy demonstrated a loss of large myelinated fibers and perivascular lymphocytic (CD8 T cells) inflammation involving endoneurial or perineurial vessels.[1–3] Biopsy of the dorsal root ganglion may reveal lymphocytic (mainly CD8 T-cells) infiltration and degeneration of cell bodies.[3]

Reduced epidermal nerve fiber density or abnormal morphology may be demonstrated on skin biopsies in a non-length-dependent manner, suggesting that patients with painful small fiber neuropathies commonly have a small fiber sensory neuronopathy/ganglionopathy rather than a "dying-back" axonopathy.[13]

Pathogenesis

The pathogenic basis of the distal sensory or sensorimotor polyneuropathy is unknown but is presumably autoimmune in nature. Some cases may cause vasculitis. The sensory neuronopathy/ganglionopathy appears to be the result of cell-mediated autoimmune attack directed against the sensory ganglia. The specific antigen(s) and trigger of the autoimmune attack are not known.

Treatment

There is no specific treatment for neuropathies related to Sjögren syndrome. When vasculitis is suspected, immunosuppressive agents may be beneficial. Occasionally, the sensory neuronopathy/ganglionopathy stabilizes or improves with immunotherapy such as IVIG.[3,11,18,23,24]

RHEUMATOID ARTHRITIS

Clinical Features

Peripheral neuropathy occurs in at least 50% of patients with rheumatoid arthritis (RA). Vasculitic neuropathy develops in 40–50% of patients with RA, making it the third most common cause of vasculitic neuropathy following polyarteritis nodosa (PAN) and isolated peripheral nervous system vasculitis.[12,25–28] Symptoms usually manifests 10–15 years after manifestations of other symptoms of RA, although rarely the neuropathy can be the presenting feature.[27] Rheumatoid vasculitis can present with a mononeuropathy multiplex, overlapping mononeuropathy multiplex, or generalized symmetric pattern of involvement. Neuropathies may also be due to drugs used to treat the RA (e.g., tumor necrosis blockers and leflunomide).

Laboratory Features

Antinuclear antibodies, elevated ESR, and rheumatoid factor are often detected in the serum. NCS in patients demonstrate absent or reduced amplitudes of SNAPs with normal or only mildly slow conduction velocities.

Histopathology

Nerve biopsies often reveal thickening of the epineurial and endoneurial blood vessels as well as perivascular inflammation, perhaps related to the so-called microvasculitis (Fig. 14–2). Occasionally, there is true vasculitis with transmural inflammatory cell infiltration and fibrinoid necrosis of vessel walls.

Treatment

Presumably the neuropathy is autoimmune in nature and may respond to immunomodulating therapies.

SYSTEMIC LUPUS ERYTHEMATOSUS

Clinical Features

Systemic lupus erythematosus (SLE) is a common connective tissue disease with prevalence in adults of approximately one in 2000 and can be associated

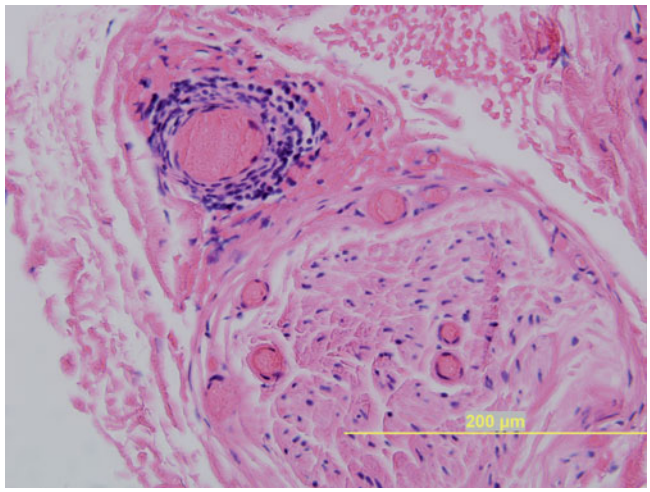


Figure 14–2. Rheumatoid arthritis. Sural nerve biopsy reveals an epineurial vessel perivascular inflammation and scattered perineurial and endoneurial dilated capillaries with thickened walls. Paraffin section stained with Hematoxylin & Eosin (H&E).

with multiple organ system involvement and laboratory abnormalities.[1280] CNS complications are more common than peripheral neuropathies. However, 2–27% of individuals with SLE clinically develop a peripheral neuropathy.[12,29–32] Patients who are affected typically complain slowly progressive sensory loss beginning in the feet. Some patients develop burning pain and paresthesia with normal reflexes and NCS suggestive of a pure small fiber neuropathy.[33,34] Less common are multiple mononeuropathies presumably secondary to necrotizing vasculitis.[29,35,36] The longer the disease progresses, the more likely the multiple mononeuropathies are to fuse and overlap, creating an increasingly symmetric, generalized axonal sensorimotor polyneuropathy. Rarely, patients manifest with generalized sensorimotor polyneuropathy meeting clinical, laboratory, electrophysiological, and histological criteria for either acute or chronic inflammatory demyelinating polyneuropathy (AIDP or CIDP).[37–39]

Laboratory Features

Antinuclear antibodies, anti-double-stranded DNA, and anti-Ro antibodies may be demonstrated in the serum. Abnormal NCS occur in 24–56% of patients with SLE.[31,32] Most commonly, the NCS reveal a length-dependent, axonal sensory polyneuropathy.[40]

Histopathology

Nerve biopsies may demonstrate endoneurial mononuclear inflammatory infiltrate and increased expression of class II antigens within nerve fascicles and on endothelial cells, suggesting an autoimmune pathogenesis.[30]

Upregulation of matrix metalloproteinase-3 and matrix metalloproteinase-9 within the vessel walls has also been observed.[41] Skin biopsies may reveal decreased density of epidermal nerve fibers suggestive of a small fiber neuropathy.[33,34]

Pathogenesis

The pathogenic basis of the associated neuropathy is likely multifactorial. Neuropathy may be related to the underlying vasculopathy characteristic of SLE. Some patients may develop neuropathy due to other systemic complications of SLE (i.e., renal failure and uremic neuropathy).

Treatment

Immunosuppressive therapy is beneficial in patients with SLE, with neuropathy being related to vasculitis. Immunosuppressive agents are less likely to be effective in patients with a generalized sensory or sensorimotor polyneuropathy without evidence of vasculitis. Patients with an AIDP- or CIDP-like neuropathy should be treated accordingly (see Chapters 11 and 12).

SYSTEMIC SCLEROSIS (SCLERODERMA)

Scleroderma is associated with progressive fibrosis of the skin, gastrointestinal tract, kidney, and lung.[12,42–46] A distal symmetric, mainly sensory, polyneuropathy complicates 5–67 % of cases. Cranial mononeuropathies can also develop, most commonly the trigeminal nerve, leading to numbness and dysesthesias in the face. Occasionally, seventh and ninth cranial neuropathies develop.

The CREST syndrome (calcinosis, Raynaud's phenomena, esophageal dysmotility, sclerodactyly, and telangiectasis) is considered a limited form of scleroderma. Multiple mononeuropathies have been described in a small percentage (1–2%) of patients with CREST syndrome.[47] The electrophysiological and histological features of nerve biopsies are those of an axonal sensory greater than motor polyneuropathy.

MIXED CONNECTIVE TISSUE DISEASE

Mixed connective tissue disease represents an overlap syndrome of SLE, scleroderma, and myositis. A mild distal axonal sensorimotor polyneuropathy reportedly occurs in approximately 10% of patients.[12,48]

▶ OTHER PRESUMABLY IMMUNE-MEDIATED NEUROPATHIES

SARCOIDOSIS

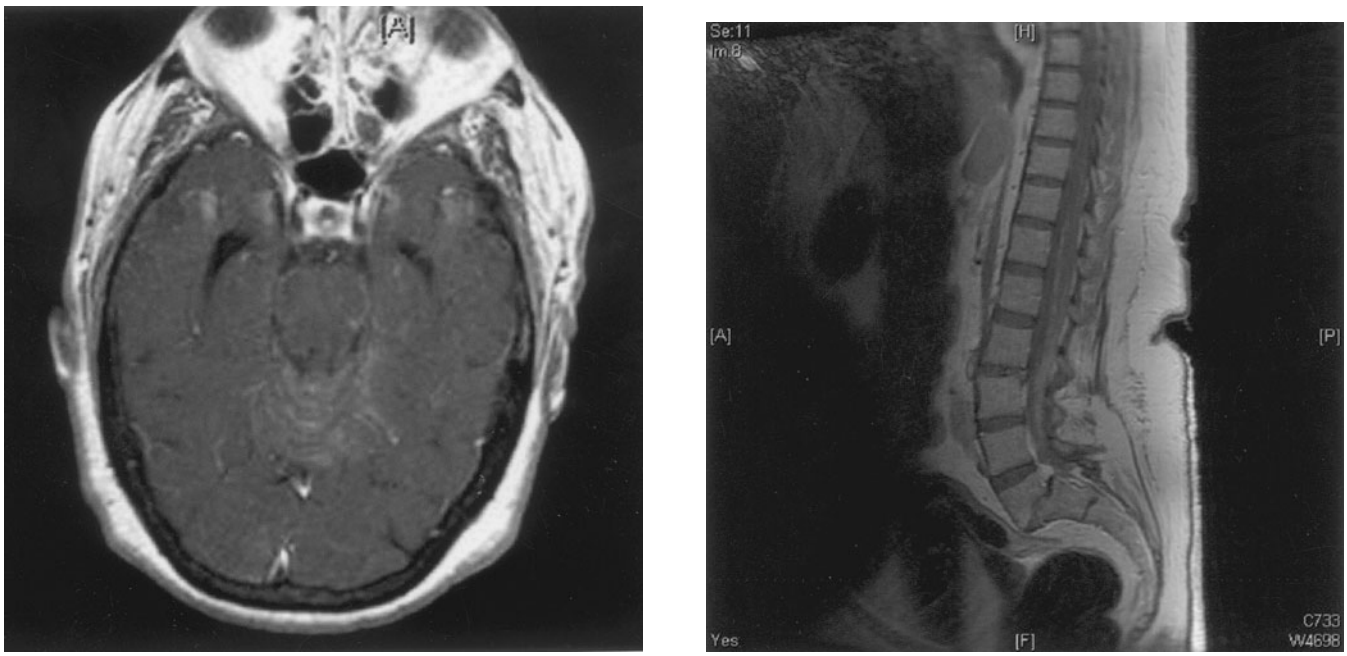
Clinical Features

Sarcoidosis systemic granulomatous disorder can affect the CNS, peripheral nerves, and muscle.[49–52] The etiology is unknown. Women are more commonly affected than men. Nonspecific constitutional symptoms of fever, weight loss, arthralgias, and fatigue are usually the presenting complaints of most patients. Erythematous subcutaneous nodules about the anterior shin and enlarged peripheral lymph nodes may be noted. Granulomatous uveitis can lead to significant visual impairment and even blindness. Mucosal lesions of the nose and sinuses are common.

The peripheral or central nervous systems are involved in about 5% of patients with sarcoidosis.[49–51] Granulomas most typically involve the meninges, hypothalamus, and pituitary gland. Cranial nerves are also frequently involved. The most common cranial nerve to be involved is the seventh nerve, which can be affected bilaterally. The second and eighth cranial nerves are also frequently affected. However, any of the cranial nerves may be involved, and often the neuropathy is relapsing and remitting in nature. Some patients develop radiculopathy or polyradiculopathy. With a generalized root involvement, the clinical presentation can mimic AIDP or CIDP. Rarely, patients may present with an acute sensory ataxia with sphincter dysfunction.[53] Patients can also present with multiple mononeuropathies or a generalized, slowly progressive, primarily sensory greater than motor polyneuropathy.[54] Some have features of a pure small fiber neuropathy.[55,56]

Laboratory Features

Hilar adenopathy is often but not always appreciated on chest radiographs. MRI scans may demonstrate enhancement of the meninges in the brain, particularly in the posterior fossa, and of affected spinal roots in patients with radiculopathy (Fig. 14–3). Angiotensin converting enzyme (ACE) levels may be elevated in those with lung disease but it is not a very sensitive test. In patients with subclinical neuropathy, the most common finding is an absence or reduction in SNAP amplitudes in a mononeuropathy multiplex pattern.[52,57] In patients with the symmetric sensorimotor peripheral neuropathy, the SNAPs may be absent or reduced in amplitude.[52,58] Motor NCS also reveal reduced or absent compound muscle action potential (CMAP) amplitudes in the lower limbs, with decreased or borderline normal CMAPs in the upper limbs. Patients may also show EMG changes suggestive of a



A B

Figure 14–3. Sarcoidosis. MRI scan of the brain with contrast demonstrates enhancement of the meninges around the cerebellum (A) and of the cauda equina (B) in a patient who presented with multiple cranial neuropathies and a polyradiculopathy.

radiculopathy or polyradiculopathy.[50] Quantitative sensory testing often reveals abnormal thermal thresholds, and autonomic testing may be abnormal as well indicative of small fiber involvement.[56]

Histopathology

Nerve biopsies can reveal noncaseating granulomas infiltrating the endoneurium, perineurium, and epineurium along with lymphocytic necrotizing angiitis (Fig. 14–4).[52] There is a combination of axonal loss as well as demyelination. Muscle biopsies likewise can demonstrate noncaseating granulomas in the endomysium even in patients without an underlying myopathy.[52] Skin biopsies may reveal reduced intraepidermal nerve fiber suggestive of a small fiber in some patients.[55]

Pathogenesis

Sarcoidosis is an autoimmune disorder, although the etiology and pathogenic mechanism of the disorder is unclear. Peripheral neuropathy may result from direct compression, ischemia, a combination of these two insults, or other ill-defined factors. The cranial nerves and mononeuropathies of the peripheral nervous system are likely to result from direct neural invasion and compression. The AIDP- and CIDP-like neuropathies may be the result of diffuse infiltration of nerve and nerve roots or the result of poorly defined immunologic compromise related to the sarcoidosis itself.

Treatment

Neurosarcoidosis, particularly of the cranial nerves, may respond well to corticosteroid treatment.[50] If patients are resistant to corticosteroids, other immunosuppressive agents can be tried (e.g., cyclosporine, methotrexate, and IVIG).[59] Unfortunately, following cessation of treatment, the patients appear to return to a

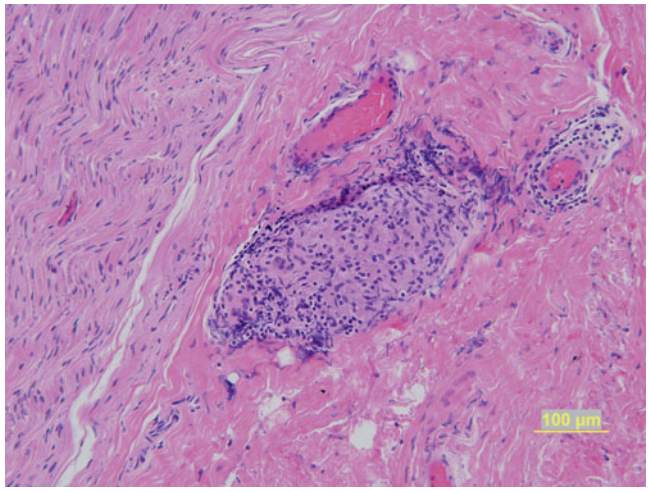


Figure 14–4. Sarcoidosis. Superficial peroneal nerve biopsies reveal a noncaseating granuloma in the epineurium and perivascular inflammation. Paraffin section stained with H&E.

propensity for developing compromise of their nervous system.

CELIAC DISEASE (GLUTEN-INDUCED ENTEROPATHY OR NONTROPICAL SPRUE)

Clinical Features

Intolerance to gluten, which is a protein found in wheat and wheat products, results in a malabsorption syndrome (weight loss, abdominal distention, and steatorrhea). Diagnosis of celiac disease is based on the documentation of (1) malabsorption, (2) demonstration of blunting and flattening of jejunal villi, and (3) clinical and histologic improvement following the institution of a gluten-free diet.[60] Neurologic complications are estimated to occur in 10% of patients who are affected, with ataxia and peripheral neuropathy being the most common problems.[61,62] The neuropathy associated with celiac disease usually manifests as distal sensory loss, paresthesias, and imbalance.[60,61,63–68] Generalized sensorimotor polyneuropathy, motor neuropathy, multiple mononeuropathies, autonomic neuropathy, and neuromyotonia also have all been reported in association with celiac disease or antigliadin/antiendomysial antibodies. Neurological examination often demonstrates loss of large fiber sensory modalities, mild distal muscle weakness, reduced or absent muscle stretch reflexes, and an ataxic gait. Signs of a small fiber neuropathy or autonomic neuropathy may be evident.[67,68]

Laboratory Features

Antigliadin and endomysial antibodies are often detected in the serum of patients with celiac disease. However, these antibodies are not specific. NCS usually demonstrate reduced SNAP amplitudes with only mildly reduced NCVs or prolonged distal latencies.[61,62,65,66,69,70] Motor conduction studies demonstrate a mild reduction in the nerve conduction velocities (NCV) with preservation of distal motor latencies and CMAP amplitudes. Autonomic studies may be abnormal in patients with autonomic neuropathy.[68] Rare cases with neuromyotonic discharges have been appreciated.[65]

Histopathology

Nerve biopsy reveal a loss of large myelinated fibers.[61] Skin biopsies can demonstrate loss of epidermal nerve fibers suggestive of a small fiber neuropathy in some patients.[67] On autopsy, a loss of Purkinje cells in the cerebellum has been demonstrated, along with degeneration of the posterior columns and corticospinal tracts, cortical atrophy and loss of neurons in the thalamus, basal ganglia, and brainstem.[64]

Pathogenesis

The neuropathy may be secondary to malabsorption of vitamins B12 and E. However, some patients have no appreciable vitamin deficiencies. The pathogenic basis for the neuropathy in these patients is unclear but may be autoimmune in etiology.[61,69]

Treatment

The neuropathy does not appear to be responsive to a gluten-free diet.[60,71] In patients with vitamin B12 or E deficiency, replacement therapy may improve or stabilize the neuropathy.

INFLAMMATORY BOWEL DISEASE

Ulcerative colitis and Crohn disease are inflammatory disorders of the bowel and are associated with various neurological abnormalities including peripheral neuropathy. Acute or chronic demyelinating neuropathies (including multifocal motor neuropathy),[72–77] generalized axonal sensory or sensorimotor polyneuropathy,[77,78] small fiber neuropathy,[77] brachial plexopathy,[75,79] multiple mononeuropathies,[75] and cranial neuropathies[75] can complicate ulcerative colitis and Crohn disease. The neuropathies in these cases may be autoimmune in nature, secondary to toxicity of treatment (e.g., metronidazole), nutritional (e.g., vitamin B12 deficiency), or idiopathic. An acute neuropathy with multiple conduction blocks on NCS has been reported in a few patients with inflammatory bowel disease treated with tumor necrosis factor-alpha blockers.[80] In addition, patients can develop weakness secondary to myasthenia gravis or myositis (including polymyositis, dermatomyositis, and granulomatous myositis).[75]

PRIMARY BILIARY CIRRHOSIS

Clinical Features

Primary biliary cirrhosis (PBC) is an autoimmune disorder directed against the biliary ducts in the liver. Peripheral neuropathy characterized by distal numbness and tingling can complicate PBC.[81–83] Large fiber sensory modalities are predominantly affected, leading to reduced or absent muscle stretch reflexes. Muscle strength is typically normal but may be weak in patients with a CIDP-like neuropathy. Myasthenia gravis, Lambert–Eaton syndrome, and myositis can also complicate PBC.

Laboratory Features

Liver function tests are elevated, and antimitochondrial antibodies can be detected in the sera of some patients with PBC. NCS demonstrates reduced or absent SNAPs. The motor conduction and needle EMG portions of the evaluation are typically normal.

Histopathology

Nerve biopsies usually reveal a loss of large myelinated fibers without evidence of segmental demyelination.

Pathogenesis

The neuropathy could have an immunological basis or may be related to unknown toxins that might be accumulating secondary to the liver failure.

Treatment

PBC is treated with immunosuppressive therapy and ultimately liver transplantation. Whether or not transplantation affects the peripheral neuropathy has not been adequately addressed.

HYPEREOSINOPHILIC SYNDROME

Hypereosinophilic syndrome is characterized by eosinophilia associated with various skin, cardiac, hematologic, and neurologic abnormalities.[84–86] A generalized peripheral neuropathy or a mononeuropathy multiplex occurs in 6–14% of patients. In addition, some develop an inflammatory myopathy. NCS reveal features suggestive of axonal sensorimotor peripheral neuropathy. The pathogenic basis for the neuropathy is not known but may be autoimmune in nature. The multiple organ dysfunction, including the peripheral nervous system, is believed to occur as a result of the eosinophilia or some byproducts of the eosinophils.

▶ OTHER NEUROPATHIES ASSOCIATED WITH SYSTEMIC DISEASE

UREMIC NEUROPATHY

Clinical Features

Renal failure is associated with both CNS and peripheral nervous system complications.[87–89] Approximately 60% of patients with renal failure (usually with glomerular filtration rates below 12 mL/min) develop neuropathy characterized by length-dependent numbness, tingling, and allodynia. Muscle cramps in the distal legs and occasional restless legs syndrome are also common. Reduced sensation, particularly large fiber modalities, and muscle stretch reflexes are appreciated on neurological examination. Mild distal greater than proximal muscle weakness may be noted. Rarely, patients develop rapidly progressive weakness and sensory loss very similar to AIDP, which improves with an increase in renal dialysis or transplantation.[87,88]

Mononeuropathies can also occur, the most common of which is carpal tunnel syndrome. These neuropathies are often related to hemodialysis equipment that uses a Cuprophan membrane because this membrane fails to completely remove a small ß2-microglobulin, which is normally catabolized by the healthy kidney. ß2-Microglobulin can deposit throughout the body, including the transverse carpal ligament. Individuals who are affected are also prone to developing ulnar neuropathy at the elbow and peroneal nerve injury about the fibular head. Damage to the brachial plexus or the peripheral nerves may also occur secondary to improper limb positioning or traction during renal transplant surgery. Ischemic monomelic neuropathy affecting the median, ulnar, and radial nerves can complicate arteriovenous shunts created in the arm for dialysis.[90]

NCS in patients with uremia reveal features of a length-dependent, primarily axonal, sensorimotor polyneuropathy. Sensory studies are reduced in amplitude, if unobtainable, and the distal latencies are prolonged and sensory conduction velocities are slow.[89,91] Most patients have either prolonged or absent H-reflexes, and somatosensory-evoked potential studies reveal both peripheral and central slowing of conduction. Motor conduction studies reveal normal or mildly reduced amplitudes. Distal latencies and conduction velocities can be normal or reflect moderate slowing of conduction.[89,91,92] F-waves are usually absent or demonstrate delayed latencies. The posterior tibial and peroneal motor studies are affected earlier than the median and ulnar studies.

Patients with mononeuropathies often have NCS compatible with superimposed focal demyelination or axonal loss. With ischemic monomelic neuropathy, the EMG and NCS abnormalities reveal severe axonopathy in the territory of the ischemic insult.[90] The median, radial, and ulnar SNAPs may be absent or reduced in amplitude, depending on the degree and time period of ischemia. If CMAPs are elicited, the distal motor latencies are relatively normal as are the conduction velocities. Pseudoconduction block or actual conduction block may be seen across the ischemic segment, particularly within the first week of injury before complete Wallerian degeneration of the affected nerve distal to the nerve infarct can occur. Needle EMG demonstrates a marked reduction in motor unit action potentials (MUAPs) with

abundant positive sharp waves and fibrillation potentials along with decreased recruitment.

Histopathology

Sural nerve biopsies demonstrate a loss of nerve fibers, particularly the large myelinated nerve fibers; active axonal degeneration; and segmental and paranodal demyelination.[93] At autopsy, chromatolysis of anterior horn cells and degeneration of the fasciculus gracilis have been noted in the spinal cord.

Pathogenesis

It is unclear whether the Schwann cell or the axon is the primary target of the essential metabolic or toxic abnormality in uremia or what the primary pathophysiology mechanism of the uremic neuropathy may be.

Treatment

The sensorimotor polyneuropathy can be stabilized by hemodialysis and improved upon successful renal transplant, if performed prior to the loss of large numbers of axons.[94–98] Patients with carpal tunnel syndrome can be treated with surgical release. Median neuropathy at the wrist related to amyloid deposition in the form of ß2-microglobulin is much less common nowadays with newer dialysis techniques currently in use. Patients with ischemic monomelic should undergo revision of their shunt so as to allow more blood flow to the nerves. If treated early enough, the motor and sensory symptoms can resolve quickly, indicating an ischemic-induced conduction block rather than peripheral nerve infarction. Severe ischemia resulting in infarction is associated with a delayed and incomplete recovery.

CHRONIC LIVER DISEASE

Generalized sensorimotor peripheral neuropathy, characterized by numbness, tingling, and minor weakness in the distal aspects of primarily the lower limbs, commonly occurs in patients with chronic liver failure.[82,99–103] In addition, autonomic dysfunction is present in approximately 50% of patients with severe liver disease.[103] NCS demonstrate reduced SNAP amplitudes, while motor NCS are usually normal. Quantitative sensory and autonomic tests are abnormal in most patients.[82,103] Sural nerve biopsies reveal both segmental demyelination and axonal loss. It is not known if hepatic failure in and of itself can cause peripheral neuropathy. Perhaps, toxins accumulate secondary to the liver disease that could damage peripheral nerves. However, the majority of patients have liver disease secondary to other disorders such as alcoholism or viral hepatitis, which can cause peripheral neuropathies.

WHIPPLE DISEASE

Clinical Features

Whipple disease is characterized by abdominal pain, diarrhea, malabsorption weight loss, arthralgias, fever, and peripheral lymphadenopathy, accompanied by enlargement of the celiac, mesenteric, and periaortic lymph nodes.[60,104,105] CNS involvement can lead to dementia, supranuclear ophthalmoparesis, convergence nystagmus, myoclonus, oromandibular myorhythmia, insomnia, hyperphagia, and polydipsia. Rarely, patients develop a sensorimotor polyneuropathy.[104,106]

Laboratory Features

The cerebral spinal fluid examination in patients with CNS involvement typically demonstrates polymorphonuclear cells and macrophages.[60] MRI scans reveal gadolinium enhancement suggestive of ependymitis/meningitis. Sensory and motor NCS may demonstrate reduced amplitudes with mild impairment of conduction velocities.[104]

Histopathology

Small bowel biopsies demonstrate PAS-positive macrophages containing the gram-positive rod-shaped bacterium, *Tropheryma whippeli*, in the mucosa. The organism can also be identified in the CNS but there have been no reports of peripheral nerve or muscle histopathology in patients with suspected neuropathy or myopathy.

Pathogenesis

Whipple disease is caused by the actinomycete—*T. whippeli*. The pathogenic basis of the neuropathy is not known, but some symptoms of the polyneuropathy may be the result of malabsorption of necessary vitamins. Alternatively, the neuropathy may be caused by bacterial infiltration and subsequent inflammatory involvement of the peripheral nerves.

Treatment

Whipple disease can be treated with chloramphenical and trimethoprim-sulphmethoxazone.[60]

▶ GOUT

Some patients with gout may develop a sensorimotor peripheral neuropathy, characterized by length-dependent sensory loss or mononeuropathies at the usual sites of compression at the wrist and elbow.[107] Sensory and motor NCS may reveal reduced amplitudes with normal or only mild alterations of conduction velocities or distal latencies.

CRITICAL ILLNESS POLYNEUROPATHY

Background

The most common causes of acute generalized weakness leading to admission to a medical intensive care unit (ICU) are Guillain-Barre syndrome (GBS) and myasthenia gravis. However, weakness developing in patients who are critically ill while in the ICU is usually caused by critical illness polyneuropathy (CIP),[108–111] critical illness myopathy (CIM) (also known as acute quadriplegic myopathy),[112–118] or, much less commonly, prolonged neuromuscular blockade.[119] From a clinical and electrophysiological standpoint, it can be quite difficult to distinguish these disorders. Although some authorities feel that CIP is more frequent than CIM,[110] most specialists and the authors' own anecdotal experiences suggest that CIM is more common than CIP.[115,117,120] In a series of 88 patients who developed weakness while in an ICU, CIM was three times as common as CIP (42% vs. 13%); prolonged neuromuscular blockade occurred in only one patient who also had CIM.[115] In patients who survive the underlying sepsis and multiorgan failure, muscle strength recovers slowly over several months.

Clinical Features

CIP can develop as a complication of sepsis and multiple organ failure.[108–111] Neuropathies are common in the subset of critically ill patients due to extensive burns surface.[121,122] Often, CIP presents as an inability to wean a patient from a ventilator. Concomitant encephalopathy may limit the neurological examination, in particular the sensory examination; however, generalized weakness can still be appreciated. Muscles innervated are relatively spared, although mild facial weakness can occur. Muscle stretch reflexes are absent or reduced.

Laboratory Features

Serum creatine kinase (CK) is usually normal and an elevated serum CK would point to CIM as opposed to CIP.

The electrophysiological hallmark is markedly reduced amplitudes or absent CMAPs with preserved motor conduction velocities and distal motor latencies.[109–111,123] Repetitive stimulation studies should be normal. The SNAPs should also be significantly diminished in amplitude or absent. Importantly, low-amplitude SNAPs do not necessarily imply that the patient's weakness is secondary to CIP. Patients may have an age-related decrease in SNAP amplitudes or the SNAPs may be abnormal, secondary to an underlying condition (e.g., diabetes mellitus and uremia); thus, the patients could still have CIM rather than CIP even if the SNAPs are abnormal, Further, patients may have a mixture of CIP and CIM.

Needle EMG usually reveals profuse positive sharp waves and fibrillation potentials, and it is not unusual in patients with severe weakness to be unable to recruit MUAPs. When MUAPs are recruited, these are often small and polyphasic in morphology. These small units have been attributed to early reinnervation, but such units are more commonly seen in myopathies. Most published studies fail to discuss the recruitment pattern of MUAPs. One would expect to see decreased recruitment of these small MUAPs in a neurogenic process. However, decreased recruitment can also be seen in severe myopathies. Nevertheless, if one sees early recruitment of small duration, polyphasic MUAPs, CIM is most likely.

Direct muscle stimulation may help distinguish CIP from CIP, as it bypasses the distal motor nerve and neuromuscular junction.[116,117] In a neuropathic process or prolonged neuromuscular blockade, the muscle membranes should retain its excitability and the direct muscle stimulation CMAP should be near normal compared to the low or absent nerve stimulation-evoked CMAP. In contrast, in CIM in which there is reduced muscle membrane excitability, both the nerve stimulation-evoked and the direct muscle stimulation CMAPs are reduced. The ratio of nerve stimulation-evoked CMAP to direct muscle stimulation CMAP should be close to 1:1 (greater than 0.9) in CIM and should approach zero (0.1 or less) in a CIP or neuromuscular junction disorder.[116,117]

Histopathology

Nerve biopsies demonstrated axonal degeneration.[111] On autopsies, chromatolysis of anterior horn cells, loss of dorsal root ganglion cells, and axonal degeneration of motor and sensory nerves have been observed.[111] Muscle biopsies may reveal atrophic and targetoid or core-like lesion fibers suggestive of acute neurogenic process.[111] However, these light microscopic features can be seen in myopathies, and other studies have found loss of myosin thick filaments on muscle biopsy and morphology of intramuscular nerves and those of

multiple nerve roots and proximal nerves to be normal on autopsy, suggesting that these cases may all be CIM.[120]

Pathogenesis

The pathogenic basis of CIP is not known. Perhaps, circulating toxins and metabolic abnormalities associated with sepsis and multiorgan failure impair axonal transport or mitochondrial function, leading to axonal degeneration.[111] Notably, some have questioned the existence of CIP and suggested that most, if not all, such cases are CIM.[124]

Treatment

There is no specific therapy for critical illness neuropathy other than supportive care and treatment of the underlying sepsis and organ failure.

▶ AMYLOID POLYNEUROPATHY

Amyloid is comprised of 10–20 nm, nonbranching protein fibrils, which aggregate to form three-dimensional β-pleated sheets that are resistant to proteolytic decomposition.[125,126] Amyloidosis can be hereditary or acquired and is associated with systemic proteinaceous deposition (e.g., kidney, liver, heart, and GI tract) including peripheral nerves and muscle (Table 14–2). Familial forms of amyloidosis are inherited in an autosomal-dominant fashion and can be caused by mutations in the transthyretin (TTR), apolipoprotein A-1, or gelsolin genes. In primary or AL amyloidosis, the abnormal protein deposition is composed of immunoglobulin light chains. AL amyloidosis occurs in the setting of multiple myeloma, Waldenström macroglobulinemia, lymphoma, other plasmacytomas, or lymphoproliferative disorders, or without any other identifiable disease.[127] Approximately 10% of patients with presumptive diagnosis of systemic AL amyloidosis actually have hereditary amyloidosis with genetic testing.[128] Secondary amyloidosis (AA) can complicate RA and other chronic inflammatory diseases and is associated with the accumulation of protein A but is not associated with a polyneuropathy.

Amyloid deposits have a characteristic apple-green birefringence when stained with Congo red and observed under polarized light and bright red under rhodamine fluorescence. Amyloid is also metachromatic when stained with methyl violet or crystal violet and also stains with Alscian blue. On nerve biopsies, amyloid deposition may be demonstrated in the endoneurium, perineurium, or epineurium and around blood vessels optics (Fig. 14–5).[129] Chronic inflammatory cell infiltrate may be appreciated. Concomitant muscle biopsies may also reveal amyloid deposits encasing muscle fibers or around blood vessels. The appearance of the Congo red or metachromatic staining does not distinguish between the various subtypes of amyloidosis. Immunohistochemistry using antibodies directed against light chains, apolipoprotein A, gelsolin, and TTR and genetic testing is required to distinguish between the various forms of amyloidosis.

▶ **TABLE 14–2. AMYLOID NEUROPATHY**

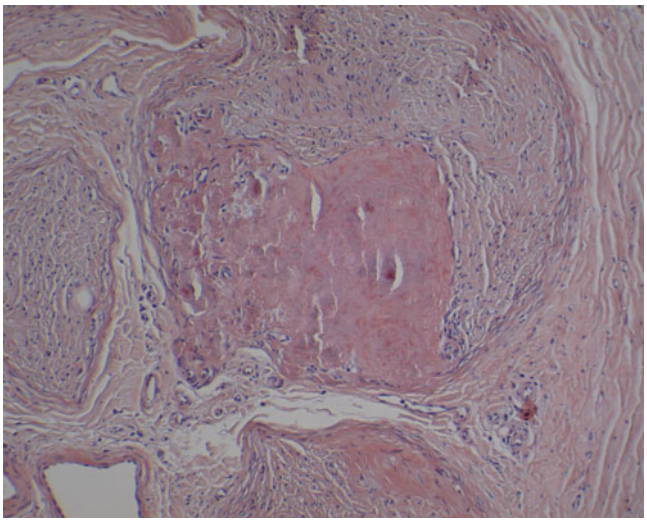
Acquired
Primary or AL amyloidosis
Secondary amyloidosis
Familial amyloid polyneuropathy (FAP)
Transthyretin-related amyloidosis (FAP types I and II)
Apolipoprotein A1-related amyloidosis (type III FAP or Van Allen type)
Gelsolin-related amyloidosis (FAP type IV, Finnish type)

PRIMARY OR AL AMYLOIDOSIS

Clinical Features

Patients with primary (AL) amyloidosis can present with nephrotic syndrome, congestive heart failure, cardiac arrhythmia, purpura, bruises, sicca syndrome, dyspnea due to pleural effusions, gastrointestinal dysmotility (nausea/constipation/diarrhea/pain), splenomegaly, hepatomegaly, lymphadenopathy, fatigue, weight loss, myopathy, carpal tunnel syndrome, or polyneuropathy typically.[130,131] It is more common in men over 50 years of age, which may help distinguish AL from familial amyloidosis, which usually presents earlier in adult life. However, AL amyloidosis can develop in the thirties and hereditary amyloidosis can present later in life.

Polyneuropathy develops in as many as 30% of patients with AL amyloidosis and can be the presenting manifestation.[131,132] There is an early predilection for small fiber modalities resulting in painful dysesthesias and burning sensations along with diminished pain and temperature sensation and allodynia on examination. The legs are usually affected in a symmetric, length-dependent fashion; however, the trunk can be involved and as many as 20% or more present asymmetrically in a mononeuropathy multiplex pattern.[133] Carpal tunnel syndrome ccurs in 25% of patients and may be the initial complication. Cranial nerves may be affected. The neuropathy is slowly progressive, and eventually weakness develops along with large fiber sensory loss. Most patients develop autonomic involvement with postural hypertension, syncope, impotence, bowel and bladder incontinence, constipation, impotence, and impaired sweating. Occasionally, enlarged peripheral nerves are



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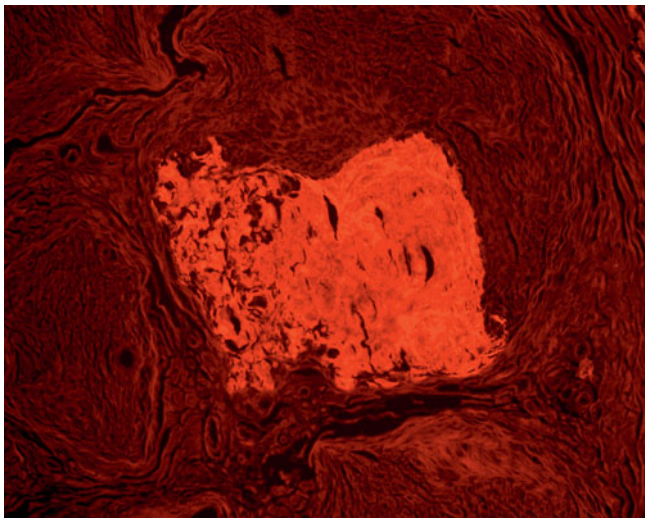

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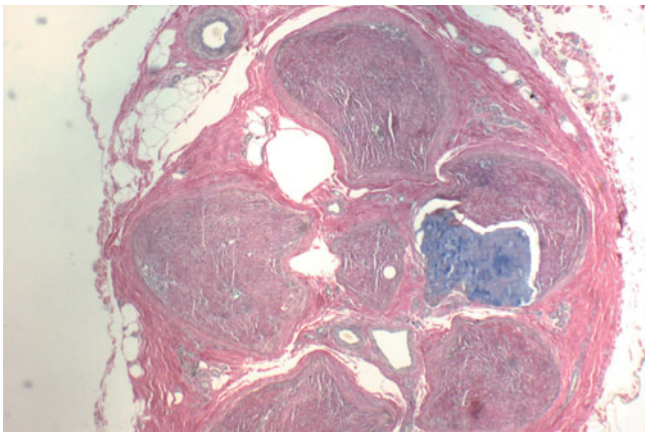

C

Figure 14–5. Familial amyloid polyneuropathy. Sural nerve biopsy in a patient with mutations in the transthyretin gene reveals large globular deposition of amyloid in the endoneurium that is appreciated using Congo red stain. (A) The amyloid stains pinkish-red under routine light microscope without polarization, and under rhodamine fluorescence (B) the amyloid deposition appears bright red. The amyloid deposit stains blue with Alcian blue (C).

appreciated by the astute clinician. The general physical examination can demonstrate limb edema, hoarse voice, hepatomegaly, and macroglossia. Patients generally die from their systemic illness (renal failure and cardiac disease).

Laboratory Features

The monoclonal protein be can be composed of IgG, IgA, IgM, or only free light chain. Lambda (λ) is more common than κ light chain (>2:1) in AL amyloidosis, in contrast to multiple myeloma in which κ light chains are more common. Immunoelectrophoresis or immunofixation of the serum and urine is more sensitive in identifying these light chains than serum or urine protein electrophoresis (SPEP or UPEP) and thus should be performed on patients with possible amyloid neuropathy, regardless of the results of the protein electrophoresis. Hypogammaglobulinemia, anemia, renal failure, proteinuria, and transaminitis due to liver involvement may be seen. The serum CK levels can also be elevated in patients with concurrent amyloid myopathy. The cerebral spinal fluid protein is often increased (with normal cell count), and thus the neuropathy may be mistaken for CIDP.

Sensory nerve action amplitudes are usually reduced or absent in involved nerves. When obtainable, the distal sensory latencies can be normal or only moderately prolonged and the conduction velocities are similarly normal or moderately slow. Motor conductions are less involved than the sensory conduction but, nonetheless, are frequently abnormal. Motor nerve conduction velocities can be normal or moderately reduced.[131,133–136] The distal motor latencies are normal or only moderately prolonged in the upper limbs and usually prolonged in the lower limbs. CMAP amplitudes are normal or only mildly reduced during the early course of the disease and not as severely affected as the

SNAP. The motor and sensory conduction abnormalities are usually symmetric but can be asymmetric in patients with multifocal neuropathies.[133] Electrophysiological evidence of superimposed median neuropathy at the wrist (carpal tunnel syndrome) is common.

Needle EMG examination usually reveals positive sharp waves and fibrillation potentials along with reduced recruitment of long-duration, high-amplitude, polyphasic MUAPs in affected muscles. Myotonic discharges and myopathic MUAPs, particularly in more proximal muscles, may be seen in patients with superimposed amyloid myopathy.

Histopathology

Nerve biopsies reveal axonal degeneration and severe loss of small myelinated and unmyelinated fibers. There is a less pronounced but obvious degeneration of the large myelinated nerve fibers as well. Congo red stains usually, but not always, amyloid deposition in either the globular or the diffuse pattern, infiltrating the perineurial, epineurial, and endoneurial connected tissue in blood vessel walls.[132] Amyloid deposition can also be demonstrated in the sympathetic and dorsal root ganglion. Because of the patchy, multifocal pattern of amyloid deposition, biopsies are not always diagnostic. Other sites commonly biopsied include the kidney, rectal mucosa, stomach, abdominal fat pad, salivary glands, muscle, and skin. Abdominal fat-pad biopsies seem to be the most sensitive method to detect amyloid deposits and these are found by this method in 85% of patients. Immunohistochemistry is helpful in demonstrating that the amyloid is composed of λ, or less frequently κ, light chains.

Pathogenesis

The pathogenic basis for the neuropathy associated with amyloidosis is unclear and may be multifactorial. Amyloid deposition in the epineurial and endoneurial connective tissue may lead to compression of nerve fibers with focal demyelination and axonal degeneration. Deposition around blood vessels might cause ischemic damage to nerve fibers.[137] Transport of nutrients into the erve and waste products out of the nerves may also be affected by amyloid deposition within the endoneurium and epineurium and around blood vessels.

Treatment

The prognosis of patients with primary amyloidosis is poor, with a median survival of less than 2 years. Death is generally secondary to progressive congestive heart failure or renal failure. Chemotherapy with melphalan, prednisone, colchicine that reduces the concentration of monoclonal proteins, and autologous stem cell transplantation may prolong survival.[138,139] Some studies have noted a benefit in the neuropathy,[138] while others have not.

FAMILIAL AMYLOID POLYNEUROPATHIES

Familial amyloid polyneuropathy (FAP) is phenotypic and genetic heterogeneic and is caused by mutations in the genes for TTR (prealbumin), apolipoprotein A1, or gelsolin.[127,135,140–145] Diagnosis of familial amyloidosis is made by detection of amyloid deposition in abdominal fat pad, rectal, or nerve biopsies and on genetic testing. Unlike, the nonhereditary forms of amyloidosis, monoclonal gammopathies are not present and the abnormal amyloid deposits do not immunostain for immunoglobulin light chains. However, these amyloid deposits may stain for TTR, apolipoprotein A1, or gelsolin.

Nerve biopsies in the different forms of FAP reveal findings similar to that seen in AL amyloidosis. Amyloid deposition can be multifocal or diffuse within the endoneurium, epineurium, or perineurium, as well as around blood vessels in autonomic ganglia and in peripheral nerves.[135,142] There is a loss of myelinated nerve fibers, particularly small myelinated and unmyelinated nerve fibers. These deposits encroach upon the nerve fibers, resulting in axonal degeneration and segmental demyelination. The clinical features, histopathology, and electrophysiological studies reveal abnormalities consistent with a generalized or multifocal, predominantly axonal but occasionally demyelinating, sensorimotor polyneuropathy.[18,139–146] The pathogenic bases for the FAP neuropathies are likely similar to that noted with AL neuropathy.

TTR-RELATED AMYLOIDOSIS (FAP TYPES I AND II)

Clinical Features

The majority of patients with FAP have mutations in the TTR gene. There appear to be two somewhat different clinical phenotypes associated with TTR-related amyloidosis: FAP I and a less severe FAP II. FAP I was originally reported in the Portuguese,[148] but it affects multiple ethnic groups with particularly large foci in Sweden and Japan.[124,140,143–145,149,150] Patients usually develop insidious onset of numbness and painful paresthesia in the distal lower limbs in the third to fourth decade of life, although some patients develop the disorder later in life.[149,150] Pain and thermal sensation are the most common modalities affected. Carpal tunnel syndrome is uncommon. Autonomic

involvement can be severe, leading to postural hypotension, constipation or persistent diarrhea, erectile dysfunction, and impaired sweating. Distal extremity atrophy and weakness develop over time along with occasional cranial neuropathies, leading to pupillary changes, decreased saliva secretion, diminished facial (including corneal) sensation, dysphonia, dysphagia, and facial weakness. Amyloid deposition also occurs in the heart, kidneys, liver, and the corneas. Patients usually die by the 10–15 years after the onset of symptoms from cardiac failure or complications from malnutrition.

A milder form of TTR-associated FAP (Type II FAP) was initially described in families in Indiana and Switzerland and is characterized by the development of carpal tunnel syndrome and later by a mild generalized sensorimotor polyneuropathy.[124,126,143] Although erectile dysfunction can be seen, severe autonomic dysfunction is unusual. As with FAP I, vitreous opacities may be appreciated. Although there can be systemic involvement, severe nephropathy or cardiomyopathy usually does not develop. Thus, most patients with FAP II have a relatively long survival, with little morbidity related to the amyloidosis. The symptoms of carpal tunnel syndrome can be relieved with surgical decompression.

Molecular Genetics and Pathogenesis

More than 80 different mutations within the TTR gene located on chromosome 18q11.2–12.1 have been associated with FAP types I and II.[127,143,146,151] A mutation involving a methionine to valine substitution at position 30 (Val30Met) in the TTR is the most common mutation associated with type I FAP, while serine substitutions at position 84 and histidine at position 58 are the most common mutations associated with FAP type II. There can be variability in the age of onset and severity even within families with the Val30Met mutations. TTR functions as a transport protein for vitamin A and thyroxin. Over 90% of the body's TTR is synthesized in the liver. The amino acid substitutions lead to the formation of the β-pleated sheet structure of the protein and its resistance to degradation by proteases, thus its amyloidogenic properties.

Treatment

Because the liver produces much of the body's TTR, liver transplantation has been used to treat FAP related to TTR mutations. Serum TTR levels decrease after transplantation and improvement in clinical and neurophysiological features has been reported.[146,151,152] However, abnormal TTR can continue to be synthesized in the CNS (by the choroid plexus) and within the eyes and potentially result in progressive deficits form local accumulation in these areas.

APOLIPOPROTEIN A1-RELATED AMYLOIDOSIS (TYPE III FAP OR VAN ALLEN TYPE)

Clinical Features

FAP type III was originally described by Dr. Van Allen in a family from Iowa.[153,154] The neuropathy usually manifests as numbness and painful dysesthesias in the lower limbs in the fourth decade of life. Gradually, the symptoms progress to the distal upper limbs and more proximally muscle weakness and atrophy develop. Although autonomic neuropathy is not severe, some patients develop diarrhea, constipation, or gastroparesis. Most patients die from systemic complications of amyloidosis (e.g., renal failure) 12–15 years after the onset of the neuropathy.

Molecular Genetics and Pathogenesis

FAP type III is caused by mutations leading to arginine for glycine substitution at position 26 in the apolipoprotein A1 gene on chromosome 11q23–qter.[155] Apolipoprotein A1 is a major component of high-density lipoproteins. As with TTR mutations, the amino acid substitution probably impairs its degradation by proteases.

GELSOLIN-RELATED AMYLOIDOSIS (FAP TYPE IV, FINNISH)

Clinical Features

FAP IV was initially described in Finland and is characterized by the combination of lattice corneal dystrophy and multiple cranial neuropathies (e.g., facial palsies and bulbar weakness).[156,157] Onset of symptoms is usually in the third decade of life. Over time, a mild generalized sensorimotor polyneuropathy develops. Autonomic dysfunction does not occur.

Histopathology

Autopsy studies have demonstrated a different distribution of amyloid deposition in FAP type IV than the other types of amyloidosis.[158] Histological, immunohistochemical, and electron microscopic studies revealed deposition of gelsolin amyloid, particularly in the vascular walls and perineurial sheaths. Nerve roots were more severely affected than distal nerves. The marked proximal nerve involvement with gelsolin-related angiopathy is an essential feature of FAP type IV. There was also preferential large fiber loss, not generally seen in other forms of amyloid neuropathy.

Molecular Genetics and Pathogenesis

Type IV amyloidosis is caused by mutations in the gelsolin gene on chromosome[159–161] Gelsolon is an actin-binding protein found in plasma, leukocytes, and other cell types. The resultant mutations and amino acid substitutions lead to a charge change on the protein, which may render the molecule resistant to proteases.

▶ SUMMARY

As discussed, neuropathies may complicate many different systemic disorders. It is important to distinguish neuropathies that may be directly related to the underlying disorder, caused by treatment (toxic neuropathy), or just be coincidental occurrence as management may differ according to the etiology. Thus, as discussed in Chapter 1 it is always important to take a detailed medical history and examination to assess for an underlying systemic disorder that may be associated with the neuropathy.

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CHAPTER 15

Neuropathies Associated with Infections

Neuropathies can develop as a direct result of various bacterial and viral infections, as well as an indirect or parainfectious autoimmune response to the infection (Table 15–1). Neuropathies as a consequence of parainfectious responses (e.g., Gullain–Barre syndrome associated with various infections and vasculitis associated with hepatitis) are discussed in detail in other chapters.

▶ LEPROSY (HANSEN DISEASE)

CLINICAL FEATURES

Leprosy is caused by infection by the acid-fast bacteria *Mycobacterium leprae*. Leprosy is the most common cause of peripheral neuropathy in Southeast Asia, Africa, and South America. There is a spectrum of clinical manifestations ranging from tuberculoid leprosy at one end to lepromatous leprosy on the other end of the spectrum, with borderline leprosy in between (Table 15–2).[1–3] The clinical manifestations of the disease are determined by the immunological response of the host to the infection.

In tuberculoid leprosy, the cell-mediated immune response is intact.[1,2,4] Thus, there are focal, circumscribed inflammatory responses to the bacteria within the affected areas of skin and nerves. The resulting skin lesions appear as well-defined, scattered hypopigmented patches and plaques with raised, erythematous borders (Figs. 15–1 and 15–2). Cutaneous nerves are often affected, resulting in a loss of sensation in the center of these skin lesions. Cooler regions of the body (e.g., face and limbs) are more susceptible than warmer regions such as the groin or axilla. In addition, the ulnar nerve at the medial epicondyle, the median nerve at the distal forearm, the peroneal nerve at the fibular head, the sural nerve, the greater auricular nerve, and the superficial radial nerve at the wrist are common sites of involvement and become encased with granulomas, leading to mononeuropathy or mononeuropathy multiplex. These nerves are thickened and often palpable.

In lepromatous leprosy, cell-mediated immunity is severely impaired, leading to extensive infiltration of the bacilli and hematogenous dissemination, producing confluent and symmetrical areas of rash, anesthesia, and anhidrosis.[1,2,4] The clinical manifestations tend to be more severe in the lepromatous subtype. As in the tuberculoid form, there is a predilection for involvement of cooler regions of the body. Infiltration of the organism in the face leads to the loss of eyebrows and eyelashes and exaggeration of the natural skin folds, leading to the so-called "leonine facies." Superficial cutaneous nerves of the ears and distal limbs are also commonly affected. A slowly progressive symmetric sensorimotor polyneuropathy gradually develops due to widespread invasion of the bacilli into the epi-, peri-, and endoneurium. Distal extremity weakness may be seen, but large sensory fiber modalities and muscle stretch reflexes are relatively spared. Involvement of nerve trunks leads to superimposed mononeuropathies, including facial neuropathy.

Neuropathies are most common in patients with borderline leprosy.[1,2,4] Patients can develop generalized symmetric sensorimotor polyneuropathies, mononeuropathies, and mononeuropathy multiplex, including multiple mononeuropathies in atypical locations, such as the brachial plexus. Borderline leprosy is associated with clinical and histological features of both the lepromatous and the tuberculoid forms of leprosy (Table 15–2, Fig. 15–3). There is partial impairment in cellular immunity in patients with borderline leprosy such that there is some degree of mycobacterial spread as well as an inflammatory response. The immunological state is considered unstable in patients with borderline leprosy in that the immune response and clinical manifestations can shift up and down the spectrum.

Patients with leprosy may present with isolated peripheral neuropathy without skin lesions, particularly in endemic areas.[5,6] Most cases of the so-called pure neuritic leprosy have the tuberculoid or borderline tuberculoid subtypes of the disease.

LABORATORY FEATURES

Sensory nerve conduction studies (NCS) are usually absent in the lower limb and are reduced in amplitude in arms.[1,6,7] Motor NCS may demonstrate reduced amplitudes in affected nerves.[7,8] Motor NCS are normal or slightly reduced; however, a few patients may demonstrate values less than 20 m/s in both the upper and the lower limb. Electromyography (EMG) reveals mild-to-moderate degrees of active denervation. The pattern of involvement on the EMG and NCS can be generalized

TABLE 15–1. INFECTIOUS AGENTS ASSOCIATED WITH NEUROPATHIES

Bacterial:
Mycobacterium leprae (Leprosy)
Borrelia burdorferi (Lyme disease)
Corynebacterium diphtheriae (Diphtheria)

Viral:
Human immunodeficiency virus (HIV)
- Distal symmetric polyneuropathy
- Acute inflammatory demyelinating polyradiculoneuropathy
- Chronic inflammatory demyelinating polyradiculoneuropathy
- Other polyradiculoneuropathy
- Mononeuropathy multiplex
- Autonomic neuropathy
- Sensory ganglionopathy

Human T-lymphocytic type 1 (HTLV-1)
Cytomegalovirus (CMV)
Hepatitis B and C
Herpes varicella zoster (HVZ)

as symmetric or reflective of a mononeuropathy or multiple mononeuropathies, as apparent from the clinical features.

HISTOPATHOLOGY

Leprosy is usually diagnosed with skin lesion biopsy and using the Fite method to stain the acid-fast bacilli red.[2] Nerve biopsies can also be diagnostic, particularly when there are no apparent skin lesions. The host's immune response to the bacilli determines the histopathology (Table 15–2).[2,3,6] The tuberculoid form is characterized by granulomas formed by macrophages and Th1 cells, which are surrounded by Th2 cells. Caseation may or may not be present, and typical lesions extend throughout the dermis. Importantly, bacilli are not seen. In contrast with lepromatous leprosy, large number of infiltrating bacilli, Th2 lymphocytes,

TABLE 15–2. CLINICAL, LABORATORY, IMMUNOLOGICAL, AND HISTOPATHOLOGICAL FEATURES OF LEPROSY

	Tuberculous Leprosy (TT)	Mid-Borderline Leprosy (BB)	Lepromatous Leprosy (LL)
Lepromin test	Positive (>5 mm induration)	+/− (2–5 mm induration)	Negative (0–2 mm induration)
Bacterial index	0	2–4	5–6
Morphological index (MI)	Low (down to zero)	Moderate	High (up to 10)
Immunology	Cell-mediated immunity: intact; Th 1 > Th2 lymphocytes; cytokines expressed: IL-2 and γ-IF	Cell-mediated immunity: unstable (can range and switch from intact to absent)	Cell-mediated immunity: absent; Th 2 > Th1 lymphocytes; cytokines expressed: IL-4, IL-5, and IL-10
Skin lesions	Few localized and well-demarcated large skin lesions; erythematous macules and plaques with raised borders; centers of lesions may be hypopigmented	Size, number, and appearance of the skin lesions are intermediate between that seen in the TT and LL poles	Multiple, symmetrical small macules and papules; older lesions form plaques and nodules
Histopathology	Localized granulomas and giant cells encompassed by dense lymphocytic infiltrate extending to epidermis; Fite stain: negative for bacteria	Granulomas with epithelioid cells but no giant cells. Not localized by zones of lymphocytes. Lymphocytes, if present, are diffusely infiltrating Fite stain: slightly positive	Scant lymphocytes, but if present diffuse along with organism-laden foamy macrophages Fite stain: marked positive
Neuropathies	Mononeuropathy of the superficial cutaneous nerves or large nerve trunks (i.e., ulnar, median, and peroneal nerves), multiple mononeuropathies; pure neuritic leprosy may be seen	The neuropathies can range in the spectrum of that seen in TT to LL	Distal symmetric sensory and sensorimotor polyneuropathies are more common than mononeuropathy; pure neuritic leprosy is not seen
Treatment*	Dapsone 100 mg/d Rifampin 600 mg/d Duration 12 months	As per LL	Dapsone 100 mg/d Rifampin 600 mg/d Clofazimine 50 mg/d Duration: 2 yr or until skin smears (MI) is zero.

The features of the borderline tuberculoid (BT) form ranges between the TT and BB forms. The features of the borderline lepromatous (BL) form ranges between that seen in BB and LL forms of leprosy.
*Treatment is as recommended by the Hansen Disease Center, Carville, LA.
IL, interleukin.
With permission from Altman D, Amato AA. Lepromatous neuropathy. J Clin Neuromusc Dis 1999;1:68–73.

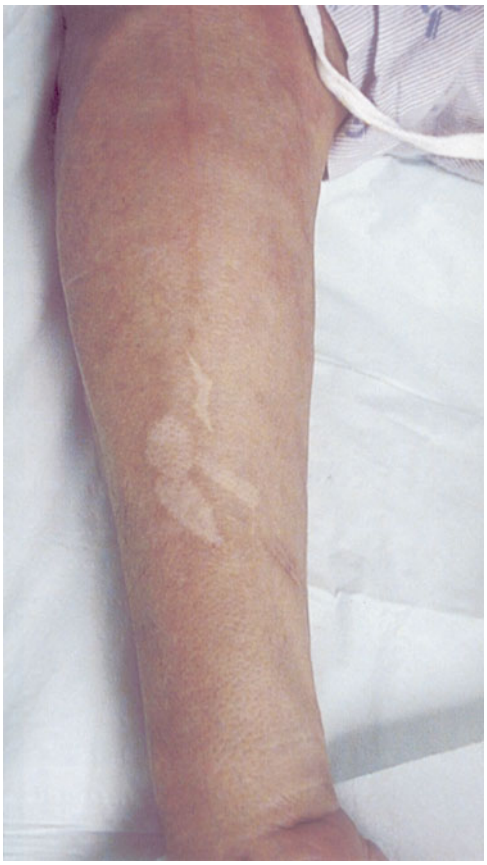


Figure 15–1. Tuberculoid leprosy. Hypopigmented skin lesions are evident on lateral aspect of forearm in a patient with tuberculoid leprosy.

and organism-laden, foamy macrophages with minimal granulomatous infiltration are evident (Fig. 15–3A). The bacilli are best appreciated using the Fite stain where they can be seen as red staining rods often in clusters free in the endoneurium, within macrophages, or within Schwann cells (Fig. 15–3B). On electron microscopy, the bacilli appear as dense osmiophilic rods surrounded by a clear halo (Fig. 15–3C and D). Borderline leprosy can have histological features of both tuberculoid and lepromatous leprosy. The morphological index, a ratio of viable to nonviable organisms, can be used to measure treatment response. The morphological index, which is between one and 10 at treatment onset, often falls to zero within 3–4 months of successful therapy. Polymerase chain reaction may also be used for diagnosis.

PATHOGENESIS

The clinical and pathological spectrum of the disease is dependent on the host's immune response to *M. leprae* and reflects the relative balance between Th1 (helper) and Th2 (suppressor) T cells (Table 15–2).[1–4] The tuberculoid form defines one end of the spectrum, in which the Th1 cells predominate. The Th1 cells produce interleukin-2 and gamma-interferon, which in turn leads to activation of macrophages. On the other extreme, the lepromatous form is dominated by Th2 cells, which produce interleukin-4, interleukin-5, and interleukin-10, thereby downregulating cell-mediated immunity and inhibiting macrophages. The borderline subtypes exhibit immune responses spanning the spectrum between the tuberculoid and lepromatous forms.

TREATMENT

Patients are generally treated with multiple drugs: dapsone, rifampin, and clofazimine. Other medications that are employed include thalidomide, perfloxacin, ofloxacin, sparfloxacin, minocycline, and clarithromycin (Table 15–2).[1–3] Patients are usually treated for 2 years.

Treatment is sometimes complicated by the so-called reversal reaction, particularly in borderline leprosy.[1,2] The reversal reaction can occur at any time during treatment and develops because of a shift to the tuberculoid end of the spectrum, with an increase in cellular immunity during treatment. The cellular response is upregulated, as evidenced by an increased release of tumor necrosis factor-alpha, gamma-interferon, and interleukin-2 with new granuloma formation. This can result in an exacerbation of the rash and the neuropathy as well as even the appearance of new lesions. High-dose corticosteroids blunt this adverse reaction and may even be used prophylactically in high-risk patients at treatment onset.

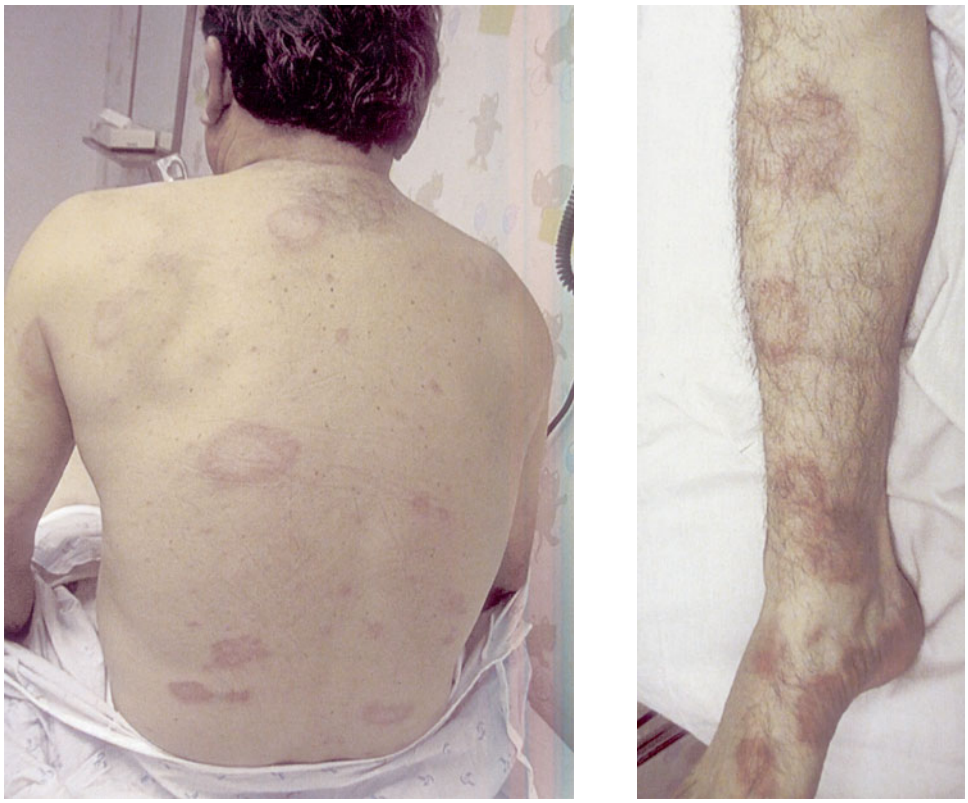
Erythema nodosum leprosum is another adverse reaction that occurs usually during treatment of patients with lepromatous leprosy.[1,2] Multiple erythematous, sometimes painful, subcutaneous nodules appear and may be associated with worsening of the neuropathy. Erythema nodosum leprosum probably results from slow degradation of bacilli and release of new antigens. Subsequently, antigen–antibody complexes form and complement is activated affected tissue. Erythema nodosum leprosum is commonly treated with corticosteroids orthalidomide.

Prevention of leprosy is of primary importance. It is recommended that children exposed to leprosy in the household be prophylactically treated with rifampin daily for 6 months.[1,2] Various vaccinations are available, including BCG, killed leprae, and chemically modified organism.

▶ LYME DISEASE

CLINICAL FEATURES

Lyme disease is caused by infection with *Borrelia burgdorferi*, a spirochete, transmitted by ticks. The deer tick, *Ixodes dammini*, is responsible for the disease in



A B

Figure 15–2. Borderline leprosy. A patient with borderline leprosy has multiple skin lesions with hypopigmented center with raised erythematous borders on the back (A) and on the leg (B). (With permission from Amato AA, Dumitru D. Acquired Neuropathies. In Dumitru D, Amato AA, Swartz MJ (eds). Electrodiagnostic Medicine, 2nd edn. Philadelphia: Hanley & Belfus, 2002, Fig. 23–8, p. 973.)

most cases. Ticks acquire the spirochetes by feeding on infected host (e.g., deer) and then transmits the spirochetes to the next hosts (e.g., humans) at a latter feed. It takes approximately 12–24 hours of tick attachment to transfer the spirochetes to the next host.

There are three recognized stages of Lyme disease: (1) early infection with localized erythema migrans, (2) disseminated infection, and (3) late-stage infection. Within 1 month of a tick bite, erythematous circular region appears around the area of the original tick bite and gradually expands, with the center of the lesion becoming clear creating a bull's eye appearance. The rash resolves spontaneously after approximately a month. Importantly, not all patients with Lyme disease develop erythema migrans. The second stage of the illness is marked by dissemination of the spirochetes throughout the body, and patients develop systemic symptoms including fever, chills, localized adenopathy, fatigue, myalgias, headache, neck and back pain, and additional skin lesions about the body. Cardiac involvement may lead to pericarditis and heart block. Inflammatory arthritis of large and small joints may also occur.

Neurological complications may develop during the second and third stages of infection (Table 15–3).[9–17] Facial neuropathy is most common and is bilateral in about half of cases, which is rare for idiopathic Bell's palsy. Involvement of nerves is frequently asymmetric. The presentation with a polyradiculoneuropathy may resemble GBS.

The late stage of infection is characterized by further destructive inflammatory changes in the joints. The distal extremities develop a bluish discoloration of the skin (acrodermatitis chronica atrophicans). Spirochetes may be readily cultured from biopsy of these sites. Approximately 50% of patients have numbness, paresthesia, weakness, and cramps in the distal extremities, and proprioception and vibration are reduced as are muscle stretch reflexes.

LABORATORY FEATURES

Immunofluorescent or enzyme-linked immunoabsorbent assay may detect antibodies directed against the

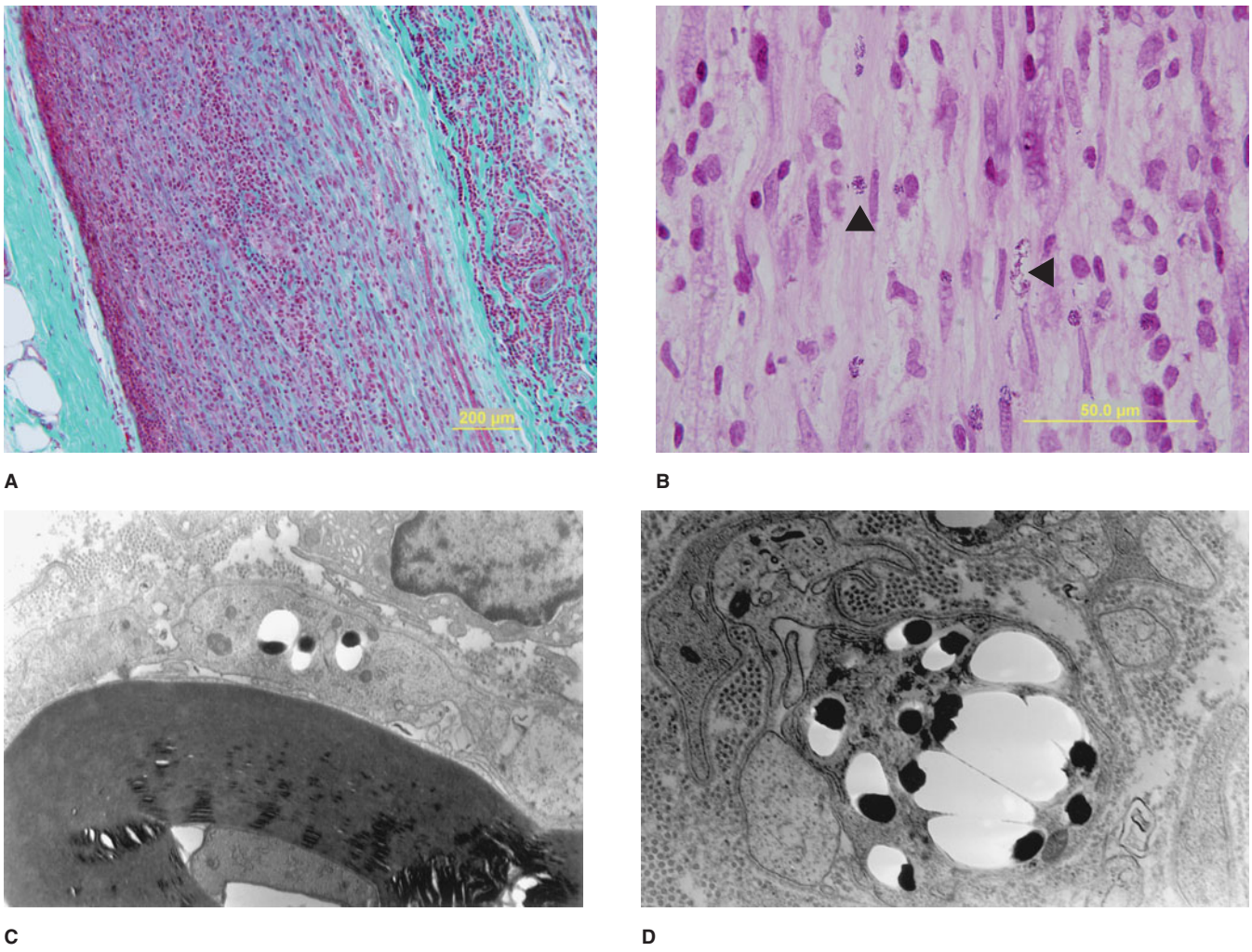


Figure 15–3. Borderline leprosy. Sural nerve biopsy perivascular and diffuse endoneurial inflammation consisting of lymphocytes and macrophages, paraffin section stained with trichrome (A). Fite stain reveals red staining bacilli (the so-called "red snappers") sometimes in clusters in the endoneurium and within Schwann cells (B). Electron microscopy reveals electron-dense bacilli with surrounding clear halos within the cytoplasm of a Schwann cell surrounding a myelinated axon (C) and on higher power within a Schwann cell surrounding unmyelinated axons (D).

spirochete. False-positive reactions are not uncommon, and, therefore, Western blot analysis should be performed to confirm a positive enzyme-linked immunoabsorbent assay. Examination of the cerebrospinal fluid (CSF) should demonstrate lymphocytic pleocytosis and increased protein in patients with polyradiculitis, cranial neuropathies, and central nervous system involvement.

▶ **TABLE 15–3. NEUROPATHIES ASSOCIATED WITH LYME DISEASE**

Encephalitis/meningitis
Myelitis
Cranial neuropathies (e.g., facial nerve palsy)
Peripheral neuropathy
Mononeuropathies
Multiple mononeuropathies
Radiculopathy
Plexopathy
Inflammatory myopathy

Electrodiagnostic studies are suggestive of a primary axonopathy. Patients with mononeuropathy or mononeuropathy multiplex NCS reveal reduced compound muscle action potential (CMAP) and sensory nerve action potential (SNAP) amplitudes.[9,13–18] H-reflexes may be absent. Those with facial nerve palsies have reduced facial nerve CMAPs and abnormal blink reflexes.[11] The electrophysiological abnormalities are often asymmetric.[18,19] Needle EMG reveals increased insertional and spontaneous activity in the form of fibrillation potentials and positive sharp waves and decreased recruitment of neurogenic-appearing motor unit action

potentials (MUAPs). Rarely, affected patients develop an inflammatory myopathy as opposed to neuropathy.[20]

HISTOPATHOLOGY

Nerve biopsies can reveal perivascular infiltration of plasma cells and lymphocytes around small endoneurial, perineurial, and epineurial blood vessels without clear necrotizing vasculitis. Axonal degeneration and secondary demyelination can be seen.

PATHOGENESIS

Peripheral nerve involvement may be the result of an indirect immunological response and/or some form of vasculopathy.

TREATMENT

Recommended treatment of facial nerve palsies in adults is the combination of amoxicillin 500 mg p.o. q.i.d. plus probenecid 500 mg q.i.d. for 2–4 weeks. Patients who are allergic to penicillin can be treated with doxycycline 100 mg p.o. b.i.d. for 2–4 weeks. Children less than 4 years of age can be treated with amoxicillin 20–40 mg/kg/d in four divided doses for 2–4 weeks. If allergic to penicillin, children can be treated with erythromycin 30 mg/kg/d in four divided doses for 2–4 weeks.

Adult patients with other types of peripheral neuropathy are treated with intravenous (IV) penicillin 20–24 million units/d for 10–14 days or ceftriaxone 2 g IV qd for 2–4 weeks. Those allergic to penicillin should receive doxycycline 100 mg p.o. b.i.d. for 30 days. Children with Lyme neuropathy can receive IV penicillin G 250,000 U/kg/d in divided doses for 10–14 days or ceftriaxone 50–80 mg/kg/d IV for 2–4 weeks.

▶ DIPHTHERITIC NEUROPATHY

CLINICAL FEATURES

Diphtheria is caused by the bacteria *Corynebacterium diphtheriae*. Individuals who are infected present with "flu-like" symptoms of generalized myalgias, headache, fatigue, low-grade fever, and irritability within a week to 10 days of the exposure. A whitish membranous exudate may be appreciated in the pharynx with or without swollen or tender cervical lymph nodes. Cardiovascular involvement can manifest as cardiac arrhythmias and hypotension. About 20–70% of patients develop a peripheral neuropathy caused by a toxin released by the bacteria.[21–24] Three to 4 weeks after infection, patients may note decreased sensation in their throat and begin to develop dysphagia, dysarthria, or hoarseness. Around the same time, patients develop blurred vision, particularly when looking at near objects, and the pupils are noted to react to light but fail to accommodate. Additional cranial nerves may also become involved. Respiratory weakness can develop due to phrenic nerve involvement. A generalized polyneuropathy may manifest 2 or 3 months following the initial infection characterized by numbness, paresthesia, and weakness of the arms and legs. Neurological examination reveals a reduction to all sensory modalities. Distal greater than proximal weakness is seen but weakness may progress over a period of weeks such that patients are unable to ambulate. Muscle stretch reflexes are diminished or absent throughout. Rarely, the bowel and bladder are affected.

LABORATORY FEATURES

Cerebral spinal fluid (CSF) protein can be elevated with or without lymphocytic pleocytosis.[25] Sensory NCS often reveal absent SNAPs.[23] Motor NCS demonstrate markedly reduced conduction velocities (<50% of mean values) in the arms and legs.[22,23,25,26] The distal motor latencies are only mildly to moderately prolonged. The NCS become abnormal by 2 weeks following onset of neuropathic symptoms and maximize by 5–8 weeks. Subsequently, there is slow and steady improvement in the NCS that lag behind clinical recovery.

HISTOPATHOLOGY

Segmental demyelination and axonal degeneration are appreciated in the nerve roots, dorsal root ganglia, and the more distal segments of the peripheral nerve.[21]

PATHOGENESIS

The bacteria release diphtheria toxin, which binds to Schwann cells and inhibits synthesis of myelin proteins.[27]

TREATMENT

Antitoxin and antibiotics should be given within 48 hours of symptom onset. Although early treatment reduces the incidence and severity of some complications (i.e., cardiomyopathy), it does not appear to alter the natural history of the associated peripheral neuropathy. The neuropathy usually resolves after several months.

TABLE 15–4. NEUROLOGICAL COMPLICATIONS ASSOCIATED WITH HIV INFECTION

Central nervous system
Opportunistic infections
Progressive multifocal leukoencephalopathy
HIV-associated encephalopathy (AIDS dementia)
Lymphomas and other malignancies
Subacute combined degeneration (B12 deficiency)
Vacuolar myelopathy
Peripheral nervous system disorders
Distal symmetric polyneuropathy
Motor neuronopathy
Acute and chronic inflammatory demyelinating polyradiculoneuropathy
Polyradiculoneuropathy/multiple mononeuropathies caused by other infections (e.g., cytomegalovirus, hepatitis B or C, and herpes zoster)
Autonomic neuropathy
Sensory ganglionopathy
Toxic neuropathy (antiretroviral medications)
Myopathy
Toxic myopathy (antiretroviral medications)
Inflammatory (polymyositis or inclusion body myositis)
Infectious (opportunistic infections)
Myopathy secondary to wasting cachexia

HUMAN IMMUNODEFICIENCY VIRUS (HIV)

HIV infection can result in a variety of neurological complications (Table 15–4) including peripheral neuropathies. Approximately 20% individuals with HIV infection develop a neuropathy as a direct result of the virus itself, other associated viral infections (e.g., cytomegalovirus [CMV] infection), or neurotoxicity secondary to antiviral medications.[28–30] The neuropathy associated with antiviral medications are discussed in Chapter 18. The major presentations of peripheral neuropathy associated with HIV infection include (1) distal symmetric polyneuropathy (DSP), (2) inflammatory demyelinating polyneuropathy (including both AIDP and CIDP), (3) multiple mononeuropathies (e.g., vasculitis, CMV related), (4) polyradiculopathy (usually CMV related), (5) autonomic neuropathy, and (6) sensory ganglionitis.[31–38]

HIV-RELATED DISTAL SYMMETRIC POLYNEUROPATHY (DSP)

CLINICAL FEATURES

DSP is the most common form of peripheral neuropathy associated with HIV infection and usually is seen in patients with AIDS.[28,29,39] It is characterized by numbness and painful paresthesia involving the distal legs and arms. Some patients are asymptomatic but have reduced sensation to all modalities on examination. Mild distal muscle weakness may be appreciated. Proximal leg and distal arm weakness may develop late in the course of the disease. Muscle stretch are reduced at the ankles but are relatively preserved at the knees and in the arms.

LABORATORY FEATURES

CSF examination may demonstrate an increased protein and mild lymphocytic pleocytosis in patients with HIV infection, regardless of the stage of the infection and the presence or absence of peripheral neuropathy.[40,41] Vitamin B12 deficiency is noted in some[42,43] but not all patients.[44–46] NCS reveal abnormalities suggestive of a symmetric, axonal sensory greater than motor polyneuropathy.[28,30,47–50]

HISTOPATHOLOGY

Nerve biopsies reveal axonal degeneration and a loss in the total number of both myelinated and demyelinated axons (Fig. 15–4).[35,47,50–53] A reduction of cell bodies in the dorsal root ganglia may be appreciated, as well as secondary degeneration of the dorsal columns. Mild perivascular inflammation consisting of macrophages and T lymphocytes is seen along with evidence of increased cytokine expression. Reduced density of small myelinated epidermal nerve fibers is appreciated on in the epidermis skin biopsies.[54]

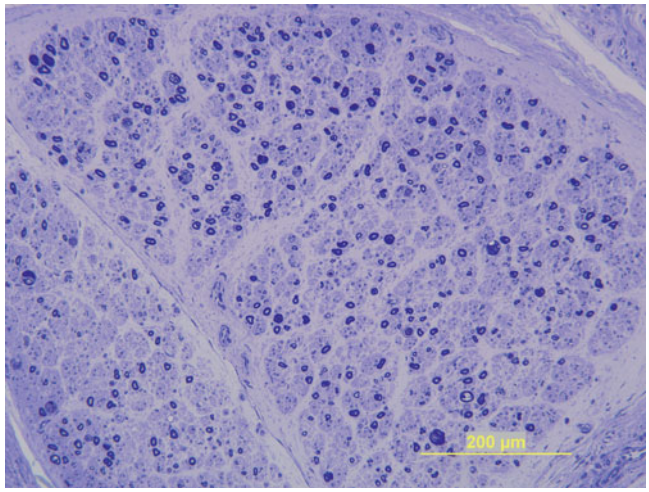


Figure 15–4. HIV neuropathy. Sural nerve biopsy in a patient with distal symmetric sensory neuropathy demonstrates a mild reduction in myelinated nerve fibers. Epoxy embedded, toluidine blue stain.

PATHOGENESIS

The pathogenic basis for DSP is unknown but is not due to actual infection of the peripheral nerves. The neuropathy may be immune mediated, perhaps caused by the release of cytokines from surrounding inflammatory cells. Vitamin B12 deficiency may contribute to some cases but is not a major cause of most cases of DSP. Various antiretroviral agents (e.g., dideoxycytidine, dideoxyinosine, and stavudine) are also neurotoxic and can cause a painful sensory neuropathy.[49,55,56] However, DSP can occur in patients not previously exposed to antiretroviral agents.

TREATMENT

The neuropathy is not responsive to treatment with antiretroviral medications and therapy is largely symptomatic. We usually initiate treatment with lidoderm patches and neurontin.

▶ HIV-RELATED INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY

CLINICAL FEATURES

Both AIDP and CIDP can occur as a complication of HIV infection.[39,57] AIDP usually develops at the time of seroconversion, while CIDP can occur anytime in the course of the infection. Clinical features are indistinguishable from idiopathic AIDP or CIDP.

LABORATORY FEATURES

In addition to elevated protein levels, lymphocytic pleocytosis is evident in the CSF— a finding that helps distinguish this HIV-associated polyradiculoneuropathy from idiopathic AIDP/CIDP. Motor and sensory NCS are similar to that seen in idiopathic AIDP and CIDP (Chapters 11 and 12).[26,57–59] Motor and sensory NCS may demonstrate slow conduction velocities, prolonged distal latencies and F-waves, conduction block or temporal dispersion.

HISTOPATHOLOGY

Nerve biopsies are identical to that of idiopathic AIDP and CIDP.[26,51]

TREATMENT

We treat patients with HIV-associated AIDP or CIDP with intravenous immunoglobulin (IVIG) or plasmapheresis (PE).[26,58] Prednisone can be used in CIDP, but we try to avoid steroids and other second-line immunosuppressive agents because of the long-term implications of immunosuppression in patients with HIV.

▶ HIV-RELATED PROGRESSIVE POLYRADICULOPATHY (SECONDARY CMV INFECTION)

CLINICAL FEATURES

An acute, progressive lumbosacral polyradiculoneuropathy secondary to CMV infection can develop in patients with AIDS.[39] Patients usually present with severe radicular pain, numbness, and weakness in the legs, which is usually asymmetric. Loss of perineal sensation with bowl and bladder incontinence is common. The arms and cranial nerves may also be affected. Reduced or absent muscle stretch reflexes are appreciated on examination. Plantar responses are usually flexor but can be extensor if a superimposed CMV myelitis is also present. Patients usually have evidence of CMV infection in other parts of the body (i.e., CMV retinitis).

LABORATORY FEATURES

CSF is abnormal, demonstrating an increased protein along with reduced glucose concentration and notably a neutrophilic pleocytosis. CMV can be cultured from the CSF, blood, and urine. NCS often demonstrate an asymmetric reduction of amplitudes of the SNAPs and CMAPs, with active denervation changes on EMG in muscles innervated by affected nerve roots and nerves.[60,61] These abnormalities are quite distinct from those found in both CIDP and DSP helping to differentiate these various disorders.

HISTOPATHOLOGY

Inflammatory infiltrates associated with varying degrees of axonal loss are evident in the ventral and dorsal roots, particularly in the lumbar regions. Occasionally, the cranial nerve root exiting from the brainstem may be involved with adjacent myelitis. CMV inclusions may be found in endothelial cells and macrophages on the nerve biopsy specimens.[62]

PATHOGENESIS

The polyradiculoneuropathy may be caused by the direct infection of neurons by CMV or ischemia secondary to associated vasculitis.

TREATMENT

The polyradiculoneuropathy may improve with gancyclovir or foscarnet, if treatment is started early.[61,63] However, the prognosis is poor, and most patients die within several weeks or months.

▶ HIV-RELATED MULTIPLE MONONEUROPATHIES

CLINICAL FEATURES

Multiple mononeuropathies can also develop in patients with HIV infection, usually in the context of AIDS.[39] Weakness, numbness, paresthesia, and pain are evident in the distribution of affected nerves.

LABORATORY FEATURES

Elevated CSF protein and mononuclear pleocytosis may be seen. EMG and NCS demonstrate features seen with other forms of multiple mononeuropathies caused by vasculitis (see Chapter 13).[64]

HISTOPATHOLOGY

Nerve biopsies can reveal axonal degeneration with necrotizing vasculitis or perivascular inflammation.[65] CMV inclusions may be seen in endothelial cells and macrophages on.[62]

PATHOGENESIS

The pathogenic basis for this disorder is likely multifactorial. The neuropathy may be caused by vasculitis related to deposition of HIV antigen–antibody complexes in the walls of blood vessel, concomitant hepatitis B or C infection, or CMV infection.

TREATMENT

Corticosteroid treatment is indicated in vasculitis directly due to HIV infection. Multiple mononeuropathies secondary to concurrent hepatitis B or C infection can be treated with plasma exchange, antiviral agents (e.g., vidarabine), or α-interferon. Short courses of prednisone and cyclophosphamide may be necessary. If CMV is suspected, treatment with gancyclovir or foscarnet should be initiated.

▶ HIV-RELATED AUTONOMIC NEUROPATHY

CLINICAL FEATURES

An autonomic neuropathy characterized by orthostatic hypotension, impaired sweating, diarrhea, impotence, and bladder dysfunction can develop acutely or insidiously in patients with HIV infection.[66–68] Clinical features are similar to those seen with idiopathic autonomic neuropathy.

LABORATORY FEATURES

CSF can reveal pleocytosis and increased protein. Most patients have electrodiagnostic features similar to that noted in DSP. In addition, autonomic function testing is usually abnormal.[67]

PATHOGENESIS

An immune-mediated mechanism similar to that suspected in idiopathic autonomic neuropathy is likely.

TREATMENT

A trial of corticosteroids IVIG or PE may be tried. Symptoms of autonomic neuropathy are treated symptomatically.

▶ HIV-RELATED SENSORY NEURONOPATHY/ GANGLIONOPATHY

Dorsal root ganglionitis is a very rare complication of HIV infection, and neuronopathy can be the presenting manifestation.[69] Patients develop sensory ataxia similar to idiopathic sensory neuronopathy/ganglionopathy. Autopsies have demonstrated inflammatory cell infiltrate in the dorsal root ganglia along with the loss of cell bodies and degeneration of myelinated nerve fibers in the peripheral nerves. NCS reveal amplitudes or absence of SNAPs. Again, a trial of corticosteroids, IVIG, or PE may be warranted.

▶ HUMAN T-LYMPHOCYTE TYPE 1 INFECTION

Besides the more common myelopathy (tropical spastic paraparesis), human T-lymphocyte type 1 infection is also associated with an axonal sensorimotor polyneuropathy.[70,71] The neuropathy can be seen even in patients without a myelopathy. Human T-lymphocyte type 1 is also associated with a myositis. NCS demonstrate abnormalities suggestive of an axonal, sensory greater than motor, length-dependent neuropathy. Sural nerve biopsy can reveal axonal degeneration with secondary demyelination and inflammatory cell infiltrates.

▶ CYTOMEGALOVIRUS

CMV can cause an acute lumbosacral polyradiculopathy and multiple mononeuropathies in patients with HIV infection or in those severely immunosuppressed as previously noted.

▶ EPSTEIN–BARR VIRUS

Epstein–Barr virus infection has been associated with AIDP, cranial neuropathies, mononeuropathy multiplex, brachial plexopathy, lumbosacral radiculoplexopathy, and sensory neuronopathies.[72]

▶ HEPATITIS VIRUSES

Hepatitis B and C can cause multiple mononeuropathies related to vasculitis, AIDP, or CIDP, as previously discussed (Chapters 11 and 12).

▶ HERPES VARICELLA-ZOSTER VIRUS

CLINICAL FEATURES

Peripheral neuropathy from herpes varicella-zoster (HVZ) infection is the result of reactivation of latent virus or a primary infection. Primary infection is the cause of "chicken pox." Reactivation of the virus later in life leads to dermal zoster. In patients who are immunocompromised, HVZ infection can be associated with severe disseminated zoster.

Two-thirds of infections in adults are characterized by dermal zoster in which severe pain and paresthesias develop in a dermatomal region, followed within a week or 2 by a vesicular rash in the same distribution. The vesicular skin lesions clear by 2 weeks; however, approximately 25% of patients who are affected have continued pain (postherpetic neuralgia). In a large series of patients, zoster developed in thoracic dermatomes in nearly 50%, lumbosacral region in 18%, trigeminal distribution in the head in an additional 18%, and the cervical dermatomes in the remainder.

Weakness in muscles innervated by roots corresponding to the dermatomal distribution of skin lesions occurs in 5–30% of patients.[73–75] The weakness usually develops within the first 2 weeks of the skin eruption but can vary between several hours and a month. Unilateral phrenic nerve involvement can lead to hemidiaphragmatic paralysis.[76] When the thoracic myotomes are involved, hernias can occur through weakened abdominal wall musculature.[77,78] Muscle strength usually improves over time.[520] Rarely, patients develop AIDP following HVZ infection.[79,80] Additional neurologic manifestations of herpes zoster infection include encephalitis and angiitis leading to vascular events.

LABORATORY FEATURES

There is elevated CSF protein concentrations with or without pleocytosis. The virus is difficult to culture from the CSF, but polymerase chain reaction can be used to confirm the presence of the virus in the CSF. Sensory NCS reveal reduced or absent SNAPs in affected nerves.[81–83] Motor NCS demonstrate normal reduced CMAP amplitudes.[74,75,81,83] Positive sharp waves and fibrillation potentials and neurogenic-appearing MUAPs and recruitment can be observed on needle EMG in muscles of affected myotomes.[74,75,81,83]

HISTOPATHOLOGY

The basic pathologic neural reaction is that of axonal degeneration with some degree of secondary segmental demyelination. With respect to the sensory system, severe infections can result in the destruction of dorsal root ganglion cells with the secondary loss of posterior column fibers.

PATHOGENESIS

Following initial infection, the HVZ migrates up the sensory nerves and takes residence in the sensory ganglia, where the virus appears to be insulated from the host's immune defense mechanisms. When the host becomes immunosuppressed, the virus can reactivate and replicate. HVZ travels down the sensory nerves including cutaneous nerves and result in the typical zoster lesions. Local neuritis in the spinal nerve and involvement of motor axons lead to muscle weakness.

TREATMENT

Acyclovir helps improve the rate of healing of the skin lesions, but acyclovir neither alone nor in combination

with corticosteroids reduces the frequency or severity of postherpetic neuralgia. Intravenous acyclovir should be administered in immunocompromised patients with severe infections. The treatment of postherpetic neuralgia is symptomatic. Our first-line treatment of choice is lidoderm patches applied over the regions with neuralgic pain. Neurontin,[84] carbamazepine, topical capsaicin ointment, and tricyclic antidepressants[85] may also reduce the pain in some patients. Narcotics are warranted as well in patients with refractory pain.[86]

▶ SUMMARY

Neuropathies associated with infection are not uncommon. In fact, lepromatous neuropathy may be the most common form of neuropathy, particularly in nonindustrialized nations. Further, neuropathies related to HIV infection have increased, owing to the spread of this infection and longer life span of treated individuals rendering them susceptible to the neurotoxic effects of the infection and antiretroviral infections. Lyme disease likewise needs to be considered in endemic regions. Notably, many of these neuropathies are treatable; thus, diagnosis is essential.

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CHAPTER 16

Neuropathies Related to Nutritional Deficiencies

Patients can develop neuropathies due to inadequate nutrition and subsequent vitamin deficiency (Table 16–1). Nutritional deficiency-related polyneuropathies are currently uncommon, especially in developed countries. However, these neuropathies do occur and are important because they are potentially treatable. Malnutrition is common in chronic alcoholics and patients with chronic illness, usual diets (food fads), and obesity surgery. Some vitamin deficiencies (e.g., vitamins B12 and E) often occur because of impaired gastrointestinal absorption rather than poor dietary intake. In other cases, as with vitamin B6, deficiency may occur secondary to the effects of medications (e.g., isoniazid). Although the clinical and laboratory features of most nutritional polyneuropathies are similar to those of the more common polyneuropathies, these certainly can serve as important indicators of a possible vitamin deficiency. Timely and accurate diagnosis is important because patients can improve with replacement therapy.

▶ THIAMINE (VITAMIN B1) DEFICIENCY

CLINICAL FEATURES

Thiamine deficiency or beriberi is uncommon nowadays and primarily occurs as a consequence of chronic alcohol abuse, recurrent vomiting, total parenteral nutrition, weight reduction surgery, and inappropriately restrictive diets.[1] The symptoms arising from insufficient dietary intake of thiamine are known as beriberi and may present in two forms: dry beriberi and wet beriberi. The difference between these two types of beriberi is simply the presence (wet beriberi) or absence (dry beriberi) of congestive heart failure and lower limb edema combined with neurologic symptoms. Affected individuals usually present with numbness, tingling, and burning in the distal lower extremity, which subsequently spread to involve the proximal legs and upper extremities.[2] On examination, a mild-to-moderate reduction in all sensory modalities is noted in a stocking distribution along with diminished muscle stretch reflexes. Mild, predominantly distal weakness may be appreciated. Congestive heart failure with edema of the lower legs is seen in the so-called wet beriberi.

LABORATORY FEATURES

Blood and urine assays for thiamine are not reliable for diagnosis of deficiency.[3] Erythrocyte transketolase activity and the percentage increase in activity (in vitro) following the addition of thiamine pyrophosphate (TPP), may be more accurate and reliable.[4–7] Sensory nerve conduction studies (NCS) reveal reduced or absent sensory nerve action potentials (SNAP) amplitudes with relative preserved distal sensory latencies and conduction velocities.[2] The motor NCS may be normal or demonstrated slightly reduced amplitudes.

Histopathology

Sural nerve biopsies reveal loss of primarily large myelinated axons.[1,8] Necropsy studies have demonstrated chromatolysis of the anterior horn cells and dorsal root ganglia cells along with axonal degeneration and secondary demyelination of the posterior columns.

PATHOGENESIS

Thiamine is present in most animal and plant tissues, but the greatest sources are unrefined cereal grains, wheat germ, yeast, soybean flour, and pork.[3] It is absorbed in the small intestine by both passive diffusion and active transport. In the jejunum, thiamine is converted to TPP, which is the main coenzyme form of thiamine.[3] Because stores of thiamine in the body are low and its half-life is only 10–14 days, a continuous source of dietary thiamine is necessary to prevent deficiency. The recommended daily allowance ranges from 1 to 1.5 mg/d.[3]

Thiamine and TPP catalyze the decarboxylation of alpha-ketoacids to coenzyme A moieties, an important process in ATP synthesis, in mitochondria.[3] TPP plays a role in the formation of myelin.[9] Thiamine may also affect neuronal conduction by altering membrane sodium channel function.[10,11]

TABLE 16–1. NUTRITIONAL DEFICIENCY ASSOCIATED WITH PERIPHERAL NEUROPATHY

Thiamine (vitamin B1) deficiency
Pyridoxine (vitamin B6) deficiency
Cobalamin (vitamin B12) deficiency
Folate deficiency
Vitamin E deficiency
Copper deficiency
Hypophosphatemia

TREATMENT

Thiamine 100 mg/d should be given intravenously or intramuscularly in deficient patients. The cardiomyopathy usually is quite responsive to thiamine replacement, although improvement in neurological function is more variable and less dramatic.[12,13] Motor deficits appear to improve more so than sensory.[14] Some improvement is expected in most patients, but this typically occurs slowly over 6–12 months, and in patients with severe neuropathy permanent deficits are typical.[2]

PYRIDOXINE (VITAMIN B6 DEFICIENCY)

Pyridoxine not only is neurotoxic when taken in large dosages (see Chapter 18)[15–18] but can also be associated with a sensorimotor polyneuropathy when deficient. Pyridoxine deficiency is usually associated with isoniazid and hydralazine treatment.[19–21] Pyridoxine deficiency may also result from the malnutrition resulting from chronic alcoholism and may occur in patients receiving chronic peritoneal dialysis.[22] The symptoms of vitamin B6 deficiency are nonspecific. Affected individuals manifest with a sensory greater than motor polyneuropathy similar to most idiopathic neuropathies. The electrophysiology studies reflect an axonal sensorimotor polyneuropathy.[19,20] Vitamin B6 deficiency can be detected by direct assay. Deficient patients should be treated with 50–100 mg/d of Vitamin B6.[23,24] This should also be given prophylactically in patients being treated with isoniazid or hydralazine.[25]

COBALAMIN (VITAMIN B12) DEFICIENCY

CLINICAL FEATURES

Patients with vitamin B12 deficiency can present with CNS or PNS abnormalities with or without hematologic findings (megaloblastic anemia).[26–34] Those affected may manifest with numbness and sensory ataxia due to posterior column dysfunction and spastic weakness due to pyramidal tract insult (subacute combined degeneration). In addition, they may have altered mental status. Most patients have signs and symptoms of both CNS and peripheral nervous system (PNS) involvement, with reduction of vibratory perception and proprioception, positive Romberg sign, sensory ataxia, decreased or absent reflexes at the ankles, and brisk reflexes elsewhere. Plantar responses can be either extensor or flexor. Because of the myelopathy, patients may present with more severe numbness in the hands than the legs and can even mimic carpal tunnel syndrome clinically. A positive Lhermitte's sign may be present owing to swelling in the cervical spinal cord.

LABORATORY FEATURES

Serum vitamin B12 assays are not sensitive, as many deficient patients may have serum vitamin B12 levels that are within the normal range.[35,36] Serum levels of the vitamin B12 metabolites methylmalonic acid (MMA) and homocysteine (Hcy) improve diagnostic sensitivity.[36,37] MMA and Hcy testing are increased (i.e., evidence of B12 deficiency) in 5–10% of those having a serum vitamin B12 level less than 300 pg/mL and in 0.1–1% of those with a serum vitamin B12 level greater than 300 pg/mL.[37] We measure MMA and Hcy levels in patients with polyneuropathy who are suspected of having vitamin B12 deficiency: those with a sudden onset of symptoms, symptoms beginning in the hands, findings suggestive of myelopathy, or risk factors for vitamin B12 malabsorption.

In the absence of symptomatic gastrointestinal disease, it probably is not necessary to seek a diagnosis of pernicious anemia in a patient with vitamin B12 deficiency because this information will not alter management.[38] The Schilling test can be performed to diagnosis pernicious anemia.[39] Anti-intrinsic factor antibodies are highly specific for pernicious anemia but are found in only approximately 50% of patients.[40] The combination of elevated gastrin and antiparietal cell antibodies is more sensitive and specific for pernicious anemia.[41]

NCS reveal that SNAP amplitudes are reduced or absent and CMAPs amplitudes are normal or slightly reduced, while the motor and sensory distal latencies and conduction velocities are essentially normal or only mildly abnormal.[26–34,42] Somatosensory-evoked potentials and magnetic stimulation studies may reveal prolongation of central conduction time.[29,32,43]

HISTOPATHOLOGY

Degeneration of the posterior columns and corticospinal tracts has been found on autopsies. Nerve biopsies reveal loss of large myelinated fibers, axonal degeneration, and secondary segmental demyelination.[31,34,44]

PATHOGENESIS

Cobalamin is found in meat, fish, and dairy products but is not present in fruits, vegetables, and grains. Also, vitamin B12 requires a transport molecule, an intrinsic factor, which is synthesized and secreted by gastric parietal cells. Vitamin B12 deficiency can result from lack of dietary intake (strict vegetarian diet), lack of intrinsic factor (pernicious anemia with autoimmune destruction of parietal cells or gastrectomy), malabsorption syndromes (sprue or lower ileum resection), genetic defects in methionine synthetase, and bacteria (blind-loop syndrome) or parasites (e.g., tapeworms) consuming the vitamin prior to its being absorbed. Cobalamin functions as an enzyme necessary for demethylation of methyltetrahydrofolate.[45] Tetrahydrofolate, in turn, is required for production of folate coenzymes that are necessary for DNA synthesis. The pathogenic mechanism for the neuropathy associated with cobalamin deficiency is not known but may be related to impairment in DNA synthesis, decreased methylation of myelin phospholipids, or build up of methylmalonic and propionic acids that serve as abnormal substrates for fatty acid synthesis, leading to aberrant myelination.[45]

TREATMENT

We generally treat deficient patients with B12 1000 μg IM per week for 1 month, followed by 1000 μg IM per month thereafter. It may be possible to treat vitamin B12 deficiency with oral replacement. There has been a randomized trial that compared treatment with 2000 mg oral vitamin B12 per day to 1000 mg intramuscular vitamin B12 per month.[46] Both groups showed similar improvements in hematologic indices, serum MMA and Hcy, and neurological symptoms. However, only eight out of 33 subjects had neurological symptoms, and the methods for assessing improvement are not described.

Approximately 2% of patients experience worse sensory symptoms for unclear reasons during the first month of treatment.[47] The response to treatment of vitamin B12 deficiency polyneuropathy, separate from other neurological complications of vitamin B12, has not been well studied. Patients with vitamin B12 deficiency polyneuropathy probably do not show an immediate response to treatment and may not respond at all.[34,48] The duration of symptoms is an important determinant of treatment response.[47,49,50]

▶ VITAMIN B12 DEFICIENCY SECONDARY TO NITROUS OXIDE INHALATION

Nitrous oxide can inactivate methylcobalamine, leading to neuropathy and subacute combine degeneration in individuals with low or borderline vitamin B12 levels.[51–54] Physical examination, electrodiagnostic findings, and nerve biopsies are similar to that seen in B12 deficiency, as described in the previous section.

▶ FOLATE DEFICIENCY

CLINICAL FEATURES

Folate deficiency is associated with neurological abnormalities similar to those complicating B_{12} deficiency.[55,56] Subacute combined degeneration of the posterior columns and corticospinal tracts, sensorimotor peripheral neuropathy, and altered mental status can develop.

LABORATORY FEATURES

Serum folate levels should be reduced. It is necessary to measure both serum folate and vitamin B_{12} levels to define a pure folic acid deficiency. Megaloblastic anemia may be evident on a complete blood count and smear. Sensory and motor NCS are similar to those seen with B12 deficiency.

PATHOGENESIS

Folate is found in fruit and vegetables and in liver. It is primarily absorbed in the proximal jejunum. Isolated folic acid deficiencies are extremely rare but can occur in the elderly on poor diets, alcoholics, young persons consuming only snack foods, partial gastrectomies, duodenojejunal resections, celiac disease, and disorders of the jejunal mucosa.[55,56] Several drugs (e.g., phenytoin, phenobarbitol, sulfasalazine, and colchicine) can also interfere with the optimal utilization of folic acid. The mechanism by which folic acid deficiency results in a polyneuropathy is not known; however, folic acid is required in DNA synthesis.

TREATMENT

Administration of folic acid usually results in good clinical recovery.

▶ VITAMIN E DEFICIENCY

CLINICAL FEATURES

Vitamin E org α-tocopherol is a lipid-soluble antioxidant vitamin that is present in the lipid bilayer constituting the cell membrane.[57,58] There is a close relationship between the metabolism of lipids and that of vitamin E. There are three major conditions associated

with vitamin E deficiency: (1) deficient fat absorption (e.g. cystic fibrosis, chronic cholestasis, short-bowel syndrome, and intestinal lymphangiectasia), (2) deficient fat transport (abetalipoproteinemia, hypobetalipoproteinemia, normotriglyceridemic abetalipoproteinemia, and chylomicron retention disease), and (3) a genetically based abnormality of vitamin E metabolism. Patients with vitamin E deficiency usually present with progressive difficulty ambulating and impaired coordination of the hands.[59–62] Some individuals complain of weakness and sensory loss. Dysarthria can also occur.

Physical examination is remarkable for ataxia of the trunk and upper and lower extremities.[59–62] There is prominent loss of proprioception and vibratory perception. Muscle stretch reflexes are reduced or absent. Manual muscle testing can be difficult secondary to the ataxia, but there can be proximal muscle weakness, suggesting a superimposed myopathic process. Ocular examination may reveal ophthalmoplegia and retinopathy.

LABORATORY FEATURES

Vitamin E (alpha-tocopherol) levels in the serum are low. With hyperlipidemia, the vitamin E level may be normal even when deficiency is present; therefore, the ratio of total serum vitamin E to the total serum lipid concentration is a more sensitive indicator of vitamin E deficiency in such cases.[63]

NCS reveal reduced amplitudes or absent SNAPs.[57–62,64] The sensory nerve conduction velocities are normal or only slightly reduced. Somatosensory-evoked potentials demonstrate normal peripheral nerve potentials with marked slowing and attenuation of central responses documenting slowing of central conduction with loss of posterior column fibers.[65] Motor NCS are normal.

HISTOPATHOLOGY

Autopsy studies demonstrate swelling and degeneration of axons in the posterior columns and spinocerebellar tracts along with neuronal loss and lipofuscin accumulation in the gracile and cuneate nuclei.[60,66,67] The basal ganglia may be involved as well. Sural nerve biopsies show nonspecific changes and loss of large myelinated fibers, axonal degeneration and regenerating clusters, occasional vacuoles in the myelin sheath, and breakup of the Schmidt–Lanterman incisures, but little in the way of primary demyelination.[68,69]

PATHOGENESIS

The term "vitamin E" is usually used for alpha-tocopherol, the most active of the four main types of vitamin E. It is a lipid-soluble vitamin that is absorbed in the small intestine. Vitamin E is incorporated into chylomicrons and is transported to the liver. In the liver, Vitamin E is transferred to very-low-density lipoproteins in a step requiring alpha-tocopherol transfer protein in Chapter 10. Vitamin E appears to have important roles in scavenging free radicals and in maintaining cell membrane structure.[71]

Since vitamin E deficiency is usually due to factors other than insufficient intake.[72] Vitamin E deficiency usually occurs in secondary lipid malabsorption or in uncommon disorders of vitamin E absorption or transport. One hereditary disorder associated with Vitamin E deficiency is abetalipoproteinemia. This is a rare autosomal-dominant disorder characterized by steatorrhea, pigmentary retinopathy, acanthocytosis, and progressive ataxia.[73] In addition, individuals with cystic fibrosis may also have vitamin E deficiency secondary to steatorrhea. There are also genetic forms of isolated vitamin E deficiency not associated with lipid malabsorption.[74,75] Mutation in the alpha-tocopherol transfer protein gene on chromosome 8q13 affects vitamin E absorption, impairing its incorporation in very-low-density lipoproteins (see Chapter 10).[70,76] Vitamin E deficiency may also occur as a consequence of various cholestatic and hepatobiliary disorders as well as short bowel syndromes, resulting in the surgical treatment of intestinal disorders.[64,77,78]

TREATMENT

The primary goal is to prevent progression, but improvement in neurological function may occur. The specific dose of vitamin E varies with the cause of deficiency.[72] With isolated vitamin E deficiency, patients are treated with 1500–6000 international units (IU) per day in divided doses. In cases of chronic cholestasis, treatment begins with 50 IU/kg/d and the dose is increased in 50 IU/kg increments up to a 200 IU/kg/d to achieve normalization of the serum tocopherol to lipid ratio. Patients with cystic fibrosis who are receiving oral pancreatic enzyme therapy require doses of 5–10 IU/kg/d. Those with short bowel syndrome are given 300–5400 IU/d. Abetalipoproteinemia is treated with vitamin E 150–300 IU/kg/d and vitamin A 15,000–20,000 IU/d.

▶ POSTGASTRECTOMY/BARIATRIC SURGERY DEFICIENCIES

Polyneuropathy may occur following gastric/bariatric surgery for ulcer, cancer, or morbid obesity. This usually occurs in the context of rapid, significant weight loss and recurrent, protracted vomiting.[14,79–82] The clinical picture is variable and may include acute or subacute sensory loss, burning feet, and generalized weakness that can resemble Guillian–Barre syndrome, mononeuropathies,

radiculoplexus neuropathy.[82–86] Some cases are complicated by CNS dysfunction resembling Wernicke–Korsakoff syndrome. In the largest retrospective series, 71 out of 435 (16%) of patients who underwent bariatric surgery develop some type of peripheral neuropathy. The neuropathy is associated with malnutrition and the rapidity of weight loss and usually develops within the first 1½ years following weight loss surgery.[79,82,86] However, the latency between surgery and symptoms can be months to years in patients following total or partial gastrectomy for ulcer or cancer.[14,87]

Weight reduction surgical procedures include gastrojejunostomy, gastric stapling, vertical banded gastroplasty, and gastrectomy with Roux-en-Y anastomosis. Although thiamine deficiency seems to be a factor (given the frequent co-occurrence of the Wernicke–Korsakoff syndrome), there is not good documentation of thiamine deficiency in the reported cases. In some cases, one or more vitamin deficiencies are identified.[88] In many cases, no specific deficiency is identified.

HISTOPATHOLOGY

Sural nerve biopsies may reveal active axonal degeneration and mild perivascular, endoneurial, and epineurial infiltrate.

PATHOGENESIS

The basis of the neuropathies is unclear but likely to be from multiple nutritional deficiencies.

TREATMENT

Management consists of parenteral vitamin supplementation to include, especially, thiamine. Improvement has been observed following supplementation, parenteral nutritional support, and reversal of the surgical bypass.[82,88,89] Patients developing vomiting after weight reduction surgery should be supported with total parenteral nutrition and vitamins. There can be good recovery if treatment is initiated quickly after symptom onset. However, a number of patients can have persistent sensory loss and weakness. The duration and severity of deficits before identification and treatment of neuropathy are important predictors of final outcome.

▶ COPPER DEFICIENCY

CLINICAL FEATURES

Copper deficiency is associated with an unusual myeloneuropathy, neutropenia, and sometimes pancytopenia.[82,90–100] Most patients manifest with numbness and tingling in the legs, weakness, spasticity, and gait difficulties. Large fiber sensory function is impaired, reflexes are brisk, and plantar responses are extensor. In some cases, light touch and pinprick sensation are affected and nerve conduction studies indicate sensorimotor axonal polyneuropathy in addition to myelopathy.[91,93] A severe motor axonopathy can also be seen.[94] In some cases,[95] brain involvement was emphasized based on demyelinating lesions on brain magnetic resonance imaging, but the clinical syndrome was primarily myelopathy. One of these patients also had saccadic dysmetria.[95]

LABORATORY FEATURES

Besides low serum copper levels, some cases are associated with high levels of zinc. Microcytic anemia and neutropenia[90,93–95,97,98,101,102] and occasionally pancytopenia[91] are seen. Bone marrow biopsy may reveal abnormalities of a myelodysplastic syndrome. Cerebrospinal fluid may be normal or show mildly elevated protein or immunoglobulin synthesis rate.[91,94,95,97] Magnetic resonance imaging may demonstrate abnormal T2-weighted signal in the dorsal columns.[90,94,95,97,98]

NCS indicate sensorimotor axonal polyneuropathy.[91,93,97,98] Somatosensory-evoked potentials demonstrate impaired conduction in the central pathways.[97,98]

HISTOPATHOLOGY

Sural nerve biopsies may show evidence of axonal degeneration.[97,98]

PATHOGENESIS

Copper is absorbed in the stomach and proximal jejunum.[103] Copper deficiency may arise as a complication of gastric surgery.[90,93] Excess zinc can cause copper deficiency. Zinc upregulates enterocyte production of metallothionein, which results in decreased absorption of copper.[104,105] Other potential causes of copper deficiency include malnutrition, prematurity, total parenteral nutrition, and ingestion of copper chelating agents.[101,103]

TREATMENT

The myeloneuropathy may improve with oral or intravenous copper replacement quickly[90,92,93] in other cases improvement was seen only after months or

years[91,95,97] or not at all.[94] Hematological indices usually completely normalize with copper replacement therapy, although the degree of clinical improvement in the myeloneuropathy is more variable and residual deficits are common.[97]

▶ HYPOPHOSPHATEMIA

Hyperalimentation can lead to hypophosphatemia and the development of a subacute and severe sensorimotor peripheral neuropathy, which can clinically resemble Guillain–Barre syndrome.[106,107] Paresthesias are initially noted in the feet and ascend to involve the upper limbs and remainder of the body. Impaired ambulation secondary to both weakness and sensory ataxia occurs over the course of hours to days. On examination, generalized weakness, ataxia, depressed muscle stretch reflexes, and reduced perception of all sensory modalities are appreciated. Weakness may also involve the respiratory muscles requiring assisted ventilation. NCS reveals an absence of SNAPs, reduced CMAP amplitudes and slow conduction velocities. Correction of the hypophosphatemia results in clinical and electrophysiologic improvement.

▶ ALCOHOLIC NEUROPATHY

CLINICAL FEATURES

Alcoholics can develop a generalized axonal sensorimotor polyneuropathy.[108–112] Usually the neuropathy is slowly progressive, although some cases with acute or subacute presentation resembling Guillian–Barre syndrome have been reported.[113,114] Unlike Guillian–Barre syndrome, CSF protein in alcohol-related acute axonal polyneuropathy is usually normal or only slightly elevated. Most cases are preceded by prominent weight loss for 2–3 months. Most patients manifest insidious onset of numbness, paresthesia, and burning pain.

Examination demonstrates a reduction of all sensory modalities in a glove and stocking distribution, worse in the lower compared to upper limbs. Muscle stretches are reduced or absent. Mild distal leg weakness may be appreciated, but proximal leg and arm strength is usually normal. An occasional patient presents with symptoms and signs suggestive of a myopathy as opposed to neuropathy. NCS reveal features suggestive of a generalized axonal sensory or sensorimotor polyneuropathy.[108–110,112]

HISTOPATHOLOGY

Nerve biopsies may reveal loss of large and small caliber myelinated fibers along with Wallerian degeneration and secondary segmental demyelination.[112,114]

PATHOGENESIS

The exact etiology of peripheral nerve insult in alcoholism is unknown but may in part be related to both a nutritional deficiency (e.g., B vitamin group and folate) and a direct toxic effect of alcohol on peripheral nerves. A dose-dependent toxic effect of alcohol on sensorimotor and autonomic nerves was noted in a case–control study.

TREATMENT

Abstaining from alcohol and consuming an optimal diet can result in an improvement of the peripheral neuropathy.[114]

▶ SUMMARY

Nutritional neuropathies are not particularly common. However, because they can be treatable with correction of the deficit, it is important to be vigilant for signs and symptoms that would suggest a nutritional deficiency. In particular, those patients with gastrointestinal disease or history of gastric bypass may be particularly vulnerable.

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CHAPTER 17

Neuropathies Associated with Malignancy

Patients with malignancy can develop peripheral neuropathies as (1) a direct effect of the cancer by invasion or compression of the nerves, (2) a remote or paraneoplastic effect, (3) a direct toxic effect of treatment, or (4) an alteration of immune status caused by immunosuppressive medications (Table 17–1).[1,2] It is difficult to estimate the frequency of polyneuropathy in patients with cancer because it is dependent on a number of factors including the type, stage, and location of the malignancy, as well as cofounding variables such as malnutrition, the toxic effects of therapy, and the background incidence of neuropathy in this frequently older population. Nevertheless, some reports indicate that 1.7–5.5% of patients with cancer have clinical symptoms or signs of a peripheral neuropathy, while neurophysiological testing (quantitative sensory testing and nerve conduction studies [NCS]) demonstrates evidence of peripheral neuropathy in 30–40% of patients with cancer.[3] The most common associated malignancy is lung cancer, but neuropathies also complicate carcinoma of the breast, ovaries, stomach, colon, rectum, and other organs including the lymphoproliferative system.

▶ PARANEOPLASTIC NEUROPATHIES

Neuropathies related to remote effects of carcinoma or the so-called paraneoplastic syndromes are quite interesting but quite rare.[1,2,4]

PARANEOPLASTIC SENSORY NEURONOPATHY/GANGLIONOPATHY

In 1948, Denny-Brown reported two patients with small cell lung cancer (SCLC) and sensory neuronopathy (SN).[5] Autopsies revealed dorsal root ganglionitis and degeneration of the posterior columns. Subsequently, many other patients present with paraneoplastic encephalomyelitis (PEM).[3,5–31] SCLC is the most common malignancy associated with PEM/SN, but cases of carcinoma of the esophagus, breast, ovaries, kidney and lymphoma have also been reported.[3,5,6] Approximately 13% of patients with SCLC have another type of concomitant malignancy.[3] Therefore, finding a malignancy other than SCLC in a patient with PEM/SN does not obviate the need to look for concurrent lung cancer.

Clinical Features

PEM/SN most commonly develops in the sixth or seventh decade.[3,5,6,32] The disease is more common in women than in men (up to a 2:1 ratio). The neurological symptoms usually precede the diagnosis of cancer. Most malignancies are detected within 4–12 months, although there are reports of cancer being diagnosed 8 years or more following the onset of the neurological symptoms.[3,5] Patients usually present with numbness, dysesthesia, and paresthesia, usually in the distal extremities. These symptoms begin in the hands in up to 60% and may be asymmetric in 27–40% of cases.[3,5] The onset can be quite acute or insidiously progressive. Diminished touch, pain, and temperature sensation and prominent loss of vibratory and position sense occur, resulting in sensory ataxia and pseudoathetosis. The causes of sensory ataxia are limited and should lead to a malignancy workup in any patient who exhibits such signs (Table 17–2). Muscle stretch reflexes are diminished or absent. While sensory symptoms predominate, mild weakness is evident in at least 20% of patients.[3] Weakness can be secondary to an associated myelitis, motor neuronopathy, or concurrent Lambert–Eaton myasthenic syndrome.[3,5,32] Autonomic neuropathy may occur as an isolated disturbance or as part of the spectrum of a paraneoplastic syndrome in up to 28% of patients and can be the presenting feature in as many as 12%.[3,5,32]

As many as 21% of affected individuals present with confusion, memory loss, depression, hallucinations, or seizures.[3,5,32] Approximately 32% of patients develop brainstem dysfunction (e.g., diplopia, vertigo, nausea, and vomiting). Cranial neuropathies, especially of the eighth cranial nerve, occur in up to 15% of patients. Cerebellar ataxia, scanning dysarthria, tremor, and peduncular reflexes attributed to cerebellar dysfunction are evident in 25% of patients. Abnormal ocular movements such as nystagmus, opsoclonus, and internal and external ophthalmoplegia are seen in up to 32% of patients. Myoclonus develops in approximately 1% of patients. Myelitis with secondary degeneration of the

TABLE 17–1. NEUROPATHIES ASSOCIATED WITH CANCER

Direct effect of the cancer by invasion or compression of the nerves
Paraneoplastic
Sensory ganglionopathy (anti-Hu syndrome)
Sensorimotor neuropathy
Autonomic neuropathy
Direct toxic effect of treatment
Neurotoxicity secondary to chemotherapy
Radiation toxicity
Alteration of immune status related to immunosuppressive medications associated with bone marrow transplantation or treatment of GVHD

GVHD, graft-vs.-host disease.

anterior horn is the presenting feature in as many as 14% of those affected.

Laboratory Features

Polyclonal antineuronal antibodies (IgG) directed against a 35–40 kD protein or complex of proteins, the so-called Hu antigen, are found in the sera or cerebral spinal fluid (CSF) in the majority of patients with paraneoplastic PEM/SN.[3,5–13,32] The presence of anti-Hu antibodies in the serum correlates with SN,[11] while antibodies in the CSF are associated with the development of PEM.[12] In a study of 49 patients with paraneoplastic sensory neuropathy, anti-Hu antibodies were present in the serum of 40/49 patients.[6] In 77 patients with idiopathic sensory neuropathy, anti-Hu antibodies were found in only one patient.[6] Thus, the sensitivity and specificity of the anti-Hu antibodies are high. However, 12% of patients with paraneoplastic SN did not have anti-Hu antibodies. Therefore, all patients suspected of having PEM/SN should undergo periodic screening for an underlying malignancy, regardless of their anti-Hu antibody status.

CSF may be normal or may demonstrate mild lymphocytic pleocytosis and elevated protein.[3,5,12,32] Oligoclonal bands and increased CSF IgG synthesis and index are evident in the majority of patients suggestive of intrathecal synthesis of the autoantibody. Magnetic resonance imaging (MRI) of the brain is usually unremarkable. However, some patients with encephalomyelitis have signal abnormalities on T2-weighted images in the temporal or frontal lobes.[3] Periventricular white matter hypodensities, frontal and temporal lobe atrophy, and cerebellar atrophy also have been reported.

Nerve conduction studies (NCS) in pure SN reveal low-amplitude or absent sensory nerve action potentials (SNAPs).[33] Compound muscle action potentials (CMAPs) and needle electromyography (EMG) are normal unless the patient has a concurrent motor neuropathy or Lambert–Eaton myasthenic syndrome. The blink reflex study is usually abnormal, while the masseter reflex study can be normal.[14,15]

TABLE 17–2. CAUSES OF SENSORY NEUROPATHY/GANGLIONOPATHY

Paraneoplastic (anti-Hu syndrome)
Sjogren syndrome
Human immunodeficiency virus infection
Toxic agents (e.g., chemotherapy, pyridoxine, and antinucleosides)
Guillain-Barre syndrome variant
Idiopathic sensory neuronopathy

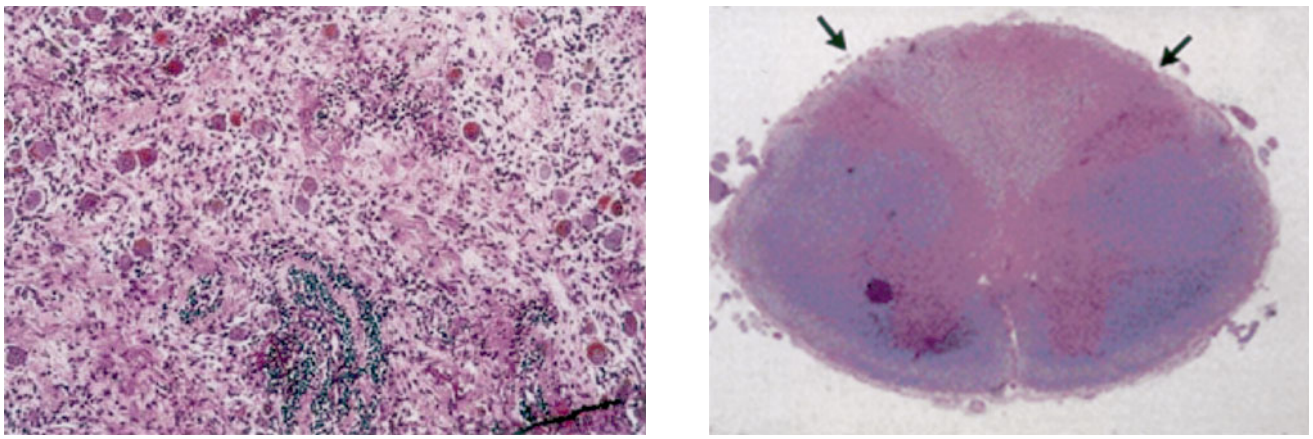
Modified with permission from Amato AA, Anderson MP. A 51 year old woman with lung cancer and neuropsychiatric abnormalities (Case 38—2001). N Engl J Med 2001;354:1758–1765.

Histopathology

Sural nerve biopsies may demonstrate perivascular inflammation comprised of plasma cells, macrophages, B cells, and T cells.[33] Autopsy studies reveal inflammation and degeneration of the dorsal root ganglia with secondary degeneration of sensory neurons and the posterior columns (Fig. 17–1).[2,3,13,16,31] In addition, inflammation and degeneration of neurons in the autonomic ganglia, including the myenteric plexus, may be evident.[16,17,19] Lennon et al reported autoantibodies (presumably anti-Hu) directed against a nuclear antigen of myenteric neurons in patients with intestinal pseudo-obstruction due to autonomic involvement.[17] In patients with PEM, autopsies have revealed perivascular and perineuronal inflammation and degeneration of neurons in the brainstem and limbic system (medial temporal lobe, cingulate gyrus, piriform cortex, orbital surface of the frontal lobes, and the insular cortex) (Fig. 17–2).[3,8,13,32] The thalamus, hypothalamus, subthalamic nucleus, deep cerebellar nuclei, and Purkinje cells may also be involved. Inflammation and degeneration of the anterior horn cells and the ventral spinal roots are evident in patients with myelitis. Deposits of anti-Hu antibody have been demonstrated in areas of the nervous system that correlate with the clinical symptoms as well as in the tumors.[13,16–19]

Pathogenesis

PEM/SN is probably the result of antigenic similarity between proteins expressed in the tumor cells and the neuron cells (e.g., Hu antigens), leading to an immune response directed against both tumor and neuronal cells.[3,5,20,21,32,34] The Hu antigen is a family of four similar RNA-binding proteins (HuD, HuC/ple21, Hel-N1, and Hel-N2). The Hu antigen is expressed in the nuclei and to a lesser extent in the cytoplasm of neurons and SCLC cells.[10] The function of this group of proteins is



A B

Figure 17–1. (A) Dorsal-root ganglia of the cervical cord, showing marked parenchymal and perivascular inflammation, loss of ganglion cells, and fibrosis (Hematoxylin and Eosin, ×100). (B) Section of cervical spinal cord showing marked pallor of the dorsal columns (arrows) (Luxol Fast Blue–Hematoxylin and Eosin, ×5). (With permission from Amato AA, Anderson MP. A 51 year old woman with lung cancer and neuropsychiatric abnormalities (Case 38—2001). N Engl J Med 2001;354:1758–1765, Figs. 5 and 7, p. 1763, 1764.)

not known, but these are thought to be crucial in the development and maintenance of the nervous system.[21] The role of the anti-Hu antibodies in the development of PEM/NS is also unclear. The antibodies appear to bind to CNS and PNS neurons affected in the syndrome.[13,16–19] There is a correlation of high anti-Hu titers in the CSF and the development of PEM,[12] and the serum titer with the occurrence of SN.[11] However, the anti-Hu antibodies have not been proved to be pathogenic. Passive transfer of autoantibodies from patients with PEM/SN and immunization with purified HuD protein have failed to reproduce the disease in animal studies.[24] Further, the anti-Hu antibodies exhibit only weak complement activation.[19,25]

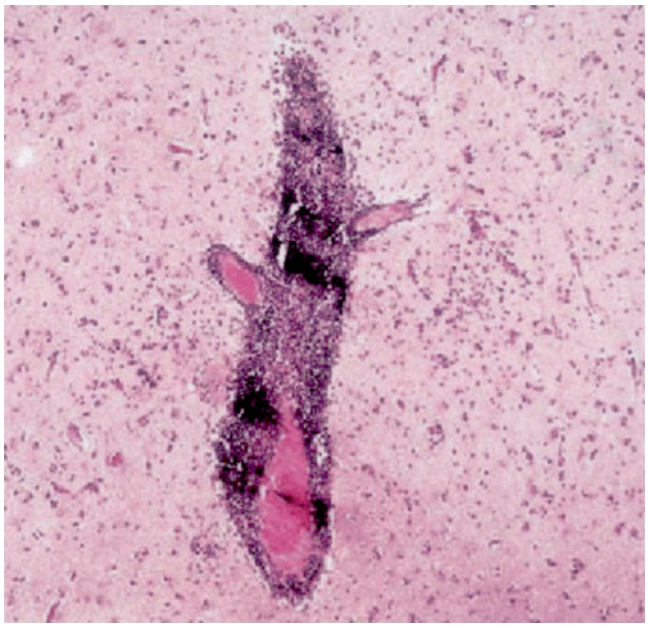


Figure 17–2. Amygdalar complex with a perivascular lymphocytic infiltrate and microglial nodules (Hematoxylin and Eosin, ×100). (With permission from Amato AA, Anderson MP. A 51 year old woman with lung cancer and neuropsychiatric abnormalities (Case 38—2001). N Engl J Med 2001;354:1758–1765, Fig. 6, p. 1764.)

More recently, the focus has shifted to the role of the cellular immune response in PEM/SN.[26] The perivascular infiltrate in tumors and the nervous system consists mainly of CD4+ cells, B cells, and macrophages, while CD4+ cells, cytotoxic T cells, and microglia-like cells predominate in the tissue immediately surrounding neurons.[19,26] T-cell receptor studies on the inflammatory infiltrate in the nervous system and within the tumors of anti-Hu-positive PEM/SN patients reveal a limited Vβ repertoire and clonal expansion suggestive of an antigen-driven cytotoxic T-cell response.[27] Studies have demonstrated an increase of CD45RO+CD4+ memory helper T cells in the peripheral blood of patients with anti-PEM/SN.[26] Antigen-specific proliferation of these T cells occurred following in vitro stimulation of cultured lymphocytes with purified HuD antigen. In addition, the cells secreted interferon-γ, suggesting that these lymphocytes were primarily of the Th1 helper subtype. The authors speculated that neoplastic cells express the Hu antigen previously produced by fetal cells but lie sequestered in adult neurons. Autoreactive CD4+ T cells that escaped thymic deletion may become activated by the tumor expressing the Hu antigen. These cells, in turn, activate CD4+ Th1 T cells that migrate to the tumor and into the nervous system as well, inducing a direct cytotoxic effect on tumor cells and on neurons.

Treatment

Treatment of the underlying cancer generally does not effect the course of PEM/SN.[3,33] However, some patients may improve with treatment of the tumor. Unfortunately, plasmapheresis (PE), intravenous immunoglobulin (IVIG), and immunosuppressive agents have also been disappointing.[3,5,30]

PARANEOPLASTIC SENSORIMOTOR POLYNEUROPATHY

Clinical Features

Sensorimotor polyneuropathies may also have an immunologic pathogenesis as part of a paraneoplastic syndrome. From a clinical and electrophysiologic standpoint, it is usually easy to distinguish neuropathy caused by direct tumor infiltration from a paraneoplastic variant or idiopathic causes by its local character, but rarely—in widespread cases—it may be difficult. While sensory symptoms predominate in PEM/SN, mild weakness is evident in many patients as noted above.[6] It is unclear if there is truly a paraneoplastic sensorimotor polyneuropathy distinct from PEM/SN described previously. Besides generalized symmetric sensorimotor polyneuropathies, multiple mononeuropathies attributed to paraneoplastic vasculitis have been reported in patients with lymphoma, SCLC, adenocarcinoma of the lungs, endometrium, prostate, and kidneys.[35–39]

Laboratory Features

Sensory NCS show absent or low-amplitude SNAPs with normal or only borderline slowing of conduction velocities and slightly prolonged distal latencies, while motor studies demonstrated normal or only mild abnormalities reflective of axon loss.[4] A primarily demyelinating neuropathy may be seen as a complication of melanoma.[40,41]

Histopathology

Nerve biopsies reveal a general reduction in all myelinated fibers often with perivascular inflammation.[4] Necrotizing vasculitis is extremely rare.

Pathogenesis

The pathogenic basis of the neuropathy is not known. Perhaps, there is immune response directed at both the sensory and the motor components of peripheral nerves.

PARANEOPLASTIC AUTONOMIC NEUROPATHY

Autonomic dysfunction can occur as an isolated disturbance or as part of the spectrum of the anti-Hu-associated PEM/SN.[6,33] Autonomic neuropathy is most commonly described as a paraneoplastic effect of SCLC but has also occurred with adenocarcinoma and carcinoid tumor of the lungs, breast and ovarian cancer, testicular cancer, pancreatic malignancy, and lymphoma.[6,42] Symptoms and signs of autonomic neuropathy include orthostatic hypotension, gastroparesis, intestinal pseudoobstruction, urinary retention, dry eyes and mouth, and pupillary dysfunction. In a study of 71 patients with anti-Hu-associated PEM/SN, 10% presented with severe orthostatic hypotension and 28% had varying degrees of dysautonomia during the course of their illness.[6] Autopsies have demonstrated loss of neurons and inflammatory infiltrate in the dorsal root and autonomic ganglia (e.g., myenteric plexus). Autoantibodies directed against a nuclear antigen of myenteric neurons have been shown.[42]

IDIOPATHIC SENSORY OR SENSORIMOTOR POLYNEUROPATHY ASSOCIATED WITH MALIGNANCY

Clinical Features

Idiopathic sensory or sensorimotor polyneuropathy complicating cancer is much more common than paraneoplastic neuropathies. The polyneuropathy is more frequent in individuals with SCLC but can be seen in most cancer. In the majority of cases, etiology of sensory or sensorimotor polyneuropathy complicating cancer remains unknown.

Most patients develop slowly progressive, distal, symmetric numbness beginning in the feet and later progressing to involve the hands. All sensory modalities can be affected, but the prominent sensory ataxia associated with PEM/SN does not occur. Usually on mild, if any, distal extremity weakness is appreciated. Muscle stretch reflexes are diminished or absent distally.

Laboratory Features

There are no specific laboratory abnormalities. NCS demonstrate features of a length-dependent, axonal, sensory, or sensorimotor polyneuropathy with reduced or absent amplitudes and relatively preserved distal latencies and conduction velocities.[2] EMG may reveal mild denervation changes distally.

Histopathology

Nerve biopsies and autopsies reveal axonal degeneration and regeneration with secondary segmental demyelination and remyelination.

Pathogenesis

The pathogenic basis for this neuropathy is not known. Neuropathies can develop in untreated patients, so

neurotoxicity from chemotherapies is not the cause in all. Patients with cancer may lose weight and appear cachectic; however, the neuropathy can manifest before they appear malnourished, and vitamin supplementation does not help. Perhaps, toxic or cytokine factors released by the tumor by inflammatory cells lead to neuronal damage. Alterations in protein and fat metabolism that are associated with cancers conceivably might cause neuropathy.

Treatment

There is no specific treatment for the neuropathy other than treating the underlying malignancy and maintaining adequate nutrition.

▶ NEUROPATHY SECONDARY TO TUMOR INFILTRATION

Malignant, in particular leukemic and lymphomatous, cells can occasionally infiltrate peripheral nerves, leading to mononeuropathy, mononeuropathy multiplex, polyradiculopathy, plexopathy, or even a generalized symmetric distal or proximal and distal polyneuropathy.[43–49] The neuropathy can begin acutely or have a more slow, insidious onset. Neuropathy related to tumor infiltration can be the presenting clinical manifestation of leukemia or lymphoma or the heralding of a relapse. The neuropathy may improve with treatment of the underlying leukemia or lymphoma or corticosteroids.

LEUKEMIA

Peripheral neuropathy occurs in up to 5.5% of patients with leukemia.[46,50–53] Mononeuropathy or mononeuropathy multiplex can occur due to hemorrhage or leukemic infiltration into cranial or peripheral nerves, including the spinal roots. As one might expect, symmetric polyneuropathy due to leukemic infiltration of the nerves is unusual but has been described.

Electrophysiological studies typically demonstrate features of a multifocal axonal sensorimotor neuropathy. Nerve biopsies can demonstrate leukemic infiltration of the nerve, axonal degeneration, and segmental demyelination. Vasculitis has also been suggested as a cause of peripheral neuropathy in hairy cell leukemia.[35,36]

ANGIOTROPHIC LARGE-CELL LYMPHOMA

This rare malignancy is characterized by intravascular proliferation of large, atypical, lymphoid B cells.[44,45,54–56] The CNS and skin are the most common sites of involvement. Nearly a quarter of patients develop a radiculopathy or polyradiculopathy, while 5% have other mononeuropathies. The diagnosis is made difficult by the absence of malignant cells in the peripheral blood or lymph nodes. Biopsy of affected nerves demonstrates intravascular and endoneurial lymphocytic infiltration (primarily B cells).

LYMPHOMATOID GRANULOMATOSIS

This angiocentric immunoproliferative disorder is associated with a pleomorphic lymphoid infiltrate of blood vessels. Infection of T cells by Epstein–Barr virus drives this inflammatory response of reactive T cells.[57] There is a predisposition for evolution into non-Hodgkin lymphoma. Distal symmetric polyneuropathy, mononeuropathy multiplex, polyradiculoneuropathies, and cranial neuropathies develop in 10–15% of patients.[58–61] Electrophysiological studies are suggestive of a multifocal axonal sensorimotor neuropathy. Nerve biopsies demonstrate perivascular lymphoplasmatoid infiltrates in the epineurium, necrosis, or thrombosis of the vessels, and asymmetric loss of axons between and within nerve fascicles due to ischemic injury.

▶ CRANIAL NEUROPATHIES AND RADICULOPATHIES

INFILTRATING TUMORS

The leptomeninges, cranial nerves, and nerve roots can also be invaded by tumor cells. Polyradiculopathies manifest as radicular pain and sensory loss, weakness, and hypo- or areflexia. Widespread involvement can mimic a generalized sensorimotor polyneuropathy. If the spinal cord is involved, superimposed upper motor neuron signs are seen. Multiple cranial neuropathies can occur due to local spread of a tumor (i.e., nasopharyngioma) or by metastasis. The sixth and fifth cranial nerves are most commonly affected in nasopharyngiomas, while the sixth cranial nerve followed by the third, fifth, and seventh are more commonly affected in metastatic processes. The so-called "numb chin syndrome," characterized by numbness of the lower lip and chin, is particularly worrisome for malignant invasion of the mental or alveolar branches of the mandibular nerve.

MRI may demonstrate enhancement or compression of the nerve roots by the tumor. CSF may be abnormal, revealing increased protein, an increased cell count, and malignant cytology. Electrodiagnostic studies can be useful to localize the site of the lesion(s).

Patients with leukemia and lymphoma may respond to irradiation and intrathecal chemotherapy. However, the response rate is much lower in other types of tumors with the possible exception of breast cancer.

BRACHIAL PLEXOPATHY

The brachial plexus can be involved due to regional spread of a local tumor (i.e., Pancoast tumor metastasi, or radiation-induced injury). Metastatic disease is responsible for most causes of brachial plexopathy in cancer patients, 78% in one large series.[62] Lung and breast cancers are the most common culprits. The tumors most often spread via the lymphatics to the lateral group of axillary lymph nodes, where divisions of the lower trunk of the brachial plexus are located. Lung cancers in the apices of the lungs may also invade the paravertebral space, the extraspinal C8–T3 mixed spinal nerves, the sympathetic chain, and the stellate ganglia.

Most patients complain of pain in the shoulder area radiating down the arm into the fingers, in particular the fourth and fifth digits. Sensory loss and weakness usually conform to the distribution of the lower trunk and a Horner's syndrome due to involvement of the sympathetic chain or stellate ganglia is often seen. The arm may appear swollen because of associated lymphedema. Signs and symptoms attributable to involvement of the upper and middle trunk of the brachial plexus are much less common and, when present, suggest epidural extension of the tumor.

Radiation plexitis is usually associated with doses greater than 6000 rads and can present 3 months to 26 years (mean 6 years) following radiation treatment to the region.[62] Paresthesias and lymphedema of the affected arm are common. Pain occurs in only 15% of patients and is usually not as severe, which may help distinguish radiation-induced plexitis from tumor invasion. Further, the upper plexus is involved in 77% and diffuse plexus involvement occurs in 23% of patients with radiation plexitis. Some studies note that the entire plexus is more commonly involved than just the upper trunk.

MRI or CT scan may demonstrate malignant invasion of the plexus and perhaps extension to the epidural space. Motor and sensory NCS reveal reduced amplitudes of involved nerves. Myokymic discharges may be appreciated on EMG and when seen are highly suggestive of radiation-induced damage. However, the absence of myokymia does not exclude radiation plexopathy. When noninvasive testing cannot differentiate between metastatic and radiation diseases, surgical exploration and biopsy may be required for definitive diagnosis.

Neoplastic invasion of the brachial plexus can be treated with radiation therapy. Pain may be improved but the prognosis for return of motor function is poor. Treatment of the pain with transcutaneous stimulation, sympathetic blockage, and dorsal rhizotomies has been disappointing.

LUMBOSACRAL PLEXOPATHY

The lumbosacral plexus may be invaded by local extension of intra-abdominal tumors (73%) or metastasis of distant neoplasms (27%).[63] Colorectal, cervical, lymphoma, sarcoma, and breast cancers are the most common associated cancers. The lumbar plexus is involved in 31%, lumbosacral trunk in 51%, and entire lumbosacral plexus in 18% of patients with malignant invasion of the plexus.[63,64] Patients usually complain of an insidious onset of pain, numbness, weakness, and edema of the lower limb. Approximately 25% of patients have involvement of both legs. Fewer than 10% of patients develop bowel or bladder incontinence or impotence.

Radiation-induced lumbosacral plexopathy can develop 1–31 years (mean 5 years) after completion of treatment. It usually manifests as slowly progressive weakness, and, unlike plexopathy secondary to tumor invasion, pain is present in only half the patients and typically is not as severe. Typically, there is symmetrical involvement of both legs, with the distal muscles being more affected than proximal muscles. Bowel and bladder incontinence may occur secondary to nerve injury or due to radiation-induced proctitis or cystitis.

MRI or CT of the lumbosacral spine and pelvis can demonstrate the tumor invading the lumbosacral plexus and perhaps extension into the epidural space. On EMG, fibrillation potentials and positive sharp waves are found in the paraspinal muscles in approximately 50% of patients with radiation-induced damage, suggesting that the disorder is more appropriately termed a radiation-induced radiculoplexopathy. Myokymic discharges are seen on EMG in over 50% of patients with radiation-induced lumbosacral radiculoplexopathy.

▶ NONINFILTRATIVE PERIPHERAL NEUROPATHIES ASSOCIATED WITH LYMPHOPROLIFERATIVE DISORDERS AND PLASMACYTOMAS

There is increased incidence of monoclonal gammopathies in patients with peripheral neuropathy, and neuropathies may be more frequent in patients with monoclonal gammopathies than in the general population.[65] Approximately 10% of patients with otherwise idiopathic peripheral neuropathies have monoclonal proteins compared to 2.5% of patients with peripheral neuropathies secondary to other diseases.[66,67] A causal relationship of demyelinating sensorimotor polyneuropathy and monoclonal IgM has been established (see Chapter 12, and discussion on DADS neuropathy).[67,68] Antibodies directed against myelin-associated glycoprotein (MAG) are present in at least 50% of patients of these patients. However, what relationship, if any, IgA and IgG monoclonal gammopathies have to the pathogenesis of the peripheral neuropathies is not clear. Unlike IgM-associated demyelinating neuropathies, IgA and IgG immunoglobulin deposition is generally not seen on nerve sheaths in patients with

neuropathies and concurrent IgA or IgG monoclonal gammopathy.

We test all patients with peripheral neuropathies for the presence of monoclonal gammopathies in the serum and urine. Serum and urine protein electrophoresis (SPEP and UPEP) are useful screening tests but are not as sensitive as immunoelectrophoresis or immunofixation. Therefore, we order serum and urine immunoelectrophoresis or immunofixation in any patient suspected of having a myeloproliferative disorder. An aggressive workup for amyloidosis, multiple myeloma, osteosclerotic myeloma, plasmacytoma, Waldenström macroglobulinemia, lymphoma, leukemia, and cryoglobulinemia should be performed in any patient in whom a monoclonal gammopathy is identified.[67,69–72] We order a radiologic skeletal survey to assess for osteolytic or sclerotic lesions and hematology consultation to consider a bone marrow biopsy. Although most patients with monoclonal gammopathies have no underlying (deemed monoclonal gammopathies of undetermined significance or MGUS), approximately 20% of MGUS patients subsequently develop lymphoma, leukemia, myeloma, or plasmacytoma.[67]

LYMPHOMA

Clinical Features

Lymphoma may cause neuropathy by infiltration or direct compression of nerves,[48] but the neuropathies can also be paraneoplastic in nature.[73] Both Hodgkin disease and non-Hodgkin lymphoma can cause sensorimotor polyneuropathies.[45,52,74,75] A prospective study reported clinical symptoms or signs of neuropathy in 8% and electrophysiologic evidence of neuropathy in 35% of patients with lymphoma.[73] The neuropathy can be purely sensory[76] or motor but most commonly is sensorimotor.[73] Autonomic neuropathy may also be seen. The pattern of involvement may be symmetric, asymmetric, or multifocal; the course may be acute,[52,74] subacute,[52,75] chronic progressive,[73,75] or relapsing and remitting.[74,75]

Laboratory Features

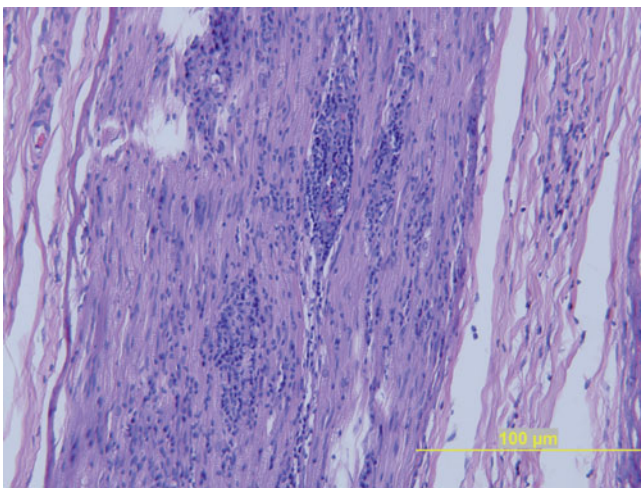
CSF may reveal lymphocytic pleocytosis and elevated protein.[48,73] Motor and sensory NCS reveal reduced amplitudes with preserved conduction velocities suggestive of a generalized axonal sensorimotor neuropathy[73] or demonstrate prolonged distal and F-wave latencies, slow conduction velocities, temporal dispersion, and conduction block,[52] similar to those observed in acute inflammatory demyelinating polyneuropathy and chronic inflammatory demyelinating polyneuropathy (CIDP).

Histopathology

Nerve biopsy may demonstrate endoneurial inflammatory cells in both the infiltrative and the presumed paraneoplastic neuropathies complicating lymphoma (Fig. 17–3). A monoclonal population of cells would favor lymphomatous invasion.[73,74]

Pathogenesis

The paraneoplastic neuropathy associated with lymphomas is presumably autoimmune in nature, but the exact antigen(s) and trigger for the immune attack are not known.



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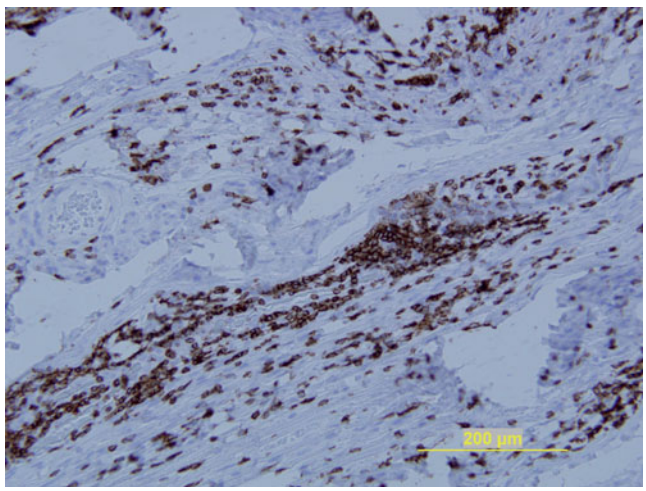

B

Figure 17–3. Lymphoma. Sural nerve biopsy demonstrates perivascular and endoneurial infiltration of lymphomatous cells on routine H&E (A) and immunoperoxidase stain using CD3 antibody (B).

Treatment

The neuropathy may respond to treatment of the underlying lymphoma or immunomodulating therapies.[48,52,76]

MULTIPLE MYELOMA

Multiple myeloma usually presents in the fifth to seventh decade of life with fatigue, bone pain, anemia, and hypercalcemia. Clinical signs and symptoms of peripheral neuropathies develop in 3–13% of patients,[66,71,77,78] while NCS demonstrate that as many as 40% of patients have a subclinical peripheral neuropathy.[78] The most common pattern is that of a distal, axonal, sensory, or sensorimotor polyneuropathy.[77,78] Less frequently, a chronic demyelinating polyneuropathy may develop.[77] Multiple myeloma can be complicated by amyloid polyneuropathy and should be considered in patients with painful paresthesias, loss of pinprick and temperature discrimination, and autonomic dysfunction (suggestive of a small fiber neuropathy) and carpal tunnel syndrome. Expanding plasmacytomas can compress cranial nerves and spinal roots as well.

Laboratory Features

Multiple myeloma is the most common hematological malignancy associated with a monoclonal gammopathy. The monoclonal protein is usually γ or μ heavy chains or κ light chains and may be identified in the serum or urine. Anemia and hypercalcemia are common. Skeletal survey typically reveals osteolytic lesions. Diagnosis of multiple myeloma requires the demonstration of at least 10% plasma cells on a bone marrow biopsy. Motor and sensory NCS usually reveal reduced amplitudes with normal or only mildly abnormal distal latencies and conduction velocities.[77,78] Superimposed median neuropathy at the wrist is common.

Histopathology

Abdominal fat-pad, rectal, or sural nerve biopsy can be performed to look for amyloid deposition. Nerve biopsies usually reveal axonal degeneration along with mild segmental demyelination,[78] although amyloid deposition is seen in only around two-thirds of nerve biopsies.[77]

Pathogenesis

The mechanism of the neuropathy in multiple myeloma is multifactorial. The neuropathy may be related to primary amyloidosis with infiltration of the nerves.[77] Other mechanisms of neuropathy may be due to the systemic consequences of multiple myeloma or (e.g., cytokines) the amyloidosis (e.g., renal failure). Chemotherapies employed to treat multiple myeloma (e.g., Bortezomib and thalidomide) commonly are associated with neuropathy. A paraneoplastic effect is speculated in demyelinating neuropathies associated with polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes (POEMS) syndrome (discussed next).

Treatment

Unfortunately, the treatment of the underlying multiple myeloma does not usually affect the course of the neuropathy.

OSTEOSCLEROTIC MYELOMA (POEMS SYNDROME)

Clinical Features

Osteosclerotic myeloma is rare and is responsible for less than 3% of myelomas. Symptomatic polyneuropathy develops in near 50% of patients with osteosclerotic myeloma and often is the presenting feature.[79] Systemic manifestations include hepatosplenomegaly, cutaneous pigmentation, hypertrichosis, edema, pericardial and pleural effusions, leukonychia, finger clubbing, gynecomastia, testicular atrophy with impotence in men, amenorrhea in women, diabetes mellitus, and hypothyroidism. This complex constitutes the Crow–Fukase or POEMS syndrome.[71,80–84] Importantly, not every patient displays all the features of POEMS syndrome. Most individuals with POEMS syndrome have osteosclerotic myeloma, but the syndrome can also occur with Castleman disease (angiofollicular lymphadenopathy), extramedullary plasmacytomas, Waldenstrom macroglobulinemia, and solitary lytic plasmacytoma, and some patients have no identifiable malignancy.

POEMS syndrome usually presents as symmetric tingling, numbness, and weakness that gradually progresses to involve proximal and distal arms and legs similar to CIDP. The sensory modalities mediated by large fibers are affected most, with decreased but relative sparing of pain and temperature sensation. Muscle stretch reflexes are reduced or absent. The cranial nerves and respiratory muscles can be affected. Papilledema is evident in 29–55% of patients,[84] a finding that is uncommon in idiopathic CIDP. Patients can also develop a myopathy secondary to associated hypothyroidism or rarely an inflammatory myopathy.[85]

Laboratory Features

POEMS is usually associated with an IgG or IgA lambda chain monoclonal gammopathy, but in up to 20% of patients, the monoclonal protein is demonstrated in the urine but not in the serum.[71] Further, because the

amount of the monoclonal protein can be small, immunoelectrophoresis and immunofixation are much more sensitive than protein electrophoresis.[84] In addition, CSF protein levels are often markedly elevated, even more so than typical CIDP.[71] POEMS syndrome is associated with high levels of serum vascular endothelial growth factor (VEGF) and, conversely, low levels of serum erythropoietin.[86,87] Serum levels of VEGF and erythropoietin normalize with a response to therapy.[86]

Skeletal survey reveals characteristic sclerotic (two-thirds of cases) or mixed sclerotic and lytic bony lesions (one-third of cases) usually in the vertebral bodies, pelvis, or ribs (Fig. 17–4).[71] In 50% of cases, these skeletal lesions are multiple and represent focal plasmacytomas. NCS can demonstrate features of a primary demyelinating or mixed axonal and demyelinating sensorimotor peripheral neuropathy.[77–79,82,88–91] NCS are usually indistinguishable from CIDP. However, conduction block is much less common in POEMS as opposed to CIDP.

Histopathology

Nerve biopsies usually reveal a combination of segmental demyelination and axonal degeneration.[82,92] A few endomysial or perivascular inflammatory cells may be seen. VEGF is highly expressed in blood vessels and some non-myelin-forming Schwann cells in nerve biopsies of patients with POEMS.[86] Light microscopy reveals an increased thickness of the basal lamina and a narrowing of the lumina of endoneurial vessels, while electron microscopy (EM) demonstrates proliferation of endothelial cells and opening of tight junctions.[86] EM may also reveal uncompacted myelin.[92]

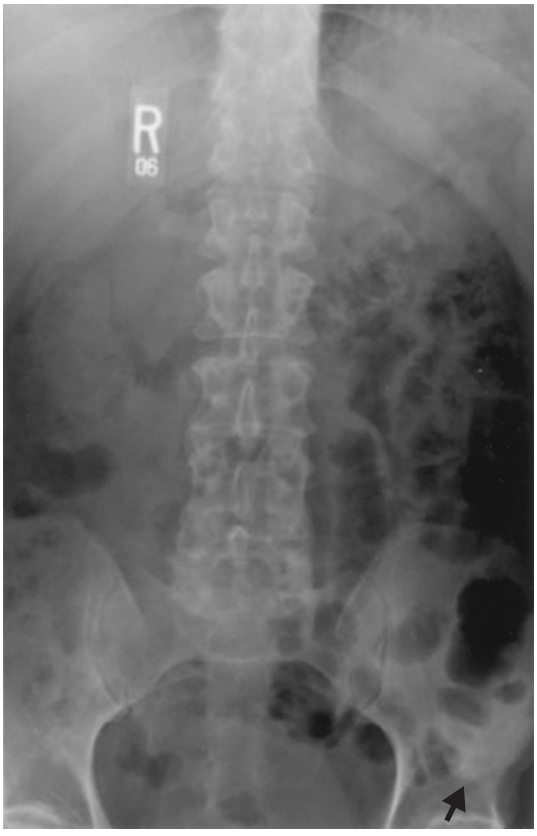

Figure 17–4. POEMS. Pelvic X-ray demonstrates a large osteosclerotic lesion (arrow) in the left iliac crest.

Pathogenesis

The pathogenesis of POEMS syndrome is not clear, but likely autoimmune in nature. Various cytokines including VEGF and matrix metalloproteinases are elevated in patients with POEMS syndrome and appear to correlate with the severity of the neuropathy.[86,87,93,94]

Treatment

The neuropathy may respond to radiation or surgical excision of the isolated plasmacytoma or to chemotherapy. The neuropathy can also improve with usual treatment given to patients with idiopathic CIDP (e.g., corticosteroids). However, the neuropathy is more refractory to treatment than typical CIDP, and POEMS needs to be suspected and re-evaluated for in all cases of refractory CIDP with repeated serum and urine immunofixation/immunoelectrophoresis and skeletal surveys. Refractory cases may respond to autologous peripheral blood stem cell transplantation.[87,94]

CASTLEMAN DISEASE (ANGIOFOLLICULAR LYMPH NODE HYPERPLASIA)

Castleman disease or angiofollicular lymph node hyperplasia is characterized by lymphoid hyperplasia associated with capillary proliferation and can be associated with POEMS syndrome (except for absence of the osteosclerotic lesions).[88] The angiofollicular lymph node hyperplasia and neuropathy may be related to increases in serum cytokine levels and VEGF, which are associated with the disorder.

WALDENSTRÖM MACROGLOBULINEMIA

Waldenström macroglobulinemia is associated with a malignant proliferation of lymphoplasmacytoid cells, which produce an IgM monoclonal protein, usually with a κ light chain.[71,95–98] It most commonly occurs in men between the ages of 50 and 70 years and usually presents with an insidious onset of progressive fatigue, weight loss, lymphadenopathy, hemorrhages (especially

nose bleeds), anemia, and weakness. Hepatomegaly and splenomegaly may be appreciated on physical examination. Nearly 50% of patients have symptoms or signs of neuropathy on clinical examination or electrophysiological testing.[99] Patients initially complain of numbness and paresthesias beginning in the feet, which then progresses proximally in the lower limbs and also affects the hands. Patients may develop difficulty in walking and loss of fine motor control of the fingers due to a sensory ataxia. Strength is normal or only slightly affected distally.

Laboratory Findings

Waldenström macroglobulinemia is responsible for about 2% of cases of monoclonal gammopathies with over 80% associated with a κ light chain. Diagnosis requires demonstration of an IgM monoclonal protein in a concentration greater than 3 g/L. The disorder is distinguished from IgM myeloma by the absence of lytic bone lesions and hypercalcemia and by the presence of hepatosplenomegaly and lymphadenopathy. Antibodies directed against MAG or sulfatide can be detected in the serum in as many as 38% of patients.[71] NCS usually demonstrate features of a demyelinating sensorimotor polyneuropathy, but sometimes an axonal sensorimotor neuropathy can be found.[71,95–99]

Histopathology

Nerve biopsies show prominent demyelination and IgM deposition on the outer myelin membranes and occasionally in the periaxonal space but not on compact myelin.[99]

Pathogenesis

The mechanism of the neuropathy is unknown. The neuropathy may be related to MAG antibodies, although a causal relationship has not been established. Some neuropathies are associated with POEMS syndrome or caused by secondary amyloidosis or nerve fiber ischemia related to serum hyperviscosity.[83]

Treatment

Some patients benefit form corticosteroids, chlorambucil, or plasma exchange. However, prospective, blinded, controlled trials have not been performed. Rituximab, a monoclonal antibody directed against CD20 that is present on B lymphocytes, is an effective treatment for Waldenström macroglobulinemia. However, there have been a few reports that rituximab may initially paradoxically worsen the associated neuropathy rather than improve it.[100,101]

NEUROPATHIES ASSOCIATED WITH MGUS

Clinical Features

MGUS neuropathy is heterogeneic in regards to clinical, laboratory, and electrophysiological features.[67,71,102–104] Neuropathies associated with an IgM monoclonal protein are typically demyelinating, while IgG and IgA monoclonal gammopathies can be axonal or demyelinating in nature. Patients with a demyelinating neuropathy can present with proximal and distal weakness and sensory symptoms typical of CIDP or just distal symptoms of distal acquired demyelinating sensory (DADS) neuropathy (see Chapter 12).[70,71,103,105,106] Individuals who are affected describe numbness and tingling in both the upper and the lower limbs beginning in the distal regions and progressing proximally. Weakness can also develop but is usually restricted to the distal limbs in the IgM-MGUS neuropathies, while patients with demyelinating neuropathies associated with IgG- and IgA-MGUS are more likely to have symmetrical proximal and distal weakness typical of idiopathic CIDP. Deep tendon reflexes are reduced or absent throughout.

Patients with an axonal neuropathy usually present with sensory symptoms in a length-dependent fashion. Their clinical, laboratory, histopathology, and electrophysiological features are indistinguishable from idiopathic sensory or sensorimotor polyneuropathies.

Laboratory Features

At least 50% of the patients with IgM-MGUS neuropathy have antibodies directed against MAG.[67,105,106] Elevated cerebrospinal fluid levels are common in patients with a demyelinating neuropathy. NCS in patients with IgG and IgA MGUS neuropathies can be either axonal or demyelinating in nature. The IgM-MGUS neuropathies are typically demyelinating with marked prolonged distal latencies, and moderately slow conduction velocities are variably reduced. Motor NCS reveal markedly prolonged distal latencies with moderate slowing of conduction velocities.[69,104–107]

Histopathology

Nerve biopsy reveals a loss of large myelinated nerve fiber population, with relative sparing of the small myelinated and unmyelinated fibers. Segmental demyelination and remyelination are also appreciated in some patients. In some patients, there is a predominance of demyelination, while in others axonal loss may be somewhat more significant. In patients with IgM-MGUS, immunohistochemistry reveals immunoglobulin deposition on the outer myelin membranes and occasionally in the periaxonal space but not on compact myelin.[72] On EM the

myelin sheaths appear to be separated, and IgM deposits are evident in these zones of myelin splitting.

Pathogenesis

IgM-MGUS is associated with a demyelinating neuropathy. Endoneurial injection or passive transfer of serum from patients with IgM-MAG antibodies to animals leads to conduction block and demyelination. However, response to plasmapheresis and other immunotherapies is less satisfactory in this IgM-MGUS subgroup than in IgG/IgA demyelinating neuropathies where a causal link is even less well established.

Except for cases of amyloid neuropathy, there is no pathogenically proven casual relationship of monoclonal gammopathy and axonal sensorimotor polyneuropathy.

Treatment

Patients with MGUS neuropathy who fulfill clinical and electrophysiological criteria for CIDP with proximal and distal weakness can improve with immunotherapy (discussed in Chapter 12).[105,106] However, those demyelinating neuropathies with mainly sensory symptoms and only mild distal weakness, particularly the IgM-MGUS neuropathies, are usually refractory to treatment. The demyelinating sensorimotor polyneuropathies associated with IgG MGUS and IgA MGUS are more amenable to treatment than the IgM-MGUS neuropathies. There is no strong medical evidence that treating the MGUS in patients has any impact on axonal neuropathies.

▶ NEUROPATHY AS A COMPLICATION OF BONE MARROW TRANSPLANTATION/ GRAFT-VS.-HOST DISEASE

Neuropathies may develop in patients who undergo bone marrow transplantation because of toxic effects of chemotherapy, radiation, infection, or an autoimmune response directed against the peripheral nerves.[34,108,109] Carcinomatous or infectious meningitis with infiltration of nerves, malnutrition, and sepsis with multiorgan failure are other causes of polyneuropathy in critically ill patients. Many cranial neuropathies and radiculopathies are related to herpes zoster infection. Thrombocytopenia can lead to hemorrhage within the nerve or plexus.

Peripheral neuropathy in bone marrow transplantation patients is often associated with graft-vs.-host disease (GVHD).[34] Chronic GVHD shares many features with a variety of autoimmune disorders, and it is possible that an immune-mediated response can be directed against peripheral nerves. Patients with chronic GVHD may develop cranial neuropathies including loss of olfactory and gustatory sensation,[110] sensorimotor polyneuropathy, multiple mononeuropathies, and severe generalized peripheral neuropathies resembling Guillain–Barre syndrome (GBS)[108,111,112] or CIDP.[34] NCS may demonstrate primary axonal, demyelinating, or mixed features. Some cases of GBS have been attributed to chemotherapy, cytomegalovirus, or *Campylobacter jejuni* infections and have improved with plasma exchange[111] or IVIG. The neuropathy may also improve with increased immunosuppressive or immunomodulating therapy and resolution of the GVHD.[34]

▶ TOXIC NEUROPATHIES SECONDARY TO CHEMOTHERAPY

Many of the commonly used chemotherapy agents can cause a toxic neuropathy (Table 17–3).[1,2,133] The mechanisms by which these agents cause toxic neuropathies vary, as can the specific type of neuropathy. The risk of developing a toxic neuropathy or more severe neuropathy appears to be greater in patients with a preexisting neuropathy (e.g., Charcot–Marie–Tooth disease and diabetes) and in those who also take other potentially neurotoxic drugs (e.g., nitrofurantoin, isoniazid, disulfiram, pyridoxine, etc.). Chemotherapeutic agents usually cause a sensory greater than motor length-dependent axonal neuropathy or neuronopathy/ganglionopathy.

CISPLATIN

Clinical Features

Cisplatin is used for a variety of cancers and can cause a predominantly sensory neuropathy (ganglionopathy), usually at cumulative doses of 225–500 mg/m^2.[114–122] There is a predilection for involvement of large myelinated nerve fibers leading to paresthesia, hypesthesia, loss of vibratory perception and proprioception with gait ataxia, and pseudoathetoid movements. Muscle stretch reflexes are reduced or absent throughout. Interestingly, as many as 40% of patients can develop Lhermitte's sign, perhaps due to demyelination and edema of the posterior columns. Only a few patients (approximately 2%) develop weakness.[116] Onset of symptoms can appear as late as 8 weeks after the drug has been stopped and may progress up to 6 months following discontinuation of cisplatin, a phenomenon known as coasting.

Laboratory Features

NCS demonstrate low-amplitude or absent SNAPs with normal or only slightly prolonged distal latencies or slow

▶ TABLE 17–3. TOXIC NEUROPATHIES SECONDARY TO CHEMOTHERAPY

Drug	Mechanism of Neurotoxicity	Clinical Features	Nerve Histopathology	EMG/NCS
Vinca alkaloids (vincristine, vinblastine, vindesine, and vinorelbine)	Interfere with axonal microtubule assembly; impairs axonal transport	Symmetric, S-M, large/small fiber PN; autonomic symptoms common; infrequent cranial neuropathies	Axonal degeneration of myelinated and unmyelinated fibers; regenerating clusters, minimal segmental demyelination	Axonal sensorimotor PN; distal denervation on EMG; abnormal QST, particularly vibratory perception
Cisplatin	Preferential damage to dorsal root ganglia: • binds to and cross-links DNA • inhibits protein synthesis • impairs axonal transport	Predominant large fiber sensory neuronopathy; sensory ataxia	Loss of large > small myelinated and unmyelinated fibers; axonal degeneration with small clusters of regenerating fibers; secondary segmental demyelination	Low-amplitude or unobtainable SNAPs with normal CMAPs and EMG; Abnormal QST, particularly vibratory perception
Taxanes (paclitaxel, docetaxel)	Promotes axonal microtubule assembly; interferes with axonal transport	Symmetric, predominantly sensory, PN; large fiber modalities affected more than small fiber	Loss of large > small myelinated and unmyelinated fibers; axonal degeneration with small clusters of regenerating fibers; secondary segmental demyelination	Axonal sensorimotor PN; distal denervation on EMG; abnormal QST, particularly vibratory perception
Suramin				
Axonal PN	Unknown; ? inhibition of neurotrophic growth factor binding ? neuronal lysosomal storage	Symmetric, length-dependent, sensory-predominant PN	None described	Abnormalities consistent with an axonal S-M PN
Demyelinating PN	Unknown; ? immunomodulating effects	Subacute, S-M PN with diffuse proximal and distal weakness; areflexia; increased CSF protein	Loss of large and small myelinated fibers with primary demyelination and secondary axonal degeneration; occasional epi- and endoneurial inflammatory cell infiltrates	Features suggestive of an acquired demyelinating sensorimotor PN (e.g., slow CVs, prolonged distal latencies and F-wave latencies, conduction block, and temporal dispersion)
ARA-C	Unknown; ? selective Schwann cell toxicity; ? immunomodulating effects	GBS-like syndrome; pure sensory neuropathy; brachial plexopathy	Loss of myelinated nerve fibers; axonal degeneration; segmental demyelination; no inflammation	Axonal, demyelinating, or mixed S-M PN; denervation on EMG
Etopside (VP-16)	Unknown; ? selective dorsal root ganglia toxicity	Length-dependent, sensory-predominant PN; autonomic neuropathy	None described	Abnormalities consistent with an axonal S-M PN
Bortezomib (Velcade)	Unknown	Length-dependent, sensory, predominantly small fiber PN	Not reported	Abnormalities consistent with an axonal sensory neuropathy with early small fiber involvement (abnormal autonomic studies and temperature perception on QST)

S-M, sensorimotor; PN, polyneuropathy; EMG, electromyography; NCS, nerve conduction studies; QST, quantitative sensory testing; SNAP, sensory nerve action potential; CMAP, compound muscle action potential; GBS, Guillain–Barré syndrome, ARA-C, cytosine arabinoside.

Modified with permission from Amato AA, Collins MP. Neuropathies associated with malignancy. Semin Neurol 1998;18:125–144.

sensory conduction velocities.[118–120] Vibratory perception is usually impaired on quantitative sensory testing. Motor NCS and needle EMG are usually normal.

Histopathology

Sural nerve biopsies reveal a predominant loss of large myelinated nerve fibers with axonal degeneration, segmental demyelination, and regenerating axonal sprouts.[115,117,118] Degeneration of neurons in the dorsal root ganglion and secondary axonal degeneration on both central and peripheral nerve processes are seen in rats given toxic doses of cisplatin.[119]

Pathogenesis

Cisplatin covalently binds DNA creating inter- and intrastrand cross-links. Pathological and electrophysiological studies suggest that neurons in the dorsal root ganglion are preferentially affected. Binding of the drug to neuronal DNA may inhibit transcription of important proteins and impair axonal transport.

OXALIPLATIN

Oxaliplatin causes a very unique, but frequent, acute sensory neuropathy, which is triggered or aggravated by exposure to cold but is rapidly reversible, without persistent impairment of sensory function.[123]

VINCRISTINE

Clinical Features

Vincristine is commonly associated with a toxic sensorimotor and autonomic neuropathy.[113,124–126] Affected patients develop paresthesias and numbness, which can at times occur in the fingers before the toes. The loss of ankle jerks often precedes the subjective loss of sensation. Weakness of the hands and feet may occur in 25–35% of patients with increased dosage. Autonomic neuropathy characterized by constipation, urinary retention, impotence, and orthostatic hypotension may occur as well. Cranial neuropathies are uncommon but optic neuropathy, oculomotor palsies, facial weakness, hearing loss, and laryngeal paralysis have been described. Neuropathic symptoms and signs are more prominent after a cumulative dose of 12 mg of vincristine.[113] However, neuropathy can develop as early as 2 weeks following a single 2 mg/m^2 dose. A coasting effect can be seen such that 24–30% of patients continue to worsen the first month after discontinuation of vincristine.[113] The median duration of symptoms after stopping the medication is around 3 months.[113]

Laboratory Features

Sensory and motor NCS reveal diminished amplitudes or absent responses with normal or only mildly prolonged distal latencies and slow conduction velocities.[113,126] The SNAP and CMAP amplitudes improve following discontinuation of cisplatin but do not usually return to pretreatment levels. Active denervation in the form of fibrillation potentials and positive sharp waves may be seen on EMG in distal muscles.

Histopathology

Nerve biopsies demonstrate axonal degeneration and loss of myelinated and unmyelinated nerve fibers and clusters of regenerating axonal sprouts.

Pathogenesis

Vinca alkaloids inhibit microtubule formation by binding to tubulin. This, in turn, impairs axoplasmic transport and leads to cytoskeletal disarray and axonal degeneration.[127]

VINORELBINE

Clinical Features

Vinorelbine is a semisynthetic vinca alkaloid that causes a dose-related peripheral neuropathy in 20–50% of patients.[128–130] It is less neurotoxic than vincristine, and the associated neuropathy is severe in only 1% of cases. Patients present with distal sensory loss and paresthesia, and motor weakness can occur after 3–6 months of treatment. After 12 cycles of vinorelbine, most patients have reduced or absent muscle stretch reflexes at the ankles.[130] As with vincristine, symptoms and signs of autonomic neuropathy may develop but are less common.

Laboratory Features

Serial NCS reveal a dose-dependent reduction of SNAP and CMAP amplitudes, with preservation of distal latencies and conduction velocities.[130] The SNAP and CMAP amplitudes improve following discontinuation of the vinorelbine.

Histopathology

Nerve pathology has not been reported.

Pathogenesis

The pathogenesis is presumably similar to that of vincristine.

ETOPSIDE (VP-16)

Clinical Features

VP-16 is a semisynthetic derivative of podophyllotoxin, which causes a moderate-to-severe predominantly sensory axonal neuropathy or ganglionopathy in 4–10% of patients.[131] Severe autonomic neuropathy can develop, leading to orthostatic hypotension and gastroparesis. The neuropathy gradually improves over several weeks or months following discontinuation.

Laboratory Features

NCS reveal low-amplitude SNAPs and CMAPs.

Histopathology

In mice, VP-16 causes degeneration of the cell bodies within the dorsal root ganglion.[131] However, histopathology has not been well described in humans with the neuropathy.

Pathogenesis

VP-16 inhibits microtubule function, and the pathogenic basis of the neuropathy is probably similar to vincristine and vinorelbine.

PACLITAXEL (TAXOL)

Clinical Features

Taxol is associated with a dose-dependent, predominantly sensory neuropathy.[132–140] A subclinical or mild neuropathy develops in up to 85% of patients after three to seven cycles of taxol at doses of 135–200 mg/m^2. A severe neuropathy occurs in 2% of patients at this lower dose range. However, at doses between 250 and 350 mg/m^2, neuropathic symptoms develop after first or second cycle, sometimes within 24 hours of the initial infusion. As many as 70% of patients have a severe neuropathy after high-dose paclitaxel.[134,135] With cumulative doses above 1500 mg/m^2, preexisting neuropathy and prior or concurrent exposure to neurotoxic agents are additional risk factors for developing a severe neuropathy.[135]

Laboratory Features

Sensory and motor NCS demonstrated reduced SNAP and CMAP amplitudes, which correlate with the cumulative dose of taxol.[132–138] Distal latencies and conduction velocities are usually normal, although demyelinating features have been described.[133,137] Quantitative sensory testing reveals impairment of vibratory perception more often than abnormal thermal thresholds.[132,138] Needle fibrillation potentials may be seen on EMG of distal limb muscles.[133,136]

Histopathology

Sural nerve biopsies reveal a preferential loss of large myelinated nerve fibers along with axonal degeneration with secondary demyelination and remyelination.[136,137] Regenerating axonal sprouts are uncommon. On EM, there is accumulation of tubular and membranous structures within the axons.[136]

Pathogenesis

Taxol may have a toxic effect on the neuronal cell body, the axon, or both. In contrast to the vinca alkaloids, which disassemble microtubules, the taxanes (taxol and taxotere) promote microtubule assembly by increasing tubulin polymerization. The subsequent aggregation and accumulation of abnormal bundles of microtubules in dorsal root ganglia, axons, and Schwann cells impair axoplasmic transport.[141]

DOCETAXEL (TAXOTERE)

Clinical Features

Taxotere, a semisynthetic analogue of taxol is also associated with a dose-dependent, predominantly sensory neuropathy, although neuropathies are less frequent and severe than that seen with taxol.[142–146] Patients describe pain in the hands and feet and also have Lhermitte's sign. On examination, large fiber sensory modalities are preferentially affected and most patients have reduced or absent muscle stretch reflexes at the ankles. Mild proximal and distal weakness is evident in 5–19% of patients. Most patients improve 1–2 months after cessation of the chemotherapy; however, neuropathic symptoms can continue to worsen for several months after discontinuation of the docetaxel.

Laboratory Features

Sensory and motor NCS reveal diminished amplitudes with only mild slowing of conduction velocities.[142,144]

Histopathology

Sensory nerve biopsy may reveal a loss of large myelinated fibers, with scattered fibers undergoing axonal degeneration.[144]

Pathogenesis

The pathogenic mechanism is presumably similar to taxol.

SURAMIN

Clinical Features

Suramin is a hexasulfonated naphthylurea that causes a peripheral neuropathy in 25–90% treated patients.[147–149] Neurotoxicity is the dose-limiting side effect, and there

appears to be two distinct types of toxic neuropathy: (1) a dose-dependent, distal, axonal sensorimotor polyneuropathy and (2) a subacute demyelinating polyradiculoneuropathy.

The distal axonopathy is more common and manifests with distal numbness and paresthesias.[147,149] Examination reveals reduced light touch, pain, and vibratory perception; mild weakness of the distal limbs (e.g., toe extensors); and diminished ankle reflexes. This neuropathy is reversible upon suramin discontinuation.

A subacute sensorimotor demyelinating polyradiculoneuropathy is more severe and develops in 10–20% of patients after 1–5 months of treatment.[147–149] It is associated with peak plasma concentrations of over 300 μg/L, exposure to greater than 200 μg/L for more than 25 days per month, or cumulative dose of 40,000 mg-h/L. Patients present with numbness and paresthesias of the distal limbs or face, followed by symmetric, proximal greater than distal weakness. Muscle stretch reflexes are decreased or absent throughout. The weakness is insidiously progressive and can involve the respiratory muscles. Up to 25% of affected patients become bedridden and require mechanical ventilation. The neuropathy can continue to progress for 1 month following suramin discontinuation. It can take several months for patients to recover, and there frequently are residual numbness and weakness. Plasma exchange has been tried in an uncontrolled fashion with mixed results.

Laboratory Features

CSF protein may be elevated in patients with subacute demyelinating polyradiculoneuropathy.[147,149] NCS in the more common distal sensorimotor polyneuropathy reveal decreased amplitudes of SNAPs and CMAPs with relatively preserved distal latencies and conduction velocities.[147,149] Abnormal vibratory and cooling thresholds are seen with quantitative sensory testing.[147] Needle EMG may reveal fibrillation potentials and neurogenic MUAPs in distal muscles.

Electrodiagnostic studies in the subacute sensorimotor polyradiculoneuropathy reveal features of demyelination: prolonged distal latencies and F-waves, slow conduction velocities, temporal dispersion, and conduction block.[147–149] As in the distal axonopathy, quantitative sensory testing shows increased vibratory and cooling thresholds.[147] EMG demonstrates decreased recruitment of MUAPs in proximal and distal muscles and occasional fibrillation potentials.

Histopathology

Sural nerve biopsies in patients with the subacute demyelinating polyradiculoneuropathy demonstrate loss of large and small myelinated nerve fibers, demyelination and remyelination, and secondary axonal degeneration.[147–149] Epi- and endoneurial mononuclear inflammatory infiltrates may be seen. In animal models, suramin induces a length-, dose-, and time-dependent axonal sensorimotor polyneuropathy associated with axonal degeneration, atrophy, and accumulation of glycolipid lysosomal inclusions.[150]

Pathogenesis

The mechanism of neurotoxicity is unknown. Suramin may inhibit the interaction of neurotrophic factors with its peripheral nerve receptors[151] or induce a form of lysosomal storage disease. The demyelinating neuropathy may be immune-mediated, related to the immunomodulating effects of suramin.[152]

CYTOSINE ARABINOSIDE

Clinical Features

Cytosine arabinoside (ARA-C) is an antimetabolite used in the treatment of leukemia and lymphoma. Sensory neuropathy and severe sensorimotor polyneuropathy resembling GBS[153–158] have been reported with cumulative doses ranging from 60 mg/m^2 to 36 g/m^2. These neuropathies can begin within hours or weeks following treatment.

Laboratory Features

Patients with a GBS-like neuropathy have increased CSF protein.[156] EMG and NCS can be compatible with a primary axonal[157] or an acquired demyelinating sensorimotor polyneuropathy.[154]

Histopathology

Sural nerve biopsies may reveal demyelination or axonal degeneration.[153,156,157]

Pathogenesis

The pathophysiological mechanism(s) for the neuropathies are not known. The antimetabolite action of ARA-C may inhibit proteins necessary for myelin production, axonal structure, or axonal transport. Alternatively, the immunomodulating effects of ARA-C may predispose patients to an immune attack against the peripheral nerves.

IFOSFAMIDE

Ifosfamide, a cyclophosphamide analog, has been associated with polyneuropathy with a total doses of 14 g/m^2 or more.[159] Patients manifest numbness, and painful paresthesias begin in the hands and feet 10–14 days after treatment and gradually resolve but recur if they are rechallenged with the chemotherapy. Electrodiagnostic and histopathologic data are lacking, but the occasional

onset beginning in the hands rather than the feet is suggestive of a ganglionopathy.

BORTEZOMIB (VELCADE)

Bortezomib, a selective, reversible inhibitor of the proteasome, was recently approved for treatment of multiple myeloma.[157] Treatment-emergent neuropathy or symptomatic worsening of the neuropathy developed in 35% (90/256) of myeloma patients in treatment trials: 37% (84/228) of patients receiving bortezomib 1.3 mg/m^2 and 21% (6/28) receiving 1.0 mg/m^2.[160,161] Polyneuropathy also occurred in 9/21 patients with renal cell carcinoma treated with bortezomib.[162] The risk of neuropathy correlates with the cumulative dose of bortezomib. After reaching a cumulative dose of approximately 30 mg/m^2, the estimated probability of experiencing peripheral neuropathy was 50% in the overall population and 37% in the subset of patients without peripheral neuropathy at baseline.[160,161] Patients usually complain of paresthesia, burning dysesthesia, and numbness in a length-dependent distribution. The neuropathy usually improves when the dose is reduced or drug is discontinued. The electrophysiological characteristics of the treatment-emergent neuropathy suggest a length-dependent, axonal, sensory polyneuropathy.[161,163] The absence of electrophysiological changes in some patients with symptoms of burning and dysesthesias in their feet suggests involvement of small-diameter nerve fibers (i.e., a small fiber neuropathy) as well. Recent studies and our own research suggest that bortezomib may block the ubiquitin–proteasome pathway, possibly causing a build-up of proteins that should be degraded by the proteasome, resulting in impairment of neuronal function, initially in the dorsal root ganglia, and then leading to retrograde (or "dying-back") axonopathy of small nerve fibers followed by larger nerve fibers.

▶ SUMMARY

Neuropathy is not an uncommon complication in a cancer patient with cancer. Although a paraneoplastic etiology is often considered, most neuropathies in the setting of cancer are not the result of an immune-mediated remote effect of cancer. The neuropathy may be due to adverse side effects of chemotherapeutic agents (toxic neuropathy), nutritional, or due to compression or infiltration of the tumor. Treatment and prognosis are dependent on the etiology of the neuropathy.

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CHAPTER 18

Toxic Neuropathies

Neuropathies can develop as complications of toxic effects of various drugs and other environmental exposures (Table 18–1).[1] Toxic neuropathies due to chemotherapeutic agents are discussed in Chapter 17. This chapter deals with toxic neuropathies related to other medications.

MISONIDAZOLE

Clinical Features

Misonidazole is used as an adjuvant agent in the treatment of various malignancies.[1–3] Some patients develop painful paresthesias and sometimes distal weakness in a length-dependent pattern after approximately 3–5 weeks of therapeutic drug administration (total dose greater than 18 g). Vibratory and temperature perception are usually reduced, but muscle stretch reflexes are preserved. The neuropathy usually improves following discontinuation of the drug.

Laboratory Features

Sensory nerve conduction studies (NCS) reveal reduced amplitudes or unobtainable responses in the legs more than the arms. Motor conduction studies are typically normal.

Histopathology

A reduction in the large myelinated fibers with axonal degeneration and segmental demyelination and remyelination is apparent on sural nerve biopsies. Accumulation of neurofilaments with axonal swellings can be found on electron microscopy (EM).

Pathogenesis

The pathogenic basis of the neuropathy is not known.

METRONIDAZOLE

Clinical Features

Metronidazole is used to treat a variety of protozoan infections and Crohn disease.[4–6] As with misonidazole, metronidazole is a member of the nitroimidazole group and has been associated with hyperalgesia and hypesthesia in a length-dependent pattern. Motor strength is typically normal.

Laboratory Features

Nerve conduction studies (NCS) reveal reduced amplitudes or absent sensory nerve action potentials (SNAPs) in the legs worse than in the arms, along with normal motor conduction studies.

Histopathology

Nerve biopsies reveal loss of myelinated nerve fibers.

Pathogenesis

The pathogenic basis of the neuropathy is not known.

CHLOROQUINE

Clinical Features

Chloroquine is used in the treatment of malaria, sarcoidosis, systemic lupus erythematosus, scleroderma, and rheumatoid arthritis.[7–9] Chloroquine can cause a toxic myopathy characterized by slowly progressive, painless, proximal weakness and atrophy, which are worse in the legs than in the arms (discussed in Chapter 32). A neuropathy can also develop with or without the myopathy, leading to sensory loss, distal weakness, and reduced muscle stretch reflexes. The "neuromyopathy" usually appears in patients taking 500 mg for a year or more but has been reported with doses as low as 200 mg/d. The signs and symptoms of the neuropathy and myopathy are usually reversible following discontinuation of chloroquine.

Laboratory Features

Serum creatine kinase (CK) levels are usually elevated due to the superimposed myopathy. NCS reveal mild slowing of motor and sensory nerve conduction velocities (NCVs) with a mild to moderate reduction in the amplitudes, although NCS may be normal in patients with only the myopathy.[7–9] Electromyography (EMG) demonstrates myopathic motor unit action potentials (MUAPs), increased insertional activity in the form of positive sharp waves, fibrillation potentials, and occasionally myotonic potentials, particularly in the proximal muscles.

▶ **TABLE 18–1. TOXIC NEUROPATHIES**

Drug	Mechanism of Neurotoxicity	Clinical Features	Nerve Histopathology	EMG/NCS
Misonidazole	Unknown	Painful paresthesias and loss of large and small fiber sensory modalities and sometimes distal weakness in length-dependent pattern	Axonal degeneration of large myelinated fibers; axonal swellings; segmental demyelination	Low-amplitude or unobtainable SNAPs with normal or only slightly reduced CMAP amplitudes
Metronidazole	Unknown	Painful paresthesias and loss of large and small fiber sensory modalities and sometimes distal weakness in length-dependent pattern	Axonal degeneration	Low-amplitude or unobtainable SNAPs with normal CMAP
Chloroquine and hydroxychloroquine	Amphiphilic properties may lead to drug–lipid complexes that are indigestible and result in accumulation of autophagic vacuoles	Loss of large and small fiber sensory modalities and distal weakness in length-dependent pattern; superimposed myopathy may lead to proximal weakness	Axonal degeneration with autophagic vacuoles in nerves as well as muscle fibers	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes; distal denervation on EMG; irritability and myopathic appearing MUAPs proximally in patients with superimposed toxic myopathy
Amiodarone	Amphiphilic properties may lead to drug–lipid complexes that are indigestible and result in accumulation of autophagic vacuoles	Paresthesia and pain with loss of large and small fiber sensory modalities and distal weakness in length-dependent pattern; superimposed myopathy may lead to proximal weakness	Axonal degeneration and segmental demyelination with myeloid inclusions in nerves and muscle fibers	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes; can also have prominent slowing of CVs; distal denervation on EMG; irritability and myopathic appearing MUAPs proximally in patients with superimposed toxic myopathy
Colchicine	Inhibits polymerization of tubulin in microtubules and impairs axoplasmic flow	Numbness and paresthesia with loss of large fiber modalities in a length-dependent fashion; superimposed myopathy may lead to proximal in addition to distal weakness	Nerve biopsies demonstrate axonal degeneration; muscle biopsies reveal fibers with vacuoles	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes; irritability and myopathic appearing MUAPs proximally in patients with superimposed toxic myopathy
Podophyllin	Binds to microtubules and impairs axoplasmic flow	Sensory loss, tingling, muscle weakness, and diminished muscle stretch reflexes in length-dependent pattern; autonomic neuropathy	Axonal degeneration	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes

(*continued*)

▶ **TABLE 18–1. (CONTINUED)**

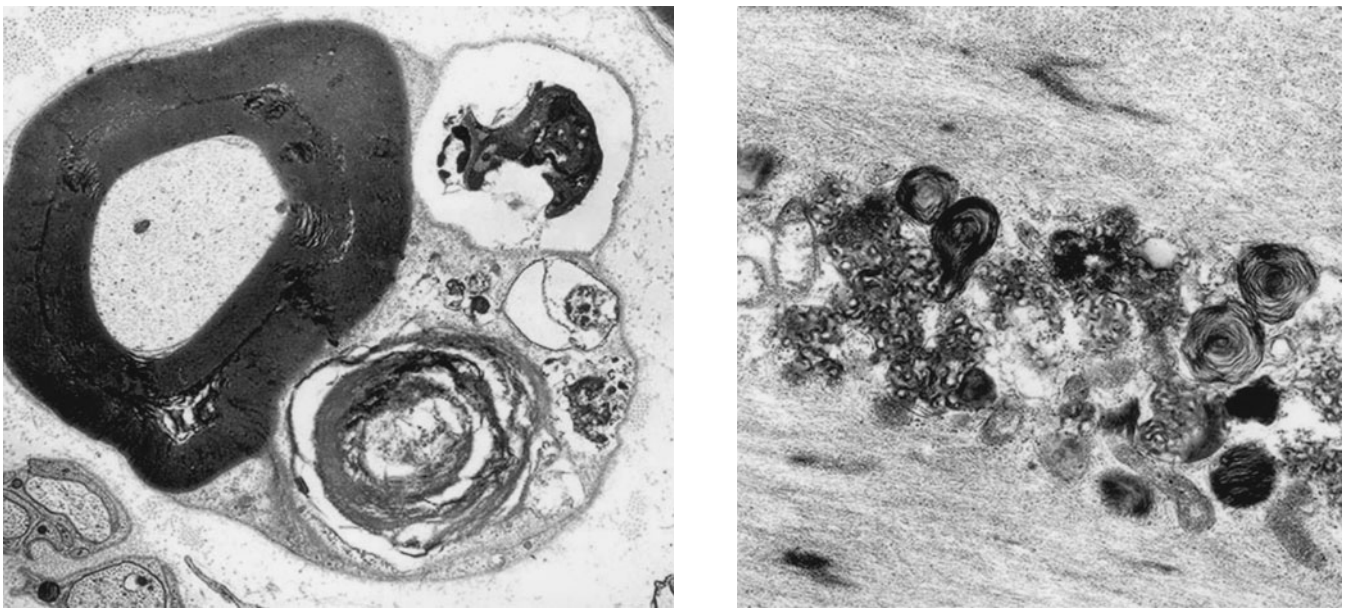
Drug	Mechanism of Neurotoxicity	Clinical Features	Nerve Histopathology	EMG/NCS
Thalidomide	Unknown	Numbness, tingling, and burning pain and weakness in a length-dependent pattern	Axonal degeneration; Autopsy studies reveal degeneration of dorsal root ganglia	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes
Disulfiram	Accumulation of neurofilaments and impaired axoplasmic flow	Numbness, tingling, and burning pain in a length-dependent pattern	Axonal degeneration with accumulation of neurofilaments in the axons	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes
Dapsone	Unknown	Distal weakness that may progress to proximal muscles; sensory loss	Axonal degeneration and segmental demyelination	Low-amplitude or unobtainable CMAPs with normal or reduced SNAP amplitudes
Leflunomide	Unknown	Paresthesia and numbness in a length-dependent pattern	Unknown	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes
Nitrofurantoin	Unknown	Numbness, painful paresthesia, and severe weakness that may resemble GBS	Axonal degeneration; autopsy studies reveal degeneration of dorsal root ganglia and anterior horn cells	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes
Pyridoxine (vitamin B6)	Unknown	Dysesthesia and sensory ataxia; impaired large fiber sensory modalities on examination	Marked loss of sensory axons and cell bodies in dorsal root ganglia	Reduced amplitudes or absent SNAPs
Isoniazid	Inhibit pyridoxal phosphokinase leading to pyridoxine deficiency	Dysesthesia and sensory ataxia; impaired large fiber sensory modalities on examination	Marked loss of sensory axons and cell bodies in dorsal root ganglia and degeneration of the dorsal columns	Reduced amplitudes or absent SNAPs and to a lesser extent CMAPs
Ethambutol	Unknown	Numbness with loss of large fiber modalities on examination	Axonal degeneration	Reduced amplitudes or absent SNAPs
Antinucleosides	Unknown	Dysesthesia and sensory ataxia; impaired large fiber sensory modalities on examination	Axonal degeneration	Reduced amplitudes or absent SNAPs
Phenytoin	Unknown	Numbness with loss of large fiber modalities on examination	Axonal degeneration and segmental demyelination	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes
Lithium	Unknown	Numbness with loss of large fiber modalities on examination	Axonal degeneration	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes
Acrylamide	Unknown; may be caused by impaired axonal transport	Numbness with loss of large fiber modalities on examination; sensory ataxia; mild distal weakness	Degeneration of sensory axons in peripheral nerves and posterior columns, spinocerebellar tracts, mamillary bodies, optic tracts, and corticospinal tracts in the CNS	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes

(*continued*)

▶ **TABLE 18–1. (CONTINUED)**

Drug	Mechanism of Neurotoxicity	Clinical Features	Nerve Histopathology	EMG/NCS
Carbon disulfide	Unknown	Length-dependent numbness and tingling with mild distal weakness	Axonal swellings with accumulation of neurofilaments	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes
Ethylene oxide	Unknown; may act as alkylating agent and bind DNA	Length-dependent numbness and tingling; may have mild distal weakness	Axonal degeneration	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes
Organophosphates	Binds and inhibits neuropathy target esterase	Early features are those of neuromuscular blockade with generalized weakness; later axonal sensorimotor PN ensues	Axonal degeneration along with degeneration of gracile fasciculus and corticospinal tracts	Early: repetitive firing of CMAPs and decrement with repetitive nerve stimulation Late: axonal sensorimotor PN
Hexacarbons	Unknown; may lead to covalent cross-linking between neurofilaments	Acute, severe sensorimotor PN that may resemble GBS	Axonal degeneration and giant axons swollen with neurofilaments	Features of a mixed axonal and/or demyelinating sensorimotor axonal PN—reduced amplitudes, prolonged distal latencies, conduction block, and slowing of CVs
Lead	Unknown; may interfere with mitochondria	Encephalopathy; motor neuropathy (often resembles radial neuropathy with wrist and finger drop); autonomic neuropathy; bluish-black discoloration of gums	Axonal degeneration of motor axons	Reduction of CMAP amplitudes with active denervation on EMG
Mercury	Unknown; may combine with sulfhydryl groups	Abdominal pain and nephrotic syndrome; encephalopathy; ataxia; paresthesia	Axonal degeneration; degeneration of dorsal root ganglia, calcarine, and cerebellar cortex	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes
Thallium	Unknown	Encephalopathy; painful sensory symptoms; mild loss of vibration; distal or generalized weakness may also develop; autonomic neuropathy; alopecia	Axonal degeneration	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes
Arsenic	Unknown; may combine with sulfhydryl groups	Abdominal discomfort, burning pain, and paresthesia; generalized weakness; autonomic insufficiency; can resemble GBS	Axonal degeneration	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes may have demyelinating features: prolonged distal latencies and slowing of CVs
Gold	Unknown	Distal paresthesia and reduction of all sensory modalities	Axonal degeneration	Low-amplitude or unobtainable SNAPs

S-M, sensorimotor; PN, polyneuropathy; EMG, electromyography; NCS, nerve conduction studies; GBS, Guillain–Barre syndrome; CMAP, compound muscle action potential; SNAP, sensory nerve action potential; CV, conduction velocity.



A B

Figure 18–1. Chloroquine neuropathy. Ultrastructural examination confirmed the presence of cytoplasmic lamellar inclusions in the Schwann cell cytoplasm (A). Close examination show the dimorphism of the inclusions made up of both curvilinear bodies and laminated (myeloid) osmophilic material in smooth muscle cell (B). (With permission from Juan M. Bilbao. Neuropathology. Case 173–SLE, Paraproteinemia and Polyneuropathy (Images 7 and 8). Published on line in November 1998.)

Neurogenic MUAPs and reduced recruitment are found in more distal muscles.

Histopathology

Nerve biopsies demonstrate autophagic vacuoles and inclusions within Schwann cells (Fig. 18–1). Vacuoles may also be evident in muscle biopsies.

Pathogenesis

The pathogenic basis of the neuropathy is not known but may be related to the amphiphilic properties of the drug. Chloroquine contains both hydrophobic and hydrophilic regions that allow chloroquine to interact with the anionic phospholipids of cell membranes and organelles. This drug–lipid complex may be resistant to digestion by lysosomal enzymes, leading to the formation of autophagic vacuoles filled with myeloid debris that may, in turn, cause degeneration of nerves and muscle fibers.

HYDROXYCHLOROQUINE

Hydroxychloroquine is structurally similar to chloroquine and not surprisingly has also been associated with a toxic neuromyopathy.[8] Weakness and histological abnormalities are usually not as severe as seen in chloroquine myopathy. Vacuoles are typically absent on biopsy, but EM still usually demonstrates the abnormal accumulation of myeloid and curvilinear bodies.

AMIODARONE

Clinical Features

Amiodarone is an antiarrhythmic medication that is also associated with a neuromyopathy similar to chloroquine.[10–15] Severe proximal and distal weakness can develop in the legs worse than in the arms, combined with distal sensory loss, tingling, and burning pain. In addition, amiodarone is also associated with tremor, thyroid dysfunction, keratitis, pigmentary skin changes, hepatitis, pulmonary fibrosis, and parotid gland hypertrophy. The neuromyopathy typically appears after patients have taken the medication for 2–3 years. Physical examination demonstrates distal arm and leg weakness, reduced sensation to all modalities, and diminished muscle stretch reflexes.

Laboratory Features

Sensory NCS reveal markedly reduced amplitudes and, when obtainable, mild to moderately slow conduction velocities and prolonged distal latencies.[11,13–15] Motor NCS may also be abnormal but usually not to the same degree as sensory studies. EMG demonstrates fibrillation

potentials, positive sharp waves, and occasionally myotonic discharges with a mixture of myopathic and neurogenic appearing MUAPs.

Histopathology

Muscle biopsies demonstrate autophagic vacuoles with myeloid and dense inclusions on EM and neurogenic atrophy, particularly, in distal muscles. Sural nerve biopsies demonstrate a combination of segmental demyelination and axonal loss. EM reveals lamellar or dense inclusions in Schwann cells, pericytes, and endothelial cells. The inclusions in muscle and nerve biopsies have persisted as long as 2 years following discontinuation of the medication.

Pathogenesis

The pathogenesis is presumably similar to other amphiphilic medications (e.g., chloroquine).

COLCHICINE

Clinical Features

Colchicine is used primarily to treat patients with gout and is also associated with a toxic neuropathy and myopathy.[16–18] Affected individuals usually present with proximal weakness and numbness and tingling in the distal extremities. Reduced sensation to touch, vibration, and position sense and diminished muscle stretch reflexes are found on examination.

Laboratory Features

Motor and sensory NCS demonstrated reduced amplitudes.[16–18] The distal motor and sensory latencies can be normal or slightly prolonged and conduction velocities are normal or mildly slow. EMG demonstrates fibrillation potentials and positive sharp waves along with short-duration, low-amplitude MUAPs in the proximal limb muscles and long-duration, large-amplitude MUAPs distally.

Histopathology

Muscle biopsies reveal a vacuolar myopathy, while sensory nerves demonstrate axonal degeneration.

Pathogenesis

Colchicine inhibits the polymerization of tubulin into microtubules. The disruption of the microtubules probably leads to defective intracellular movement of important proteins, nutrients, and waste products in muscle and nerves.[17]

PODOPHYLLIN

Clinical Features

Podophyllin is a topical agent used to treat condylomata acuminata. Systemic side effects include gastrointestinal paresis, urinary retention, pancytopenia, and liver and renal dysfunction.[19–23] Podophyllin is also potentially toxic to both the central and the peripheral nervous systems, leading to psychosis, altered consciousness, and polyneuropathy. The neuropathy is characterized by slowly progressive sensory loss, paresthesias, muscle weakness, and diminished muscle stretch reflexes in length-dependent pattern. Autonomic neuropathy with nausea, vomiting, constipation, urinary retention, orthostatic hypotension, and tachycardia may also occur. The signs and symptoms of this toxic neuropathy can progress for a couple months even after stopping the medication. The neuropathy gradually improves with discontinuation of the podophyllin, but it can take several months to over a year and residual deficits may remain.

Laboratory Features

Cerebrospinal fluid (CSF) protein levels can be elevated. Laboratory evaluation may also demonstrate pancytopenia, liver function abnormalities, and renal insufficiency. Sensory nerve conduction NCS reveal absent SNAPs or their reduced amplitudes.[21] Motor NCS are less affected but can demonstrate reduced amplitudes.

Histopathology

Nerve biopsies demonstrate axonal degeneration.

Pathogenesis

Podophyllin binds to microtubules similar to colchicine and probably inhibits axoplasmic flow leading to axonal degeneration.[24]

THALIDOMIDE

Clinical Features

Thalidomide is an immunomodulating agent used to treat multiple myeloma, graft-vs.-host disease, leprosy, and other autoimmune disorders.[25–31] Thalidomide is associated with severe teratogenic effects as well as peripheral neuropathy, which can be dose limiting. Most patients who develop the neuropathy have received a cumulative dose of at least 20 g of thalidomide.[30] Less then 10% of patients receiving less than 20 g of thalidomide develop a polyneuropathy. Patients complain of numbness, painful tingling, and burning discomfort in

the feet and hands and less commonly muscle weakness and atrophy. Even after stopping the drug for 4–6 years, as many as 50% patients continue to have significant symptoms. Physical examination demonstrates a reduction in vibration and position sense, hypo- or areflexia, and occasionally proximal and distal weakness.

Laboratory Features

NCS demonstrate reduced amplitudes or complete absence of the SNAPs with preserved conduction velocities when obtainable.[25–28,30,31] Motor NCS are usually normal.

Histopathology

Nerve biopsies reveal a loss of large-diameter myelinated fibers and axonal degeneration.[31] Degeneration of dorsal root ganglion cells has been appreciated on autopsies.

Pathogenesis

The pathogenic basis of the neuropathy is not known.

DISULFIRAM

Clinical Features

Disulfiram (antabuse) is used to treat alcoholism. It is metabolized to carbon disulfide, which is a neurotoxin and can have adverse effects on both the peripheral nervous system (PNS) and the central nervous system (CNS).[32–38] A neuropathy with distal weakness (e.g., foot drop) and sensory loss may develop as early as 10 days to as long as 18 months after starting the drug.

Laboratory Features

NCS are suggestive of an axonal sensorimotor polyneuropathy with reduced amplitudes or absent SNAPs and CMAPs with normal or only moderately slow conduction velocities.[32,33,36–38] Needle EMG reveals fibrillation potentials and positive sharp waves in distal muscles along with decreased recruitment of neurogenic appearing MUAPs.

Histopathology

Sural nerve biopsy demonstrates a loss of myelinated fibers, predominately large-diameter fibers, although small-diameter fibers can be affected as well.[32–36] Nerve biopsies demonstrate axonal degeneration and segmental demyelination. On EM, one may appreciate the axonal swellings caused by the accumulation of neurofilamentous debris within the myelinated and unmyelinated axons.

Pathogenesis

The neuropathy may be secondary to carbon disulfide, which is a metabolite of disufiram.[39] A similar axonal neuropathy characterized by accumulation of neurofilaments occurs with carbon disulfide toxicity.

DAPSONE

Clinical Features

Dapsone is used primarily for the treatment of leprosy and for various dermatologic conditions. A primarily motor neuropathy can develop as early as 5 days to as long as 5 years after starting the drug.[40–46] Weakness initially involves the hands and feet and over time progresses to affect more proximal muscles. Occasionally, patients complain of sensory symptoms without weakness.

Laboratory Features

Motor and sensory NCS usually demonstrate reduced amplitudes with normal or only slightly slow conduction velocities.[40–44] The NCS usually improve after the dapsone is discontinued.

Histopathology

Biopsy of the motor nerve terminal at the extensor brevis muscle has demonstrated axonal atrophy and Wallerian degeneration of the distal motor nerve terminals.[45] Sural nerve biopsy may reveal a loss of myelinated nerve fibers.

Pathogenesis

The pathogenic basis of the neuropathy is not known.

LEFLUNOMIDE

Clinical Features

Leflunomide is used for the treatment of rheumatoid arthritis. It is a prodrug for the active metabolite A77 1726, which reversibly inhibits dihydroorotate dehydrogenase, the rate-limiting step in the de novo synthesis of pyrimidines necessary for lymphocyte production. There have been several reports of patients treated with leflunomide who developed distal numbness and paresthesia.[47–51] The median duration of treatment at the onset of neuropathy was 7.5 months (range 3 weeks to 29 months) in one large study.[49]

Laboratory Features

NCS demonstrate features of a primarily axonal, sensorimotor polyneuropathy.[47–51]

Histopathology

There are no reports of nerve biopsies.

Pathogenesis

The pathogenic basis for the neuropathy is not known.

Treatment

The neuropathy usually improves after withdrawal of the medication.

NITROFURANTOIN

Clinical Features

Nitrofurantoin is an antibiotic most often used to treat urinary tract infections and may cause an acute and severe sensorimotor polyneuropathy.[52–56] Patients develop numbness, painful paresthesia, and sometimes quadriparesis. Elderly and those with baseline renal insufficiency are most at risk. Physical examination reveals decrease of all sensory modalities in the distal regions of the upper and lower limbs. Muscle stretch reflexes are reduced or absent. Most patients slowly improve following discontinuation of the drug.

Laboratory Features

NCS demonstrate reduced amplitudes or absent SNAPs and CMAPs suggestive of an axonopathy.[53,55–57]

Histopathology

Sural nerve biopsy reveals loss of large myelinated fibers with signs of active Wallerian degeneration. An autopsy study has shown degeneration of the spinal roots, dorsal more severely affected than ventral roots, and chromatolysis of the anterior horn cells.[58]

Pathogenesis

The pathogenic basis of the neuropathy is not known.

PYRIDOXINE (VITAMIN B6) TOXICITY

Clinical Features

Pyridoxine is an essential vitamin that serves as a coenzyme for transamination and decarboxylation.[59,60] The recommended daily allowance in adults is 2–4 mg. However, at high doses (116 mg/d), patients can develop a severe sensory neuropathy with dysesthesia and sensory ataxia. Some patients also complain of a Lhermitte's sign.

Neurological examination reveals marked impaired vibratory perception and proprioception. Sensory loss can begin and be more severe in the upper than in the lower limbs. Muscle strength is usually normal, although fine motor control. Gait is wide based and unsteady secondary to the sensory ataxia. Muscle stretch reflexes are reduced or absent.

Laboratory Features

NCS reveal absent or markedly reduced SNAP amplitudes with relatively preserved CMAPs.[60–63]

Histopathology

Nerve biopsies reveal axonal loss of all fiber diameters.[60,64,65] Loss of dorsal root ganglion cells with subsequent degeneration of both the peripheral and the central sensory tracts has been appreciated in animal models.[66,67]

Pathogenesis

The pathogenic basis for the neuropathy associated with pyridoxine toxicity is not known.

ISONIAZID

Clinical Features

Isoniazid (INH) is used for treatment of tuberculosis. One of the most common side effects of INH is peripheral neuropathy.[68–70] Standard doses of INH (3–5 mg/kg/d) are associated with a 2% incidence of neuropathy, while neuropathy develops in at least 17% of patients taking in excess of 6 mg/kg/d of INH.[70] The elderly, malnourished, and "slow acetylators" are at increased risk of developing the neuropathy. Patients present with numbness and tingling in their hands and feet. The neuropathy usually develops after 6 months in patients receiving smaller doses but can begin within a few weeks in patients on large doses. The neuropathic symptoms resolve after a few days or weeks upon stopping the INH, if done early. However, if the medication is continued, the neuropathy may progress to involve more proximal numbness as well as distal weakness. Recovery at this stage can take months and may be incomplete. Examination reveals loss of all sensory modalities, distal muscle atrophy and weakness, reduced muscle stretch reflexes, and occasionally sensory ataxia. Prophylactic

administration of pyridoxine 100 mg/d can prevent the neuropathy from developing.

Laboratory Features

NCS reveal decreased amplitudes of the SNAPs.

Histopathology

Sural nerve biopsies reveal axonal degeneration and loss of both myelinated and unmyelinated nerve fibers.[69] Autopsy studies have demonstrated degeneration of the dorsal columns.[70]

Pathogenesis

INH inhibits pyridoxal phosphokinase resulting in pyridoxine deficiency. Because INH is metabolized by acetylation, individuals who are slow acetylators (an autosomal-recessive trait) maintain a higher serum concentration of INH and are more at risk of developing the neuropathy than people with rapid acetylation.[70] Slower acetylation can also occur with age.

ETHAMBUTOL

Clinical Features

Ethambutol is used to treat tuberculous and is associated with a sensory neuropathy and a severe optic neuropathy in patients receiving prolonged doses in excess of 20 mg/kg/d.[70,71] Patients develop numbness in the hands and feet without significant weakness. Examination reveals a loss of large fiber modalities and reduced muscle stretch reflexes distally. The peripheral neuropathy gradually improves after stopping of the medication; however, recovery of the optic neuropathy is more variable.

Laboratory Features

NCS reveal decreased amplitudes of the SNAPs with normal sensory distal latencies and conduction velocities. Motor conduction studies are usually normal.[72]

Histopathology

A decreased number of myelinated nerve fibers due to axonal degeneration has been noted in human and animal studies.[72]

Pathogenesis

The pathogenic basis of the neuropathy is not known.

CHLORAMPHENICOL

Chloramphenicol is an antibiotic that can also cause a distal sensory polyneuropathy and optic neuropathy.[63,73] Sensory examination reveals a mild loss of all modalities, and deep tendon reflexes are reduced in the legs. Detailed descriptions of the histological and electrophysiological findings are lacking.

NUCLEOSIDE NEUROPATHIES

Clinical Features

The nucleoside analogs zalcitabine (dideoxycytidine or ddC), didanosine (dideoxyinosine or ddI), stavudine (d4T), lamivudine (3TC), and antiretroviral nucleoside reverse transcriptase inhibitor are used to treat HIV infection. One of the major dose-limiting side effects of these medications is a predominantly sensory, length-dependent, symmetric painful neuropathy.[74–77] ddC is the most extensively studied nucleoside analog and, at doses greater than 0.18 mg/kg/d, is associated with a subacute onset of severe burning and lancinating pains in the feet and hands. One-third of patients on lower doses of ddC (0.03 mg/kg/d) develop a neuropathy within 1 week to a year (mean of 16 weeks) after starting the medication. On examination, hyperpathia, reduced pinprick and temperature sensation, and, to a lesser degree, impaired touch and vibratory perception are found. Muscle stretch reflexes are diminished, particularly at the ankles. Occasionally, mild weakness at the ankles and in foot intrinsics is appreciated. Because of a "coasting effect," patients can continue to worsen even 2–3 weeks after stopping the medication. However, improvement in the neuropathy is seen in most patients following dose reduction after several months (mean time about 10 weeks).

Laboratory Features

NCS reveal decreased amplitudes of the SNAPs with normal sensory distal latencies and conduction velocities. Sensory NCS reveal decreased amplitudes or absent responses with normal distal latencies and CVs.[74,76,77] Motor NCS are usually normal. Impaired temperature and vibratory thresholds have been noted on QST.[74,78] The QST abnormalities, particularly vibratory perception, precede clinical symptoms or standard nerve conduction abnormalities.

Pathogenesis

These nucleoside analogs inhibit mitochondrial DNA polymerase, which is the suspected pathogenic basis for the neuropathy. Acetyl-carnitine deficiency may contribute to the neurotoxicity of these nucleoside analogs.

PHENYTOIN

Clinical Features

Phenytoin is a commonly used antiepileptic medication. A rare side effect of phenytoin is a mild, primarily sensory neuropathy associated with reduced light touch, proprioception, and vibration as well as diminished or absent muscle stretch reflexes at the ankles.[79–81] Mild distal weakness may be seen. The neuropathy improves on discontinuation of the medication.

Laboratory Features

NCS reveal decreased amplitudes of the SNAPs with normal sensory distal latencies and conduction velocities. NCS demonstrate slightly reduced amplitudes and slow CV in about 20% of patients taking only phenytoin.[82–85] Motor NCS are usually normal.

Histopathology

Sural nerve biopsy demonstrate a loss of the large myelinated axons along with segmental demyelination and remyelination.[86]

Pathogenesis

The pathogenic basis of the neuropathy is not known.

LITHIUM

Clinical Features

Lithium is more often associated with CNS toxicity (tremor, dysarthria, confusion, obtundation, sweating, and seizures), but some patients have developed sensorimotor peripheral neuropathies (distal motor and sensory loss and reduced muscle stretch reflexes).[87–90]

Laboratory Features

NCS reveal decreased amplitudes of the SNAPs with normal sensory distal latencies and conduction velocities. NCS demonstrate reduced amplitudes or absent SNAPs and CMAPs.

Histopathology

Nerve biopsy demonstrates a loss of large myelinated fibers.

Pathogenesis

The pathogenic basis of the neuropathy is not known.

▶ TOXIC NEUROPATHIES RELATED TO INDUSTRIAL AGENTS

ACRYLAMIDE

Clinical Features

Acrylamide, a vinyl monomer, is an important industrial agent used as flocculators and grouting agent. It can be absorbed through the skin, ingested (following exposure to contaminated well water due to acrylamide grouting of the wells), or inhaled into the lungs.[91–93] Following exposure, patients develop a distal sensorimotor polyneuropathy characterized by a loss of large fiber function.[93–96] Pain and paresthesia are uncommon. Some patients develop ataxia and dysarthria and increasing irritability can be seen. Chronic low-level exposure may cause mental confusion and hallucinations in addition to weakness, gait difficulties, and occasionally urinary incontinence. Exposure to the skin is associated with a contact dermatitis.

On examination, there is a loss of vibration and proprioception with relatively good preservation of touch, pain, and temperature sensation. Patients may be ataxic and demonstrate a positive Romberg sign. Muscle stretch reflexes are reduced. Mild distal muscle atrophy and weakness may be appreciated. Patients with only low levels of exposure usually make a good recovery; however, those exposed to large amounts can take a year or more for significant improvement to occur and still may not completely recover.

Laboratory Features

NCS reveal decreased amplitudes of the SNAPs with normal sensory distal latencies and conduction velocities. NCS reveal absent or markedly reduced amplitude in the SNAPs.[93–96] The CMAP amplitudes are normal or only slightly reduced but temporal dispersion of the CMAPs may be observed in patients exposed to high levels of the substance.

Histopathology

Sural nerve biopsies reveal axonal degeneration with loss of the large myelinated fibers.[94] The earliest histological abnormality in animals exposed to acrylamide is paranodal accumulation of 10 nm neurofilaments at the distal ends of the peripheral nerves.[70] Subsequently, the distal axons enlarge and degenerate as can the posterior columns, spinocerebellar tracts, optic tracts, mamillary bodies, and the corticospinal tracts.

Pathogenesis

The exact pathogenic basis for the toxic neuropathy is unknown but is felt that acrylamide impairs fast

bidirectional axonal transport as well as slow antegrade transport.[70]

CARBON DISULFIDE

Clinical Features

Carbon disulfide is used to make rayon and cellophane.[70,97] Carbon disulfide can be inhaled and absorbed through the skin. Acute exposure to high levels of carbon disulfide can lead to CNS abnormalities (e.g., psychosis), which resolve with elimination of exposure. Chronic low-level exposure to carbon disulfide can cause a toxic peripheral neuropathy characterized by length-dependent numbness and tingling.[70,97] Examination reveals a loss of all sensory modalities and diminished muscle stretch reflexes. Mild muscle atrophy and weakness may be evident distally.

Laboratory Features

NCS reveal slowing of sensory and perhaps motor CVs.[98,99]

Histopathology

Detailed descriptions of the histopathology in humans are lacking. However, experimental studies in animals have shown accumulation of 10 nm neurofilaments and axonal swellings similar to that seen in acrylamide and hexacarbon toxicity.[70]

Pathogenesis

The pathogenic basis for the neuropathy is not known.

ETHYLENE OXIDE

Clinical Features

Ethylene oxide may be used to sterilize heat-sensitive materials, and exposure to ethylene oxide usually is associated with dermatologic lesions, mucosal membrane irritation, nausea, vomiting, and altered mentation. Exposure to high levels can lead to a severe sensorimotor peripheral neuropathy characterized by distal numbness and paresthesia.[100,101] Examination demonstrates a profound reduction to sensory modalities and occasionally slight distal weakness. Dysmetria due to a sensory ataxia, unsteady gait, and diminished muscle stretch reflexes are also seen.

Laboratory Features

NCS demonstrate reduced amplitudes or absent SNAPs and CMAPs.[102–104]

Histopathology

Sensory nerve biopsies reveal the loss of primarily, but not exclusively, the large myelinated fibers.

Pathogenesis

The pathogenic basis of the neuropathy is not known. Ethylene oxide can act as an alkylating agent and can bind with many organic molecules, including DNA.

ORGANOPHOSPHATE POISONING

Clinical Features

The organophosphates are used in the production of insecticides, plastics, and petroleum products and as toxic nerve agents for biological warfare. Exposure to organophosphates can lead to severe neurological CNS and PNS side effects.[105–109] These compounds inhibit acetylcholinesterase and result in the accumulation of acetylcholine at cholinergic synapses. Thus, toxic exposure to organophosphate esters can result in muscarinic, nicotinic, and central effects, thus producing the acute clinical symptoms and signs. CNS side effects include anxiety, emotional lability, ataxia, altered mental status, unconsciousness, and seizures. The muscarinic effects can cause nausea, vomiting, abdominal cramping, diarrhea, pulmonary edema, and bradycardia. Side effects at nicotinic synapses at the neuromuscular junction result in generalized weakness and fasciculations.

Some patients with acute organophosphate toxicity later develop a distal sensorimotor peripheral neuropathy (organophosphate-induced delayed polyneuropathy or OPIDP).[70,105,110–114] OPIDP evolves after several weeks following exposure and maximizes within several weeks. Cramping in the calf muscles, burning or tingling in the feet, and distal weakness are early symptoms. Symptoms and signs may then progress to involve the hands. Increased tone and hyperreflexia may be seen because of superimposed CNS dysfunction. The prognosis is good in patients with mild peripheral neuropathy. However, those individuals with significant peripheral and CNS insult generally are left with reduced abilities to perform activities of daily living.

Laboratory Features

In the acute and subacute stages of toxic exposure,-there is electrophysiological evidence of neuromuscular dysfunction secondary to compromise of acetylcholinesterase.[110,113–115] Motor NCS may demonstrate repetitive firing of the CMAPs following a single nerve stimulus. On low rates of repetitive stimulation, a decrementing response is seen, and this can persist for about 4–11 days. At both low (2–5 Hz) and high (20 Hz) rates of repetitive

stimulation, the CMAP amplitudes initially decrement but then recover—approaching the baseline amplitudes. In OPIDP, NCS reveal decreased amplitudes of SNAPs and CMAPs consistent with an axonal sensorimotor polyneuropathy.

Histopathology

Autopsy studies have demonstrated a distal axonopathy and degeneration of the gracile fasciculus and the corticospinal tract.[70] In addition, marked loss of both myelinated and unmyelinated nerve fibers in the sural nerve and a moderate loss of nerve fibers in the sciatic nerve were observed on autopsy of a patient who died from exposure to sarin gas.[105]

Pathogenesis

The pathogenic basis for OPIDP is not clear. Organophosphates bind to and inhibit an enzyme called neuropathy target esterase (NTE).[112] However, inhibition of NTE is not sufficient for the development of OPIDP. The organophosphate–NTE complex must age, whereby a lateral side chain of NTE is cleaved. Downstream this leads to the toxic neuropathy.

HEXACARBONS (*n*-HEXANE, METHYL *n*-BUTYL KETONE)/GLUE SNIFFER'S NEUROPATHY

Clinical Features

n-Hexane and methyl *n*-butyl ketone are water-insoluble industrial organic solvents, which are also present in some glues. Exposure through inhalation, accidentally or intentionally (glue sniffing), or through skin absorption can lead to a profound subacute sensorimotor polyneuropathy progressing over the course of 4–6 weeks.[70,116–119] The neuropathy presents with numbness and tingling in the feet and later involves the proximal legs and arms. Progressive weakness also develops. Respiratory muscles are usually spared.

Laboratory Features

NCS demonstrate decreased amplitudes of the SNAPs and CMAPs with slightly slow CVs.[117,120–127] Partial conduction block has also been appreciated in motor conduction studies in some patients.[128]

Histopathology

Nerve biopsy reveals a loss of myelinated and giant axons (Fig. 18–2).[70,116,119] Segmental demyelination is also seen. EM reveals that the swollen axons are filled with 10-nm neurofilaments.

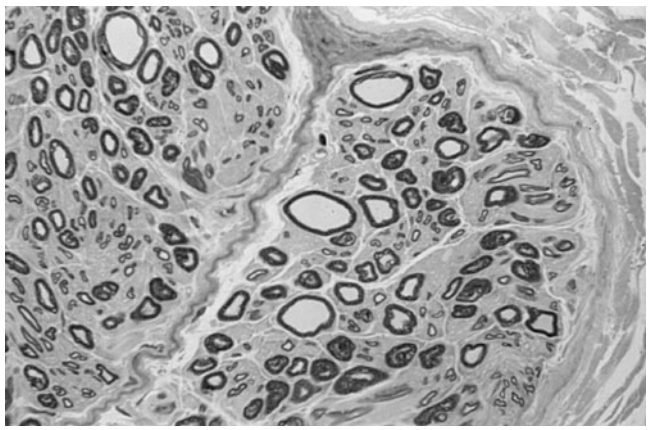


Figure 18–2. Hexacarbon toxicity. Giant axons are appreciated on this nerve biopsy in an individual who developed a severe neuropathy associated with chronic glue sniffing. (With permission from Amato AA, Dumitru D. Acquired neuropathies. In Dumitru D, Amato AA, Swartz MJ (eds). Electrodiagnostic Medicine, 2nd edn. Philadelphia: Hanley & Belfus, 2002, pp. 937–1041, Fig. 23–10, p. 1008.)

Pathogenesis

The exact mechanism by which hexacarbons cause a toxic neuropathy is not known. Hexacarbon exposure may lead to covalent cross-linking between axonal neurofilaments, which results in their aggregation, impaired axonal transport, swelling of the axons, and eventual axonal degeneration.[70]

VINYL BENZENE (STYRENE)

Vinyl benzene or styrene is used to make some plastics and synthetic rubber. Toxic exposure leads to a primarily sensory neuropathy with burning pain and paresthesia in the legs.[129] Neurological examination demonstrates a reduction in pain and temperature, with relatively good preservation of proprioception and vibration and muscle stretch. Strength is normal. NCS demonstrate a mild reduction in motor conduction velocities in the lower limbs.

▶ NEUROPATHIES CAUSED BY HEAVY METAL INTOXICATION

Heavy metals toxicity can be associated with axonal polyneuropathies.[130] The severity of the neuropathy is usually related to the amount of metal that entered the patient's system either acutely or chronically. Clinical improvement is dependent on cessation of the exposure and supportive measures. Multiple organ systems can be involved besides the peripheral nervous system.

LEAD

Clinical Features

Lead neuropathy is uncommon, but it can be seen in children who accidentally ingest lead-based paints in older buildings and in industrial workers exposed to containing lead products.[130,131] The most common presentation of lead poisoning is an encephalopathy; however symptoms and signs of a primarily motor neuropathy can also occur.[130,132–136] The neuropathy is characterized by an insidious and progressive onset of weakness usually beginning in the arms, particularly involving the wrist/finger extensor weakness such that it resembles a radial neuropathy. Foot drop can be seen. Weakness can be asymmetric. Sensation is generally preserved; however, the autonomic nervous system can be affected, leading to constipation. Muscle stretch reflexes are diminished and plantar responses are flexor. Bluish-black discoloration of gums near the teeth may be appreciated.

Laboratory Features

Laboratory investigation can reveal microcytic/hypochromic anemia with basophilic stippling of erythrocytes and an elevated serum coproporphyrin level. A 24-hour urine collection demonstrates elevated levels of lead excretion. The NCS may reveal reduced CMAP amplitudes, while the SNAPs are typically normal.[132,133,135–141]

Histopathology

Nerve biopsy may show a loss of large myelinated axons.[137]

Pathogenesis

The mechanism of nerve is unclear but may be related to abnormal porphyrin metabolism (see Chapter 10). It is not known if the primary target of the toxic insult is the anterior horn cell or more distally in the motor or peripheral nerve.[130]

Treatment

The most important treatment is removing the source of the exposure. Chelation therapy with calcium disodium ethylenediamine tetraacetate, British anti-Lewisite, and penicillamine also demonstrates variable efficacy.[130]

MERCURY

Clinical Features

Mercury toxicity may occur as a result of exposure to either organic or inorganic mercurials.[130,142–144] The organic form of mercury is usually found in methyl or ethyl mercury. Organic mercury poisoning presents with paresthesias in hands and feet, which progress proximally and may involve the face and tongue. Also, patients may have dysarthria, ataxia, reduced mentation, and visual and hearing loss.

The inorganic mercury compounds are primarily used for industrial purposes and consist of various mercury salts. Toxicity may arise from ingestion or inhalation of the compounds. Gastrointestinal symptoms and nephrotic syndrome are the primary clinically features associated with acute toxicity with inorganic mercury, but encephalopathy and sensorimotor polyneuropathy can also develop.

Laboratory Features

Organic mercury intoxication is difficult to diagnosis because the metal is very much lipid soluble and thus remains in the body, so urinary excretion can be scant. Inorganic mercury is more readily excreted and a 24-hour urine collection can reveal an increased concentration of this metal. Sensory NCS may reveal low-amplitude SNAPs and borderline CVs.[146–151] Motor conductions are normal or show borderline CVs. Somatosensory-evoked potentials of the median nerve demonstrate an absent cortical but present peripheral potentials.[151] The needle EMG is usually normal, but, occasionally, there is abnormal spontaneous activity in the form of positive sharp waves and fibrillation potentials.

Histopathology

Autopsies of patients with organic mercury toxicity through eating contaminated fish in Minimata Bay demonstrated degeneration of the calcarine aspect of the cerebral cortex, cerebellum, and axons in the sural nerves and lumbar dorsal roots that likely account for the vision loss, ataxia, and polyneuropathy.[130]

Pathogenesis

Mercury may bind to sulfhydryl groups of enzymatic or structural proteins, thereby impairing their proper function and leading to degeneration of the neurons.[130] The primary site of neuromuscular pathology appears to be the dorsal root ganglia.

Treatment

The mainstay of treatment is removing the source of exposure. Too few patients have been treated with chelating agents such as penicillamine to adequately assess efficacy.[130]

THALLIUM

Clinical Features

Thallium can exist in a monovalent or trivalent form and is primarily used as a rodenticide.[130,152,153] Thallium poisoning usually manifests as burning paresthesias of the feet, abdominal pain, and vomiting.[130,152,153] Increased thirst, sleep disturbances, and psychotic behavior may be noted. Within the first week, patients develop pigmentation of the hair, an acne-like rash in the malar area of the face, and hyperreflexia. By the second and third weeks, autonomic instability with labile heart rate and blood pressure may be seen in addition. Hyporeflexia and alopecia also occur but may not be evident until the third or fourth week following exposure.

On examination, there is a reduction in pain and temperature sensation along with a mild decrease in vibratory perception and proprioception. Muscle stretch reflexes are reduced distally but generally preserved proximally. Distal muscle atrophy and weakness gradually ensue. With severe intoxication, proximal weakness and involvement of the cranial nerves can occur. Some patients require mechanical ventilation due to respiratory muscle involvement. The lethal dose of thallium is variable, ranging from 8 to 15 mg/kg of body weight. Death can result in less than 48 hours following a particularly large dose.

Laboratory Features

Serum and urine levels of thallium are increased. Routine laboratory testing can reveal anemia, renal insufficiency, and abnormal liver function tests. CSF protein levels are also elevated. NCS demonstrate features of a primarily axonal, sensorimotor polyneuropathy.[152,154,155] Within the first few days of intoxication NCS can be normal. After 1–2 weeks, the SNAPs and CMAPs in the legs have reduced amplitudes and H-reflexes are lost.

Histopathology

Autopsy studies and nerve biopsies demonstrate chromatolysis of cranial and spinal motor nuclei and dorsal spinal ganglia and axonal degeneration of motor and sensory nerves.[152,156,157]

Pathogenesis

The pathogenic basis for the toxicity not known.

Treatment

With acute intoxication, potassium ferric ferrocyanide II may be effective in preventing absorption of thallium from the gut.[130] However, there may be no benefit once thallium has been absorbed. Unfortunately, chelating agents are not very efficacious. Adequate diuresis is essential to help eliminate thallium from the body without increasing tissue availability from the serum.[130]

ARSENIC

Clinical Features

Arsenic is another heavy metal that can cause a toxic sensorimotor polyneuropathy.[130,158–169] The neuropathy manifests 5–10 days after ingestion of arsenic and progresses for several weeks and can mimic Guillain–Barre syndrome clinically. The presenting symptoms are typically an abrupt onset of abdominal discomfort, nausea, vomiting, pain, and diarrhea, followed, within several days, by burning pain in the feet and hands. Subsequently, distal weakness ensues, and, with severe intoxication, proximal muscles and the cranial nerves are also affected. Muscle stretch reflexes are reduced. Some patients require mechanical ventilation because of respiratory muscle involvement. Increased morbidity and mortality are associated with respiratory muscle weakness and autonomic instability. Some patients appear confused due to a superimposed encephalopathy.

Examination of the skin can be helpful in diagnosing the poisoning. The loss of the superficial epidermal layer results in patchy regions of increased or decreased pigmentation on the skin several weeks after an acute exposure or with chronic low levels of ingestion. Mee's lines, which are transverse line at the base of the fingernails and toenails, do not become evident until 1 or 2 months after the exposure. Multiple Mee's lines may be appreciated in patients with long fingernails with more chronic exposure to thallium. Mee's lines are not specific for arsenic toxicity, as these can also be seen following thallium poisoning.

Laboratory Features

Because arsenic is cleared from blood rapidly, serum concentration of arsenic is not diagnostically helpful. However, arsenic levels are increased in the urine, hair, or fingernails of patients exposed to arsenic. Anemia with stippling of erythrocytes is common and occasionally pancytopenia and aplastic anemia can develop. Increased CSF protein levels without pleocytosis can be seen, which again can lead to misdiagnosis as Guillain–Barre syndrome. NCS are usually more suggestive of an axonal sensorimotor polyneuropathy; however, demyelinating features can be present.[130,158–168] Sensory NCS reveal low-amplitude or absent SNAPs with relatively preserved distal latencies and CVs. Motor conduction studies may demonstrate possible conduction block and prolongation of F-wave latencies. Serial studies demonstrate progressive deterioration of the CMAP

amplitudes to distal stimulation associated with slowing of the conduction velocities. Needle EMG demonstrate positive sharp waves and fibrillation potentials with reduced numbers of motor units in the distal muscles progressing proximally in patients exposed to significant amounts of arsenic.

Histopathology

Nerve biopsies demonstrate axonal degeneration, reduced large- and small-diameter myelinated fibers, occasional onion-bulb formations, and an increase in interstitial. Autopsy studies have revealed a loss of anterior horn cells.

Pathogenesis

The pathogenic basis of arsenic toxicity is not known. Arsenic may react with sulfhydryl groups of enzymatic (e.g., pyruvate dehydrogenase complex) and structural proteins in the neurons leading to their degeneration.[130]

Treatment

Chelation therapy with British anti-Lewisite has yielded inconsistent results and its effect is not dramatic; therefore, it is not generally recommended.[130]

GOLD

Clinical Features

Gold therapy (e.g., sodium aurothiomalate) is sometimes used to treat rheumatoid arthritis. Some patients treated with gold salts develop a sensorimotor neuropathy several months following drug initiation manifesting as distal paresthesias in the hands and feet and occasionally mild weakness.[130,170–172] In addition, a systemic reaction (e.g., rash and pruritis) to the gold usually accompanies the neuropathic symptoms. Examination reveals reduced sensation to all modalities and diminished muscle stretch reflexes. Fasciculations or myokymia may be evident on examination. It may be impossible to distinguish the toxic neuropathy related to gold to the other more common neuropathies associated with rheumatoid arthritis (see Chapter 14).

Laboratory Features

NCS reveal reduced amplitudes of SNAPs with relative preservation of motor studies.[170–172]

Histopathology

Nerve biopsies demonstrate axonal degeneration and segmental demyelination.

Pathogenesis

The pathogenic basis for the neuropathy is not known. It may be related to an immunological reaction triggered by the gold therapy.[130]

Treatment

Treatment consists of stopping the gold therapy. British anti-Lewisite has been tried as well in a few patients, but it is unclear if this therapy is effective.[130]

▶ SUMMARY

Many drugs can be associated with a toxic neuropathy and thus the need for taking an extensive medication history in any patient being evaluated for a neuromuscular disorder. The mechanisms by which these agents cause neuropathy are variable. These may have a primary effect on the neuronal cell body (ganglionopathy, the Schwann cells and myelin sheath, or axons). Most of the time, the neuropathies stabilize and improve after discontinuing the offending agent. However, there can be a coasting effect such that the neuropathy clinically worsens for a few months even after stopping the medication.

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CHAPTER 19

Neuropathies Associated with Endocrinopathies

Different types of peripheral neuropathy can complicate the various endocrinopathies (Table 19–1). In particular, peripheral neuropathy is frequently associated with diabetes mellitus (DM).

▶ DIABETIC NEUROPATHY

DM is the most common endocrinopathy and can be separated into two major subtypes: (1) insulin-dependent DM (IDDM or type 1 DM) and (2) non-insulin-dependent DM (NIDDM or type 2 DM). DM is also the most common cause of peripheral neuropathy in developed countries. DM is associated with several types of polyneuropathies: distal symmetric sensory or sensorimotor polyneuropathy, autonomic neuropathy, diabetic neuropathic cachexia (DNC), polyradiculoneuropathies, cranial neuropathies, and other mononeuropathies (Table 19–1).[1,2] The exact prevalence of each subtype of neuropathy among diabetic patients is not accurately known, but it has been estimated that between 5% and 66% of patients with diabetes develop a neuropathy.[3] Diabetic neuropathy can also occur in children.[4]

Long-standing, poorly controlled DM and the presence of retinopathy and nephropathy are risk factors for the development of peripheral neuropathy in diabetic patients.[5] In a large community-based study, 1.3% of the population had DM (27% type 1 DM and 73% type 2 DM).[5] Of these, approximately 66% of individuals with type 1 DM had some forms of neuropathies: generalized polyneuropathy, 54%; asymptomatic carpal tunnel syndrome, 22%; symptomatic carpal tunnel syndrome, 11%; autonomic neuropathy, 7%; and various other mononeuropathies/multiple mononeuropathies (ulnar neuropathy, peroneal neuropathy, lateral femoral cutaneous neuropathy, and diabetic amyotrophy), 3%. In type 2 DM group, 45% has generalized polyneuropathy, 29% had asymptomatic carpal tunnel syndrome, 6% had symptomatic carpal tunnel syndrome, 5% had autonomic neuropathy, and 3% had other mononeuropathies/multiple mononeuropathies. Considering all forms of DM, 66% of patients had some types of objective signs of a diabetic neuropathy, but only 20% of patients with DM were symptomatic.

DIABETIC DISTAL SYMMETRIC SENSORY AND SENSORIMOTOR POLYNEUROPATHY

Clinical Features

Distal symmetric sensory polyneuropathy (DSPN) is the most common form of diabetic neuropathy.[1,2] It is a length-dependent neuropathy in which individuals who are affected develop sensory loss beginning in the toes, which gradually progresses over time up the legs and into the fingers and arms.[6,7] When severe, a patient may also develop sensory loss in the trunk (chest and abdomen) in the midline that spreads out laterally towards the spine. Sensory loss is often accompanied by paresthesia, lancinating pains, burning, or a deep aching discomfort.[8] A severe loss of sensation can lead to increased risk from trauma to the extremities with secondary infection, ulceration, and Charcot joints. Patients with small fiber neuropathy can also develop symptoms and signs of an autonomic dysfunction, as the autonomic nervous system is mediated by small myelinated and unmyelinated nerve fibers. Poor control of DM and the presence of nephropathy correlate with an increased risk of developing DSPN.[3,5]

Neurological examination reveals loss of small fiber function (pain and temperature sensation) only or panmodality sensory loss. Those with large fiber sensory loss have reduced muscle stretch reflexes, particularly at the ankles, but reflexes can be normal in patients with only small fiber involvement. Muscle strength and function are typical normal, although mild atrophy and weakness of foot intrinsics and ankle dorsiflexors may be detected. Because patients without motor symptoms or signs on clinical examination often still have electrophysiological evidence of subclinical motor involvement, the term "distal symmetric sensorimotor peripheral neuropathy" is also appropriate.[9]

Laboratory Features

DSPN can be the presenting manifestation of DM, so not everyone has known history of diabetes. Further, there is an increased risk of impaired glucose tolerance on oral glucose tolerance test even in those individuals with

▶ TABLE 19–1. NEUROPATHIES ASSOCIATED WITH ENDOCRINOPATHIES

Diabetes mellitus
Distal symmetric sensory and sensorimotor polyneuropathy
Autonomic neuropathy
Diabetic neuropathic cachexia
Radiculoplexus neuropathy
Mononeuropathy/multiple mononeuropathies
Hypoglycemia/hyperinsulinemia
Generalized sensory or sensorimotor polyneuropathy
Acromegaly
Generalized sensory or sensorimotor polyneuropathy
Carpal tunnel syndrome
Hypothyroidism
Carpal tunnel syndrome
Generalized sensory or sensorimotor polyneuropathy

normal fasting blood sugars and hemoglobin A1C levels. Impaired glucose tolerance (defined as 2-hour glucose of >140 and <200 mg/dL) is found in as many as 36% and DM (defined as 2-hour glucose of >200 mg/dL or fasting blood sugar (FBS) of >126 mg/dL) in up to 31% of patients with sensory neuropathy.[10–12] In patients with painful sensory neuropathy, the incidence of impaired glucose tolerance or DM is even higher.

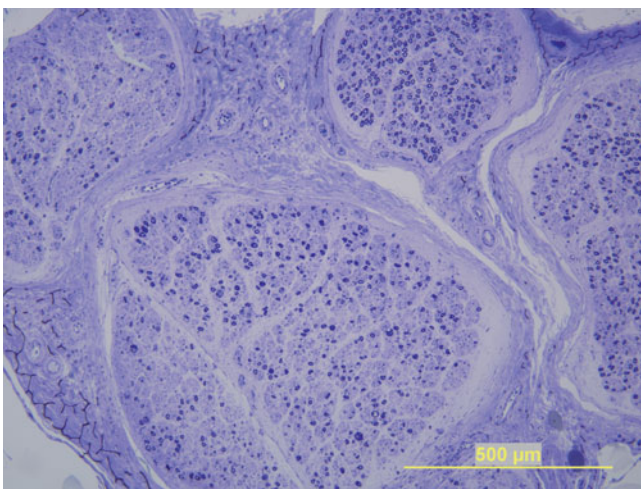
Up to 50% of patients with DM have reduced sensory nerve action potential (SNAP) amplitudes and slow conduction velocities of the sural or plantar nerves, while up to 80% of symptomatic individuals have abnormal sensory nerve conduction studies (NCS).[1,13,14] Quantitative sensory testing may reveal reduced vibratory and thermal perception. Autonomic testing may also be abnormal, in particular quantitative sweat testing.[15]

Motor NCS are less severely affected than the sensory studies but still are frequently abnormal with low amplitudes and normal or only slightly prolonged distal latencies and slow nerve conduction velocities (NCVs).[1,13] Rarely, the NCV slowing can be within the "demyelinating range" (e.g., less than 30% below the lower limit of normal); however, conduction block and temporal dispersion are not usually appreciated.[13,16] Needle electromyography (EMG) examination may demonstrate fibrillation potentials and positive sharp waves and large motor unit action potentials (MUAPs) in the distal muscles.

Histopathology

Nerve biopsies can reveal axonal degeneration, clusters of small regenerated axons, and segmental demyelination that is more pronounced distally, as expected in a length-dependent process (Fig. 19–1).[17] An asymmetric loss of axons between and within nerve fascicles may be appreciated. There is often endothelial hyperplasia of epi- and endoneurial arterioles and capillaries along with redundant basement membranes around these small blood vessels and thickening of the basement membrane of the perineurial cells (Fig. 19–2).[18] In addition, perivascular infiltrate consisting predominantly of CD8+ T cells can sometimes be seen.

Nerve biopsies may appear normal in patients with pure small fiber neuropathy. However, skin biopsies demonstrate a reduction of small myelinated intraepidermal nerve fibers.[12,19–21] Reduced intraepidermal nerve fiber densities correlate with temperature thresholds on quantitative sensory testing thresholds and duration of DM.[21] Patients with impaired glucose tolerance are more likely to have



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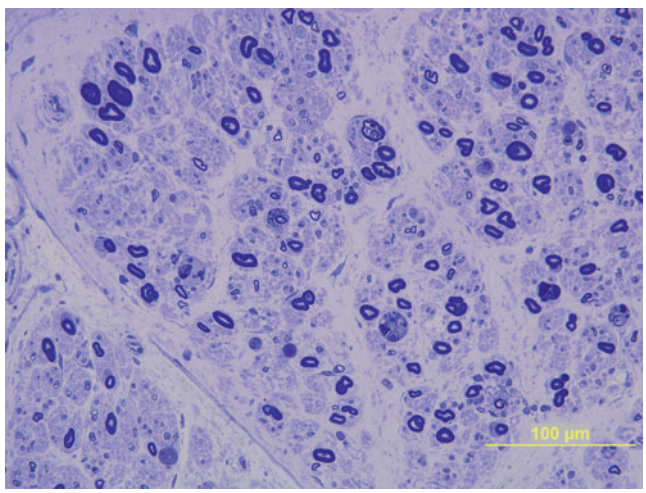

B

Figure 19–1. Diabetic neuropathy. Sural nerve biopsy demonstrates asymmetric loss of myelinated nerve fibers between and within nerve fascicles (A). Higher power reveals loss of large and small fibers and active axonal degeneration (B). Plastic sections stained with toluidine blue.

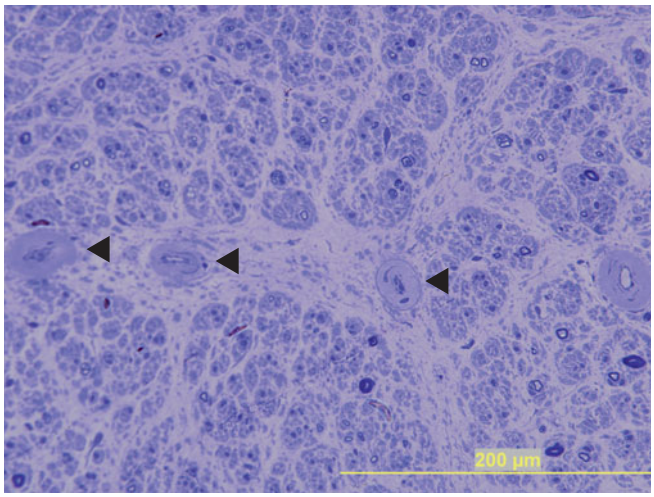

Figure 19–2. Diabetic neuropathy. Sural nerve biopsy demonstrates marked loss of myelinated nerve fibers and blood vessels with markedly thickened basement membrane. Plastic sections stained with toluidine blue.

predominantly small fiber neuropathy, compared to patients with DM, who had more involvement of large nerve fibers.[12]

Pathogenesis

The pathogenic basis for DSPN is unknown. The major theories involve a metabolic process, microangiopathic ischemia, or an immunological disorder.[17,22–25]

Treatment

The mainstay of treatment is tight control of glucose, as studies have shown that this can reduce the risk of developing neuropathy or improve the underlying neuropathy.[26,27,27–29] Pancreatic transplantation may stabilize or slightly improve sensory, motor, and autonomic function.[15,28] More than 20 trials of aldose reductase inhibitors have been performed and most have been negative[2,30]; however, a double-blind, placebo-controlled study of Fidarestat was associated with improvement of subjective symptoms and five of eight electrophysiological parameters.[31] Trials of neurotrophic growth factors have also been disappointing.[32,33] A double-blind study of alpha-lipoic acid, an antioxidant, found significant improvement in neuropathic sensory symptoms such as pain and several other neuropathic end points.[34]

A variety of medications have been used to treat painful symptoms associated with DSPN, including antiepileptic medications, antidepressants, sodium channel blockers, and other analgesics with variable success (Table 19–2).[35–40] Tricyclic antidepressant medications are helpful but are limited mainly by their anticholinergic side effects.[39,41] Selective serotonin uptake inhibitors appear to be less effective. Anticonvulsant medications are effective in some patients.[35,41,42] Tramadol has also demonstrated efficacy in double-blind, placebo-controlled trials.[38]

Our first step in patients with just distal leg pain is a trial of lidoderm patches on the feet. If this is insufficient, we add gabapentin starting at a dose of 300 mg TID (depending on patients' age and tolerability to medications). We gradually increase the gabapentin as tolerated and necessary up to 1200 mg TID. If this is still ineffective, we usually add a tricyclic antidepressant (TCA) such as nortriptyline at a low dose (10–25 mg nightly) and again gradually increase as tolerated up to 100 mg

▶ TABLE 19–2. TREATMENT OF PAINFUL SENSORY NEUROPATHIES

Therapy	Route	Dose	Side Effects
First line			
Lidoderm 5% patch	Apply to painful area	Up to three patches qd	Skin irritation
Tricyclic antidepressants (e.g., amitriptyline and nortriptyline)	p.o.	10–100 mg qhs	Cognitive changes, sedation, dry eyes and mouth, urinary retention, and constipation
Gabapentin	p.o.	300–1200 mg TID	Cognitive changes, sedation, and peripheral edema
Pregabalin	p.o.	50–100 mg TID	Cognitive changes, sedation, and peripheral edema
Duloxitine	p.o.	60 mg qd	Cognitive changes, sedation, dry eyes, diapheresis, nausea, diarrhea, and constipation
Second line			
Carbamazepine	p.o.	200–400 mg q 6–8 h	Cognitive changes, dizziness, leukopenia, and liver dysfunction
Phenytoin	p.o.	200–400 mg qhs	Cognitive changes, dizziness, and liver dysfunction
Tramadol	p.o.	50 mg qid	Cognitive changes and gastrointestinal upset
Third line			
Mexiletine	p.o.	200–300 mg tid	Arrhythmias

nightly. Other medications such as topirimate (up to 400 mg daily)[43] and dulexitine (60 mg) may be helpful. In patients with breakthrough pain, we prescribe tramadol 50 mg every 6 hours as needed.[38] Mexilitine can be tried if above medications fail to offer significant benefit.[37]

DIABETIC AUTONOMIC NEUROPATHY

Clinical Features

Autonomic neuropathy typically is seen in combination with DSPN.[44,45] The autonomic neuropathy can manifest as abnormal sweating, dysfunctional thermoregulation, dry eyes and mouth, pupillary abnormalities, cardiac arrhythmias, postural hypotension, gastrointestinal abnormalities (e.g., gastroparesis, postprandial bloating, chronic diarrhea, or constipation), and genitourinary dysfunction (e.g., impotence, retrograde ejaculation, and incontinence).

Laboratory Features

Tests of autonomic function are generally abnormal, including sympathetic skin responses and quantitative sudomotor axon reflex testing.[44,45] Sensory and motor NCS generally demonstrate features described above with DSPN.

Histopathology

Degeneration of sympathetic and parasympathetic neurons along with inflammatory infiltrates within have been appreciated.[46,47]

Pathogenesis

The pathogenic basis for autonomic neuropathy is unknown but may be similar to DSPN.

Treatment

Pancreatic transplantation may stabilize or slightly improve autonomic function.[15] In patients with symptomatic orthostatic hypotension, we initiate treatment with fluodrocortisone (starting at 0.1 mg BID) or midodrine (10 mg TID).[45] Nonsteroidal anti-inflammatory agents may also be of benefit. Metaclopramide is used to treat diabetic gastroparesis, while clonidine may help with persistent diarrhea. Sildenafil and other similar medications are used to treat erectile dysfunction.

DIABETIC NEUROPATHIC CACHEXIA

Clinical Features

DNC is very rare but can be the presenting manifestation of DM.[48,49] This form of diabetic neuropathy is more common in men (usually associated with type 2 DM) than in women (most cases associated with type 1 DM) and generally occurs in their sixth or seventh decade of life. Patients with DNC develop an abrupt onset of severe generalized painful paresthesias involving the trunk and all four limbs, usually setting off significant precipitous weight loss. Mild sensory loss may be detected on examination along with reduced muscle stretch reflexes. Weakness and atrophy are evident in some patients. DNC tends to gradually improve spontaneously, usually preceded by recovery of the weight loss. Rarely, DNC can recur.[50]

Laboratory Features

Cerebrospinal fluid (CSF) protein may be increased. Sensory nerve action potentials may be absent or have very low amplitudes.[49,50] Normal or slightly diminished compound muscle action potentials (CMAP) amplitudes with mild slowing of conduction velocities can also be observed.

Histopathology

Nerve biopsies demonstrate severe loss of axonal degeneration, with relative sparing of small myelinated and unmyelinated fibers.[50]

Pathogenesis

The pathogenic basis for the disorder is not known.

Treatment

Most patients improve spontaneously, with control over the DM within 1–3 years. Symptomatic treatment of the painful paresthesias is the same as that described for DSPN.

DIABETIC POLYRADICULOPATHY OR RADICULOPLEXUS NEUROPATHY

Two categories of diabetic radiculoplexus neuropathy can be made on the basis of clinical differences: (1) the more common asymmetric, painful, radiculoplexus neuropathy and (2) the rare symmetric, relatively painless, radiculoplexus neuropathy.[51] The latter form may represent chronic inflammatory demyelinating polyneuropathy (CIDP) in a patient with diabetes or a distinct form of diabetic neuropathy.

ASYMMETRIC, PAINFUL DIABETIC POLYRADICULOPATHY OR RADICULOPLEXUS NEUROPATHY (DIABETIC AMYOTROPHY)

Clinical Features

This is the most common form of polyradiculopathy or radiculoplexus neuropathy associated with DM (also known as diabetic amyotrophy, Bruns–Garland syndrome, diabetic lumbosacral radiculoplexopathy, and proximal diabetic neuropathy).[51–58] It more commonly affects older patients with DM type 2, but it can affect type 1 diabetic patients. It can be the presenting manifestation of DM in approximately one-third of patients. Typically, patients present with severe pain in the low back, hip, and thigh in one leg. Rarely, the diabetic polyradiculoneuropathy begins in both legs at the same time. Nevertheless, in such cases nerve involvement is generally asymmetric. Atrophy and weakness of proximal and distal muscles in the affected leg become apparent within a few days or weeks. About 50% of patients also complain of numbness and paresthesia. Unfortunately, we have seen many patients undergo unnecessary laminectomies because the severe radicular pain and weakness suggest a structural impingement. Although the onset is typically unilateral, it is not uncommon for the contralateral leg to become affected several weeks or months later. As with DNC, the polyradiculoneuropathy is often accompanied or heralded by severe weight loss.

Weakness progresses gradually or in a stepwise fashion, usually over several weeks or months, but can continue to progress for 18 months or more.[52] The term "proximal diabetic neuropathy" has led to the misconception that only proximal muscles are involved; however, examination reveals weakness of both proximal and distal lower limb muscles.[52] Most patients usually have underlying DSPN. Eventually, the disorder stabilizes and slow recovery ensues. However, in many cases there are significant residual weakness, sensory loss, and pain.

Rather than the more typical lumbosacral radiculoplexus neuropathy, some patients develop thoracic radiculopathy.[48,59] Patients describe pain radiating from the posterolateral chest wall anteriorly to the abdominal region, with associated loss of sensation anterolaterally. Weakness of the abdominal wall may lead to herniations of the viscera. Even less common are cervical polyradiculoneuropathy/brachial plexopathy and complaints of weakness, pain, and sensory loss in the upper limbs.[55,60]

Laboratory Features

Lumbar puncture usually reveals an elevated CSF protein with a normal cell count. Erythrocyte sedimentation rate is often increased. Magnetic resonance imaging (MRI) scans of the nerve roots and plexus can reveal enhancement.[52,61] NCS reveal features suggestive of multifocal axonal damage to the roots and plexus with reduced or low amplitudes of SNAPs and compound muscle actions (CMAPs).[52,53,55,58,62] Conduction velocities in the affected limbs are normal or mildly slow. Autonomic studies may be abnormal as well.[53,55] Needle EMG reveals positive sharp waves and fibrillation potentials and reduced recruitment of affected proximal and distal muscles in the affected limbs and paraspinal muscles. Large-amplitude, long-duration, polyphasic MUAPs are seen over time as reinnervation occurs.

Histopathology

Sural, superficial peroneal, and lateral femoral cutaneous nerve biopsies reveal loss of myelinated nerve fibers, which is often asymmetric between and within nerve fascicles.[52,54–58] Active axonal degeneration and clusters of small thinly myelinated regenerating fibers are appreciated. Mild perivascular inflammation and less commonly frank vasculitic change involving epineurial and perineurial blood vessels have been noted on some nerve biopsies (Fig. 19–3).[55,58,62]

Pathogenesis

Some authorities have speculated that diabetic radiculoplexus neuropathy is an immune-mediated microangiopathy; however, the pathogenic mechanism is unclear.[54,58,62]

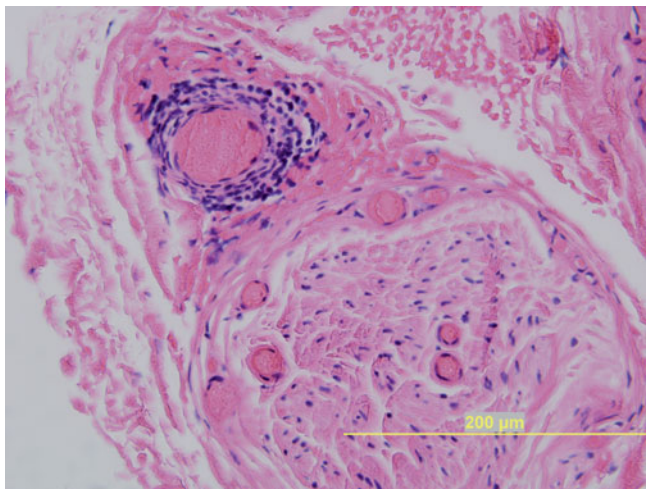

Figure 19–3. Lumbosacral radiculoplexus neuropathy. Superficial peroneal nerve biopsy reveals perivascular inflammation of a small epineurial vessel. H&E stain.

Treatment

Small retrospective studies have reported that intravenous immunoglobulin (IVIG), prednisone, and other forms of immunosuppressive therapy appear to be helpful in some patients with diabetic amyotrophy.[51,53,54,58,62] We have been impressed by the fact that short courses of corticosteroids ease the pain associated with the severe radiculoplexus neuropathy and this can allow the patients to undergo physical therapy. However, the natural history of this neuropathy is gradual improvement, so the actual effect, if any, of these immunotherapies on the radiculoplexus neuropathy is not known. Prospective, double-blinded, placebo-controlled trials are necessary to define the role of various immunotherapies in this disorder.

SYMMETRIC, PAINLESS, DIABETIC POLYRADICULOPATHY OR RADICULOPLEXUS NEUROPATHY

Clinical Features

The second major group of diabetic polyradiculopathy or radiculoplexus neuropathy presents with a progressive, relatively painless, symmetrical proximal and distal weakness that typically evolves over weeks to months such that it clinically resembles chronic inflammatory demyelinating polyneuropathy (CIDP).[51,53–55,63,64–69] Whether this neuropathy represents the coincidental occurrence of CIDP in a patient with DM or this is a distinct form of diabetic neuropathy is unclear. This type of neuropathy occurs in both types 1 and type 2 DM but may be more common in the former.

The pattern of weakness resembles CIDP in that there is symmetric distal and proximal weakness affecting the legs more than the arms. Distal muscles are more affected than proximal muscles. In our experience there is usually distal arm weakness, but proximal arm involvement is often less noticeable than seen in patients with idiopathic CIDP. Unlike the more common "diabetic amyotrophy" discussed in the previous section, the onset of weakness is not heralded or accompanied by such severe back and proximal leg pain and the motor weakness is relatively symmetric. However, distal dysesthesias, perhaps secondary to a superimposed DSPN, are occasionally present.

Laboratory Features

CSF protein concentration is usually increased. NCS demonstrate mixed axonal and demyelinating features, with absent or reduced SNAP and CMAP amplitudes combined with slowing of nerve conduction velocities, prolongation of distal latencies, and absent or prolonged latencies of F-waves.[54,55,63,65,66] Rarely, conduction block and temporal dispersion are found.[55,63,66] Occasionally, the electrophysiological features can fulfill research criteria for demyelination, but these are generally more axonal in nature than seen in idiopathic CIDP.[63,65,66] EMG reveals fibrillation potentials and positive sharp waves diffusely, including multiple levels of the paraspinal musculature. Autonomic studies may demonstrate abnormalities in sudomotor, cardiovagal, and adrenergic functions.[53,55]

Histopathology

Sural nerve biopsies demonstrate a loss of large and small myelinated nerve fibers, with axonal degeneration and clusters of small regenerating fibers.[53–55,63,65] Nerve biopsies may show immunoreactivity for matrix metalloproteinase-9 as seen in idiopathic CIDP.[69] Occasionally, demyelinated fibers and onion-bulb formations are appreciated along with scant perivascular mononuclear inflammatory cells in the peri- and epineurium. Nevertheless, these nerve biopsy abnormalities are not specific for symmetric diabetic polyradiculopathy or CIDP, as similar findings can be seen in DSPN and diabetic amyotrophy.

Pathogenesis

The pathogenic basis for this form of polyradiculoneuropathy is unknown and perhaps is multifactorial. This neuropathy may just represents a spectrum of diabetic amyotrophy. We suspect that some cases represent CIDP occurring coincidentally in patients with DM, as some appear to improve with various immunotherapies. However, this apparent response does not imply that the patients have CIDP, because these patients can improve spontaneously without treatment.[53,55] Alternatively, the disorder may be a distinct form of diabetic neuropathy caused by the associated metabolic disturbances such as uremia.

Treatment

As noted, some patients improve with immunotherapy (i.e., IVIG, plasma exchange (PE), and corticosteroids), suggesting that this type of diabetic neuropathy is immune mediated and perhaps just represents CIDP occurring in diabetic patients.[53–55,63,65,67] We often will first do a lumbar puncture on such patients. If the cerebral spinal fluid (CSF) protein is normal then we would not proceed with immunotherapy, as it is highly unlikely that the patient has CIDP. If the CSF protein is elevated, one dose not know if the patient has CIDP or the protein is elevated because of the diabetes. In these cases give a trial of plasmapheresis because it generally works quickly in patients with CIDP. If it is effective, then we would continue with the treatments or consider other forms of immunotherapy.

DIABETIC MONONEUROPATHIES OR MULTIPLE MONONEUROPATHIES

Diabetic patients are vulnerable to developing mono- and multifocal neuropathies, including cranial neuropathies.[1,70] Most of the time patients have underlying distal symmetric polyneuropathy (DSPN). The most common neuropathies are median neuropathy at the wrist and ulnar neuropathy at the elbow, but peroneal neuropathy at the fibular head and sciatic, lateral femoral cutaneous, and cranial neuropathies also occur. In regard to cranial mononeuropathies, a seventh nerve palsy is most common, followed by third, sixth, and, less frequently, fourth nerve palsies. The multiple mononeuropathies, perhaps in combination with a radiculoplexus neuropathy, may give the appearance of mononeuropathy multiplex.

▶ NEUROPATHIES ASSOCIATED WITH OTHER ENDOCRINOPATHIES

HYPOGLYCEMIA/HYPERINSULINEMIA

Clinical Features

Polyneuropathy has been associated with persistent hypoglycemia secondary to an islet cell tumor of the pancreas, hyperinsulinemia, or in early stages of treatment of DM.[71–74] The neuropathy is characterized by progressive numbness and paresthesias in the hands and feet, and, over time, distal motor weakness atrophy may develop. Muscle stretch reflexes are generally reduced. With correction of the hypoglycemia the sensory symptoms usually improve; however, muscle atrophy and weakness often remain to some extent.

Laboratory Features

NCS reveal reduced amplitudes or absent SNAPs.[72,74] The CMAP amplitudes are slightly decreased, while the conduction velocities are normal or only mildly reduced. Needle EMG may demonstrate fibrillation potentials and positive sharp waves and reduced recruitment of large polyphasic MUAPs in the distal limb muscles.[71–73]

Histopathology

Very few nerve biopsies have been performed on individuals with this disorder, but axonal loss primarily affecting the large myelinated fibers has been reported.[72]

Pathogenesis

The basis for the polyneuropathy is not known but is felt to be directly attributable to reduced glucose levels in peripheral nerves. A rat model of recurrent episodes of severe hypoglycemia was associated with early vascular anomalies in endoneurial microvessels in rat sciatic nerves without any observable changes in nerve fibers.[75] Other studies demonstrated that acute lowering of glucose levels under hypoxic conditions in rats leads to apoptosis of dorsal root ganglia neurons.[76] Hypoxia-induced death was decreased when dorsal root ganglia neurons were maintained in high-glucose medium, suggesting that high levels of substrate protected against hypoxia. Apoptosis was completely prevented by increasing the concentration of nerve growth factor.

Treatment

Patients should be treated for the underlying cause of the hyperinsulinemia.

ACROMEGALY

Clinical Features

Acromegaly can be associated with myopathy, in addition to several types of neuropathy.[77,78] Carpal tunnel syndrome is the most common neuropathy complicating acromegaly.[47,78] A generalized sensorimotor peripheral neuropathy, characterized by numbness, paresthesias, and mild distal weakness beginning in the feet and progressing to the hands, is less frequent. Clinical or electrophysiological evidence of carpal tunnel syndrome has been demonstrated in 82% of patients and a generalized sensorimotor peripheral neuropathy in 73% of patients with acromegaly.[47] In addition, the bony overgrowth in or about the spinal canal and neural foramens can result in spinal cord compression or polyradiculopathies.

Laboratory Features

NCS in patients with generalized polyneuropathy demonstrate reduced amplitudes of SNAPs with prolonged distal latencies and slow CVs.[47] The CMAPs are usually normal, but there may be slightly reduced amplitudes, prolonged distal latencies, and slow motor conduction velocities.

Histopathology

Nerve biopsies in patients with generalized polyneuropathy may reveal an increase in endoneurial and subperineurial connective tissue and an overall increase in the fascicular area combined with a loss of myelinated and unmyelinated nerve fibers.[47]

Pathogenesis

The pathogenic basis of the associated polyneuropathy acromegaly is unknown. The neuropathy may be related

to superimposed DM in some cases. Increased growth hormone and upregulation of insulin-like growth factor receptors may result in proliferation of endoneurial and subperineurial connective tissue, which could make the nerve fibers more vulnerable to pressure and trauma.

Treatment

It is unclear at this time if the polyneuropathy improves with treatment of this endocrinopathy.

HYPOTHYROIDISM

Clinical Features

Hypothyroidism disease is more commonly associated with a proximal myopathy, but some patients develop a neuropathy, most typically carpal tunnel syndrome.[47,79–82] Rarely, a generalized sensory polyneuropathy, characterized by painful paresthesias and numbness in both the hands and the legs, also complicates hypothyroidism.[81,82]

Laboratory Features

NCS features suggestive of carpal tunnel syndrome are most common, but a generalized sensorimotor polyneuropathy may be demonstrated.[47,79–82] In patients with a generalized neuropathy, the SNAP amplitudes are reduced and distal latencies may be slightly prolonged.[83,84] CMAPs reveal normal or slightly reduced amplitudes, with mild-to-moderate slowing of CVs and prolongation of slightly slow distal motor latencies.

Histopathology

Nerve biopsies have revealed a loss of myelinated nerve fibers, or mild degrees of active axonal degeneration, and segmental demyelination with small onion-bulb formations.[47,79,80,83,85]

Pathogenesis

Carpal tunnel syndrome is most likely the result of reduced space within the flexor retinaculum as a result of associated edematous changes. The etiology of the generalized neuropathy associated with hypothyroidism is not known.

Treatment

Correction of the hypothyroidism usually at least halts further progression of, if not improves, the polyneuropathy.

▶ SUMMARY

DM is the most common etiology of neuropathy (at least in industrialized nations) when the cause of the neuropathy is found. There are several types of neuropathy associated with DM as discussed. Treatment is aimed at control of the blood sugar and symptomatic management of pain. Aside from diabetic neuropathies, the endocrine neuropathies are relatively uncommon. However, hyperinsulinemia, hypothyroidism, and acromegaly have also been associated with neuropathy.

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CHAPTER 20

Idiopathic Neuropathy

In our experience, the cause of polyneuropathies cannot be found in at least one-third of patients even following extensive evaluation.[1–10] These chronic idiopathic polyneuropathies are probably caused by a heterogenous group of disorders. Most individuals have only sensory symptoms but some may have mild weakness (e.g., toe extension) or slight abnormalities on motor conduction studies. The neuropathy may affect large- or small-diameter nerve fibers. As the etiology is unknown, only symptomatic management of the neuropathic pain is available.

▶ CHRONIC IDIOPATHIC SENSORY OR SENSORIMOTOR POLYNEUROPATHY

CLINICAL FEATURES

Most individuals who are affected present with numbness, tingling, or pain (e.g., sharp stabbing paresthesias, burning, or deep aching sensation) in the feet between the ages of 45 and 70 years.[1–10] This is not uncommon, as approximately 3% of adults develop these symptoms with age. In a large series of 93 patients with idiopathic sensory polyneuropathy, 63% presented with numbness and paresthesia along with pain, 24% with numbness or paresthesia without pain, and 10% with pain alone.[10] Eventually, the majority of individuals who are affected (65–80%) do go on to develop neuropathic pain.[6,11–13] Sensory symptoms are first noted in the toes and slowly progresses up the legs and later into the arms. The average time to involvement of the hands is approximately 5 years.[6,10]

Neurological examination reveals the typical length-dependent pattern of sensory loss.[6,7,10,13] Vibratory perception is reduced in 80–100%, proprioception is impaired in 20–30%, pinprick sensation is diminished in 75–85%, and light touch is decreased in 54–92% of those with the neuropathy. Strength is usually normal, although mild distal weakness and atrophy involving foot intrinsic muscles and, occasionally, the ankle dorsiflexors and evertors may be appreciated in 40–75% of cases.[6,10,13] However, upper limb strength, including the hand intrinsic, should be normal. Muscle stretch reflexes are usually absent at the ankle and diminished at the knees and arms.[6,1013] Approximately 15–25% of individuals who are affected have generalized areflexia.

Within the category of idiopathic sensory or sensorimotor polyneuropathies are people who have only a small fiber sensory neuropathy.[2,3,7,10] By definition, these individuals should have normal nerve conduction studies (NCS), and nerve biopsies, if performed, demonstrate a relatively normal density of large myelinated nerve fibers. Most people with small fiber neuropathy (approximately 80%) complain of burning pain in the feet, while 40–60% describe sharp, lancinating pain; paresthesias; or just numbness. Symptoms may involve the distal upper extremities. Rarely, the neuropathy is restricted to the arms and face or involves the autonomic nervous system.[2,3] Examination reveals reduced pinprick or temperature sensation in almost all patients, while vibratory perception is impaired in half. Muscle strength is preserved. Likewise, muscle stretch reflexes are also usually normal, but a few patients have reduced reflexes at the ankles.

LABORATORY FEATURES

The diagnosis of chronic idiopathic polyneuropathy is one of exclusion. Laboratory testing should include fasting blood glucose (FBS), hemoglobin A1C, oral glucose tolerance test (GTT), antinuclear antibody, anti-Ro and anti-La antibodies (SSA and SSB), erythrocyte sedimentation rate, rheumatoid factor, B12, serum and urine immunolelectrophoresis/immunofixation, and thyroid, liver, and renal function tests. The most common abnormality, when one is found, in patients with sensory neuropathy is diabetes or impaired glucose tolerance (IGT). IGT (defined as 2-hour glucose of >140 and <200 mg/dL) is seen in 17–61% and frank diabetes mellitus (defined as 2-hour glucose of >200 mg/dL or FBS of >126 mg/dL) in 20–31% of patients with sensory neuropathy (Table 20–1).[14,16,18] In patients with painful sensory symptoms (not just numbness), the likelihood of IGT or DM is even higher. A population-based study of 2844 patients, aged 40–74 years, found undiagnosed DM in 2.7%, while 15.8% of those aged 40–74 years and 20.7% of those aged 60–74 years had IGT on GGT.[19] However, some authorities have not found increased risk of IGT in their patients with idiopathic neuropathy compared to age-matched controls.[20] Thus, although the risk of both previously undetected diabetes mellitus (DM) and IGT may be increased in patients with sensory neuropathy, this is still controversial

▶ **TABLE 20–1. RESULTS OF GLUCOSE TOLERANCE TESTING IN OTHERWISE IDIOPATHIC POLYNEUROPATHY**

Authors (References)	No of. Patients	Mean Age (Range)	Total with Abnormal Glucose Metabolism	Impaired Glucose Tolerance	Diabetes Mellitus
Singleton et al.[14]	89 (total) 33 (painful sensory neuropathy)	64 yr (44–92 yr)	43/89 (56%) 20/33 (60%)	15/89 (25%) 7/33 (21%)	28/89 (31%) 13/33 (39%)
Novella et al.[15]	48 (total) 24 (painful sensory neuropathy)	64 yr (41–82 yr)	24/48 (50%) 18/28 (65%)	13/48 (27%) 10/28 (36%)	11/48 (23%) 8/28 (29%)
Sumner et al.[16] Harris et al.[17]	73 (total) 2884 (normal age-matched population)	61 yr (44–91 yr)	41/73 (56%) 18.5% in patients aged 40–74 yr	26/73 (36%) 15.8% in patients aged 40–74 yr 20.7% in patients 60–74 yr	15/73 (20%) 2.7% in patients 40–74 yr

and a causal relationship has not as yet been firmly established.[21]

About 5% of patients with chronic idiopathic sensory or sensorimotor polyneuropathy have a monoclonal protein detected in the serum or urine, but this is not much higher than the age-matched normal controls.[13,18,22,23] Further, the relationship of these monoclonal proteins to the pathogenesis of most neuropathies is unclear. There is a strong pathogenic relationship established in people with demyelinating sensorimotor polyneuropathies with IgM monoclonal proteins, most of whom have myelin-associated ganglioside antibodies (discussed in Chapters 12 and 17). However, most individuals with chronic idiopathic sensory or sensorimotor polyneuropathy have axonal neuropathies histologically and electrophysiologically. Amyloidosis is the other condition in which a pathogenic relationship between the neuropathy and the monoclonal protein is clear. Thus, amyloid neuropathy needs to be excluded in patients with a monoclonal gammopathy before concluding that the neuropathy is idiopathic in nature (see Chapter 14). This may require a fat-pad, rectal, or nerve biopsy.

Although some studies have suggested that antisulfatide antibodies are common with painful small fiber neuropathy,[24–27] subsequent reports suggest that these antibodies have a very low sensitivity and poor specificity.[6,10,25,28–30] We never order them as we have found them to be of little use clinically, and a pathogenic relationship has never been demonstrated, That is, the presence of these antibodies does not imply that the patients have an immune-mediated neuropathy and that they may respond to treatment with immunotherapy. We also feel that there is no role for screening various antiganglioside and other antinerve antibodies (e.g., GM1 and Hu antibodies) in the workup of patients with chronic idiopathic sensory neuropathy.[7,31,32] CSF examination is usually normal and is also unwarranted.

In people with a large fiber neuropathy, the sensory NCS reveal either absent or reduced amplitudes that are worse in the legs.[1,3,4,6–10,13] Sensory NCV are normal or only mildly slow. Quantitative sensory testing (QST) demonstrates abnormal thermal and vibratory perception in as many as 85% of patients.[7,10] In addition, autonomic testing (e.g., quantitative sudomotor axon reflex and heart rate testing with deep breathing or Valsalva) is abnormal in some patients. Despite the fact that sensory symptoms predominate, motor NCS are often abnormal. Wolfe and colleagues reported that 60% of their patients with idiopathic polyneuropathy had abnormal motor NCS.[10] The most common motor abnormalities are reduced peroneal and posterior tibialis compound muscle action potentials (CMAP) amplitudes, while distal latencies and conduction velocities of the peroneal and posterior tibial CMAPs are normal or only slightly impaired. Abnormalities of median and ulnar CMAPs are much less common.

In patients with pure small fiber neuropathies, motor and sensory NCS are, by definition, normal.[2,3,7,33] The peripheral autonomic nervous system is often affected in small fiber neuropathies; thus, autonomic testing can be useful.[30,34–36]The quantitative sudomotor axon reflex test (QSART) can be performed in the distal and proximal aspects of the legs and arms (Fig. 20–1). Sweat glands are innervated by small nerve fibers, and impaired QSART is highly specific and sensitive for small fiber damage, with 59–80% of patients having an abnormal study (Table 20–2).[30,34–36,39] Other autonomic tests (e.g., heart rate (HR) variability with deep breathing (DB) or Valsalva maneuver) may also be abnormal in individuals.[7,39,40] In this regard, assessments can included variability of HR to DB (Fig. 20–2) and response of the HR and blood pressure to Valsalva maneuvers and positional changes (e.g., response to tilt table or supine to standing position).

Abnormal thermal and vibratory perception thresholds may be demonstrated using QST.[3,7,41,42] Unlike NCS that only assess the physiology of large-diameter sensory fibers, QST of heat and cold perception can

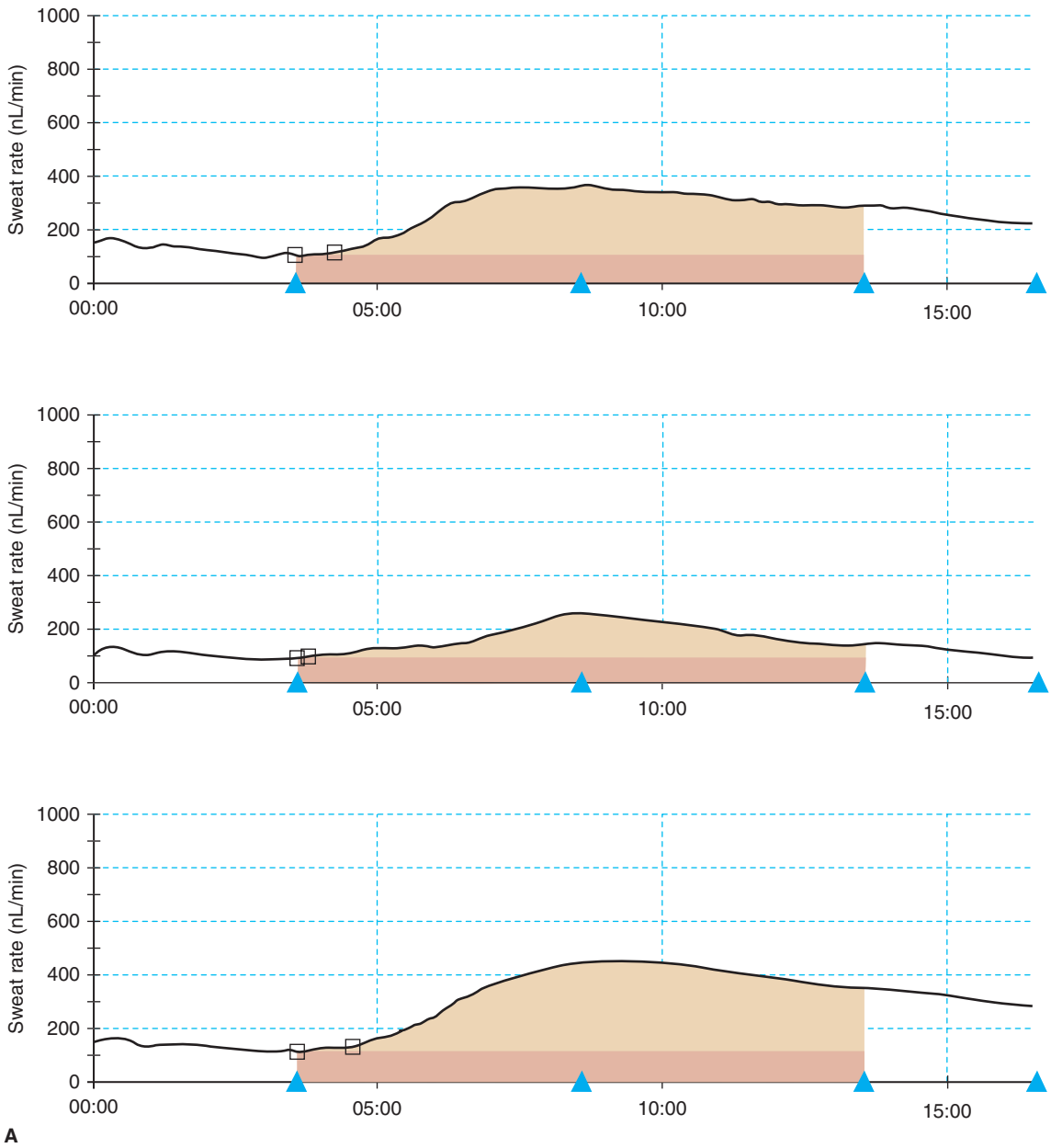


Figure 20–1. Quantitative sudomotor axon reflex test (QSART). Sudomotor function can be quantitating the amount of sweat produced in the distal and proximal aspects of the legs and arms. In (A), a normal response is seen (lower panel recorded from foot, middle panel for shin, and upper panel from thigh). Individuals with small fiber neuropathy may have reduced cumulative sweat. In length-dependent process the QSART is worse distally (e.g., at the foot compared to more proximally (B), lower panel recorded from foot, middle panel for shin, and upper panel from thigh).

evaluate small fiber function.[43] Abnormal QST has been reported in 60–85% of patients with predominantly painful sensory neuropathy (Table 20–2).[10,30,35–38,44] However, QST depends on patient attention and cooperation; it cannot differentiate between simulated sensory loss and sensory neuropathy. Further, the sensitivity and specificity of QST are lower than QSART and skin biopsies.[45,46]

HISTOPATHOLOGY

Sural nerve biopsies may reveal axonal degeneration, regenerating axonal sprouts, or axonal atrophy with or without secondary demyelination.[5–7,10,13,47] Quantitative morphometry may reveal loss of large- and small-diameter myelinated fibers and small unmyelinated fibers Occasionally, perivascular and endoneurial

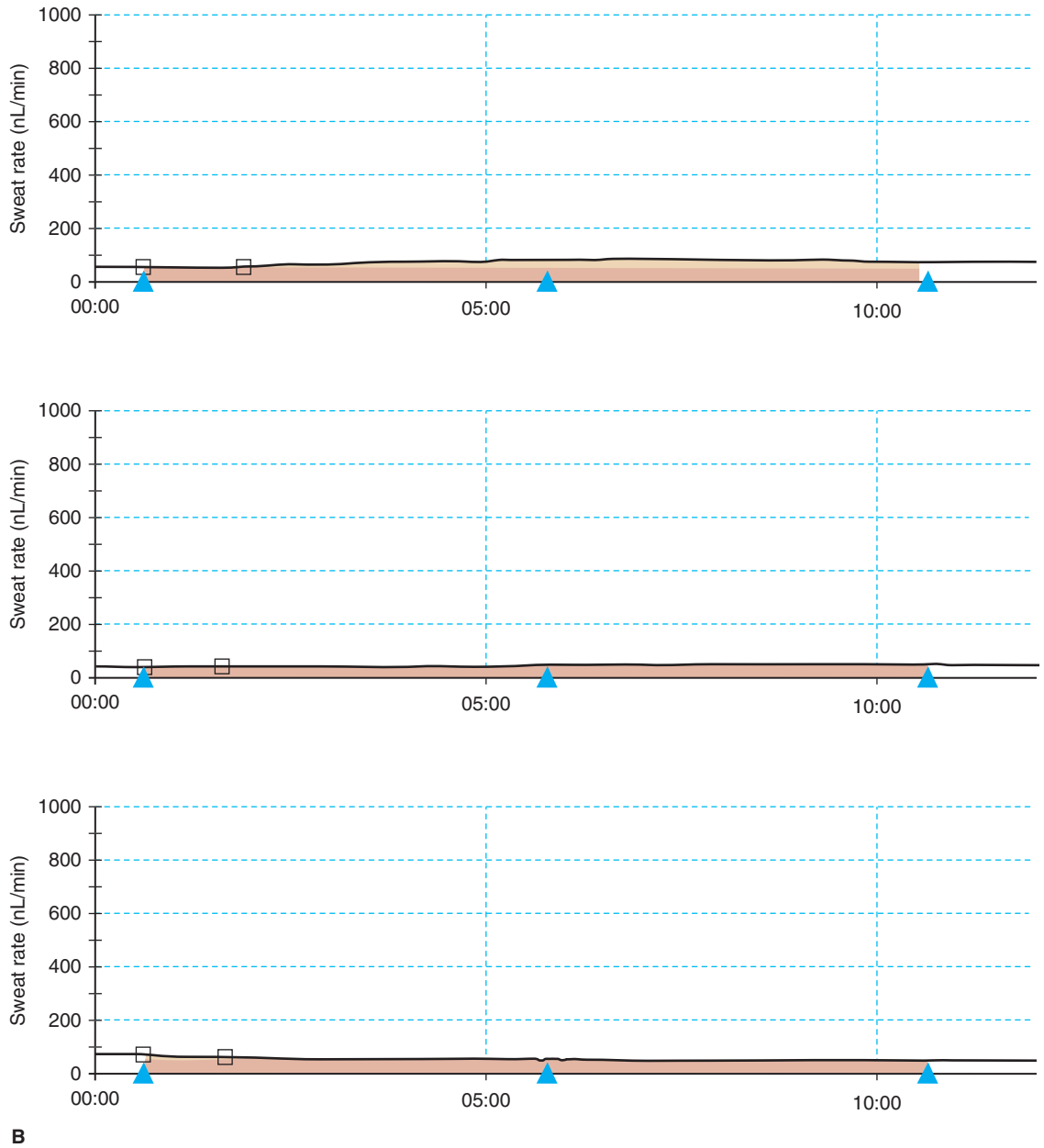


Figure 20–1. (Continued)

scattered lymphocytes may be seen on nerve biopsy,[47,48] although necrotizing vasculitis is not a feature. A clonal restriction of the variable T-cell receptor γ-chain gene has been demonstrated by one group of researchers.[49] Basal lamina area thickness, endoneurial cell area and number of endothelial cell nuclei may be increased.[50] However, the abnormalities on nerve biopsy are nonspecific and are generally not helpful in finding an etiology for the neuropathy. There, we do not routinely perform nerve biopsies on all patients with unexplained sensory polyneuropathies. We would consider biopsy of people with autonomic signs or monoclonal gammopathies to assess for amyloidosis and those with multiple mononeuropathies or underlying diseases at risk of vasculitis (e.g., connective tissue disorders and hepatitis B or C).

Nerve biopsies in individuals with small fiber neuropathies typically show selective loss of small myelinated nerves and unmyelinated nerve fibers (Fig. 20–3).[2,3,7,30,33,34,35,37,38] A more sensitive and less invasive means of assessing these small fiber neuropathies histopathologically is by measuring intraepidermal nerve fiber (IENF) density on skin biopsies (Fig. 20–4).[3,7,33,37,51–53] Assessment of intraepidermal nerve fiber density also appears to be more sensitive in identifying patients with small fiber neuropathies than sural nerve

▶ TABLE 20–2. COMPARISON OF DIAGNOSTIC TESTS IN PATIENTS WITH PREDOMINANTLY PAINFUL, SENSORY NEUROPATHY

Authors References	No. of Patients	Antinerve Antibodies No. of Patients (%)	Abnormal QST Cold or Heat Pain) No. of Patients (%)	Abnormal Cardiovagal (HR to DB or Valsalva) No. of Patients (%)	Abnormal QSART No. of Patients (%)	Reduced Epidermal Nerve Fiber Density No. of Patients (%)	Abnormal Sural Nerve Biopsy No. of Patients (%)	Abnormal NCS No. of Patients (%)
Stewart et al.[34]	**40**	–	–	11 (28%)	32 (80%)	–	–	0 (0%)
Holland et al.[37]	20 (total) 10 (idiopathic)	–	14/17 (82%) 7/9 (78%)	–	–	10/20 (50%) 7/10 (70%)	–	8/12 (67%) 6/9 (67%)
Holland et al.[3] Tobkin et al.[36]	**32**	N.D.	17/27 (63%) 67%	– 75%	– 80%	26/31 (81%)	4/6 (67%)	0 (0%)
Periquet et al.[7]	117 (total) Group 1, 60 (51%) Patients with abnormal NCS Group 2, 44 (38%) Patients with normal NCS but abnormal IENF density Group 3, 13 (11%) Pts with normal NCS and IENF density	1 (<1%) 1 (2%) 0 (0%)	23/32 (72%)*		19/32 (59%)*	28/32 (87.5%)* (0%) (by definition)		51% 100% 0% (by definition) 0% (by definition)
Novak et al.[35]	92 (total) 47 with “small fiber neuropathy and normal NCS”	–	66/75 (88%) 34/40 (85%)*	58 (63%) 27 (57%)	67 (73%) 32 (68%)	51/60 (85%) 29/37 (74%)	–	45 (49%)
Smith et al.[38]**	14	–	4/7 (57%)	–	–	11/14 (76%)	–	8/14 (57%)
Wolfe et al.[10]	92 (<5% pure small fiber neuropathy)	0/41	32/39 (82%)				13/14 (93%)	58/81(72) with abnormal sural SNAPs
Hermann, et al.[33]	26 (total) Four (small fiber neuropathy)					12/26 (46%) 4/4 (100%)		10/22 (45%) (O by definition)

*Included abnormal QST to cold or vibratory perception. Table includes only those 32 patients who each had QST, QSART, and IENF density.
**Patients with diabetes or impaired glucose tolerance.
Bold = idiopathic, predominantly small fiber neuropathy.
QSD, quantitative sensory testing; QSART, quantitative sudomotor axon reflex test; N.D., not done or not reported; NCS, nerve conduction studies.

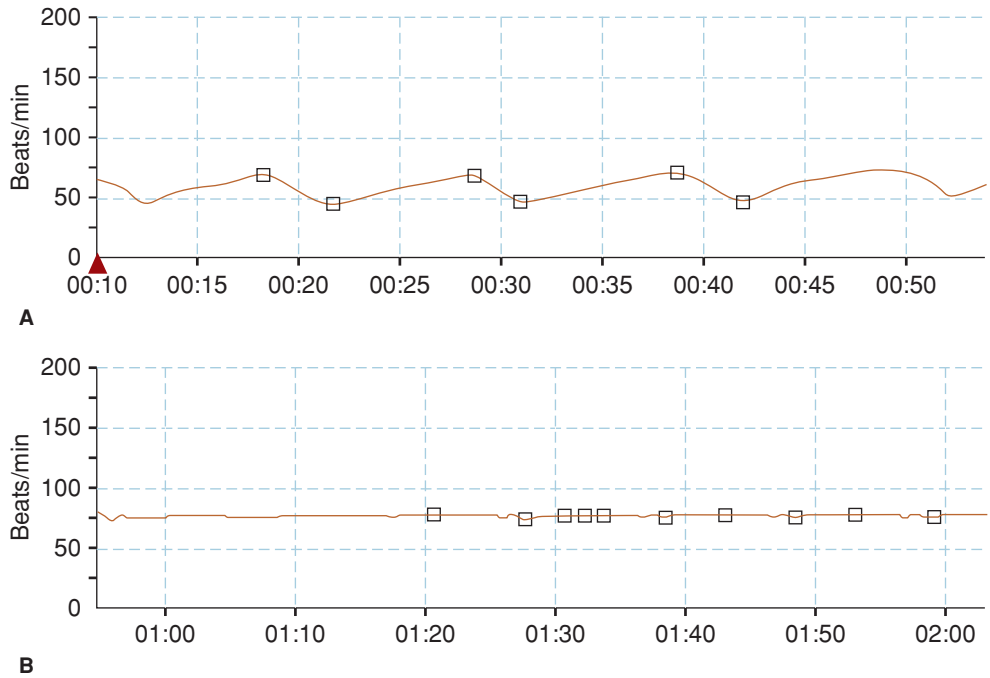
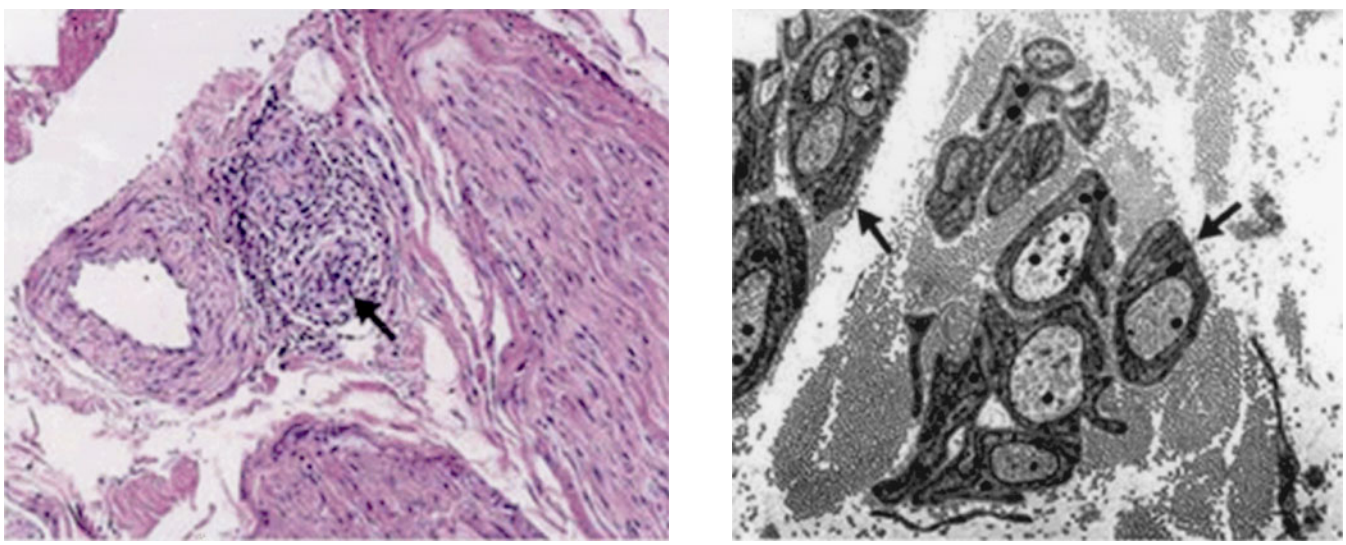


Figure 20–2. Heart-rate variability. Normally, the heart rate varies with respiration (A). Some individuals with small fiber involvement have an autonomic neuropathy with cardiovagal abnormalities, as demonstrated by reduced heart rate variability with deep breathing (B).



A B

Figure 20–3. Specimen from a sural nerve biopsy. The nerve is morphologically normal on light microscopy (A). There is a focal perivascular lymphocytic infiltrate, and in one small perineurial vessel (arrow) the infiltrate extends through the wall (hematoxylin and eosin, ×125). There is no necrosis or other evidence of vasculitis or intraneural inflammation. An electron micrograph (B) shows empty Schwann-cell processes (arrows) that are consistent with the loss of small, unmyelinated fibers (×8000). (Courtesy of Doctors Lawrence Hayward and Thomas Smith, University of Massachusetts Medical School, Worcester, MA).

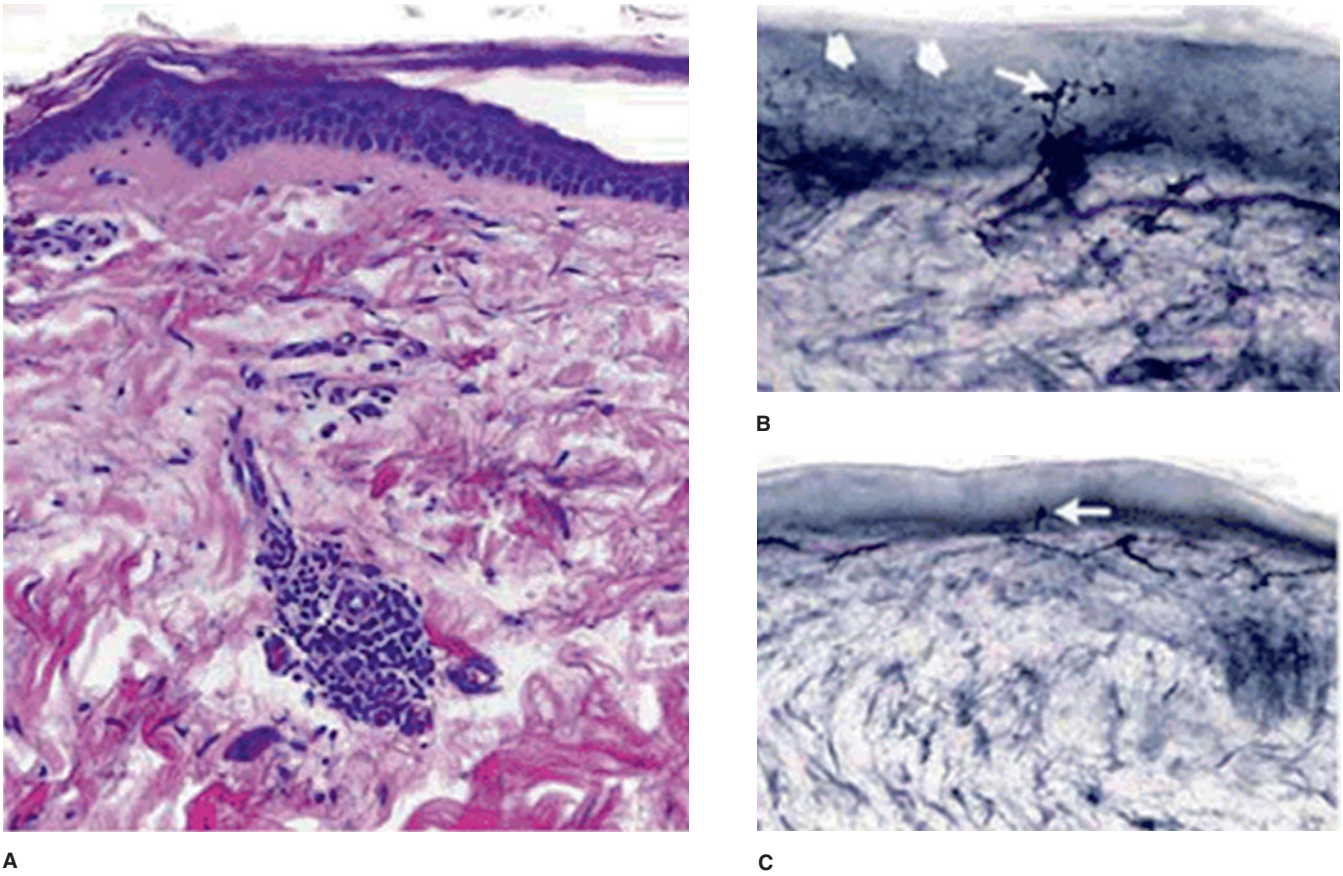


Figure 20–4. Specimens from skin-punch biopsies. A specimen obtained at the time of the patient's first evaluation at this hospital (A) shows a focal perivascular lymphocytic infiltrate (hematoxylin and eosin, ×125). A section immunolabeled against protein gene product 9.5 to reveal neural processes or axons (thick arrows) (B) shows an epidermal neurite with axonal swellings, which are abnormal (thin arrow). The density of nerve fibers is greater than normal (immunoperoxidase, ×500). A specimen obtained 11 months later (C) shows marked reduction in neurite density and axonal swelling (arrow) in a remaining neurite (×300). (With permission from Amato AA, Oaklander AL. Case 16–2004: A 76-year-old woman with numbness and pain in the feet and legs. N Engl J Med 2004;350:2181–2189, Fig. 2, p. 2187.)

biopsies, NCS, or QST (Table 20–2). Punch biopsy of the skin can be obtained at the foot, calf, or thigh, and immunohistochemistry using antibodies directed against protein gene product 9.5 (PGP 9.5) is used to stain small intraepidermal fibers. Intraepidermal nerve fibers arising entirely from the dorsal root ganglia represent the terminals of C and Aδ nociceptors. The density of these nerve fibers is reduced in patients with small fiber neuropathies in which NCS, QST, and routine nerve biopsies are often normal. In at least a third of people with painful sensory neuropathies, IENF density on skin biopsies represents the only objective abnormality present following extensive evaluation.[7]

PATHOGENESIS

As the name implies, the pathogenic basis of chronic idiopathic sensory neuropathy is unknown but likely multifactorial in etiology.[20] Some may be genetic, while others may have a primary degenerative or immunological basis. Prediabetes is part of the metabolic syndrome, which also includes hypertension, hyperlipidemia, and obesity. Individual aspects of the metabolic syndrome influence risk and progression of diabetic neuropathy and may play a causative role in neuropathy for those with both prediabetes and otherwise idiopathic neuropathy.[54]

TREATMENT

Unfortunately, there is no treatment for slowing the progression or reversing the "numbness" or lack of sensation. Therapies are aimed at symptomatic management of the neuropathic pain.[9,10,55–59] Most of the randomized controlled trials included patients with postherpetic neuralgia and painful neuropathy mainly caused by diabetes. A large number of such class I trials provide level

▶ **TABLE 20–3. TREATMENT OF PAINFUL SENSORY NEUROPATHIES**

Therapy	Route	Dose	Side Effects
Lidoderm 5% patch	Apply cutaneously	up to 3 patches daily for 12 hrs at atime	Local irritation
Gabapentin	p.o.	300–1200 mg TID	Cognitive changes and sedation
Pregabalin	p.o.	50–100 mg TID	Cognitive changes and sedation
Tricyclic antidepressants (e.g., amitriptyline and nortriptyline)	p.o.	10–100 mg qhs	Cognitive changes, sedation, dry eyes and mouth, urinary retention, and constipation
Duloxetine	p.o.	60 mg	Cognitive changes, dizziness, sedation, insomnia, nausea, constipation
Venlafaxine	p.o.	75–150 mg daily	Asthenia, sweating, nausea, constipation, anorexia, vomiting, somnolence, dry mouth, dizziness, nervousness, anxiety, tremor, and blurred vision as well as abnormal ejaculation/orgasm and impotence
Carbamazepine	p.o.	200–400 mg q 6–8 hrs	Cognitive changes, dizziness, leukopenia, and liver dysfunction
Phenytoin	p.o.	200–400 mg qhs	Cognitive changes, dizziness, and liver dysfunction
Tramadol	p.o.	50 mg qid	Cognitive changes, and GI upset
Other agents			
Mexiletine	p.o.	200–300 mg tid	Arrhythmias
Capsaicin 0.025–0.075% cream	Apply cutaneously	qid	Painful burning skin

GI, gastrointestinal.
Modified with permission from Amato AA, Dumitru D. Acquired neuropathies. In Dumitru D, Amato AA, Swartz MJ (eds). Electrodiagnostic Medicine, 2nd edn. Philadelphia: Hanley & Belfus, 2002, pp. 937–1041, Table 23–9, p. 976.

A evidence for the efficacy of tricyclic antidepressants, gabapentin, pregabalin, and opioids, followed by topical lidocaine (in postherpetic neuralgia) and the newer antidepressants venlafaxine and duloxetine (in painful neuropathy).[59]

Our approach to treating the painful paresthesias and burning sensation associated with chronic idiopathic sensory neuropathy is similar to the treatment of neuropathic pain regardless of etiology (e.g., painful sensory neuropathies related to diabetes mellitus, HIV infection, and herpes zoster infection) (Table 20–3). We start off with Lidoderm 5% patches to the feet, as this treatment is associated with less systemic side effects.[60] If this does not suffice (and it usually does not), our next step is to add an antiepileptic medication (e.g., gabapentin). We usually start at a low dose (e.g. 100–300 mg three times daily) and gradually increase up to 1200 mg three times daily, as necessary and as tolerated. Pregabalin, topiramate, phenytoin, carbamazepine, and valproate can also be tried. If these fail to adequately control the neuropathic pain, we add an antidepressant medication (e.g., nortriptyline, amitriptyline, desipramine, or duloxetine). Tramadol is used to treat breakthrough pain.

▶ SUMMARY

Chronic idiopathic polyneuropathies are not uncommon in clinical practice despite extensive laboratory evaluation. A standard laboratory workup including NCS is important to perform before concluding that the neuropathy is idiopathic in nature. Many of the patients may have IGT if an oral glucose tolerance test is performed, even if they have normal fasting blood sugar and hemoglobin A1C levels. Nerve biopsies are generally not indicated. Although skin biopsy may be informative by showing reduced epidermal nerve fibers when other studies (e.g., NCS, QST, and autonomic studies) are normal, these often do not tell you what you already know based on the history and clinical examination. That is, persons with burning and tingling pain in their feet with normal reflexes and NCS probably have a small fiber neuropathy, regardless of what the skin biopsy shows. Patients need reassurance that it is not all that unusual for an extensive workup to be performed and an etiology for their neuropathy is still not determined. Primary treatment is directed and symptomatic management of their pain.

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CHAPTER 21

Cervical and Thoracic Radiculopathies, Brachial Plexopathies, and Mononeuropathies of the Arm

Numbness, pain, and weakness involving one or both arms are common reasons for referral to the neuromuscular clinician. These symptoms may be due to radiculopathy, brachial plexopathy, or mononeuropathy. Some etiologies for these focal neuropathic disorders have been discussed in preceding chapters (e.g., Lyme disease, vasculitis, and diabetes mellitus). This chapter will focus mainly on radiculopathies secondary to compression (e.g., degenerative joint disease and herniated disks), brachial plexitis, traumatic plexopathies, and focal mononeuropathies related to compression or entrapment. Prior to discussing the evaluation and management of cervical radiculopathies, brachial plexopathies, and mononeuropathies of the arm, a review of the normal anatomy would be helpful.

▶ ANATOMY

SPINAL NERVES

Recall that there are seven cervical vertebrae, the first of which, the atlas, articulates with the skull's occipital condyles. The second cervical vertebra, the axis, has a superiorly directed bony prominence, the dens, that articulates with the atlas. The third through seventh cervical vertebrae are composed of the vertebral bodies themselves as well as short pedicles giving rise to laminae, which end in comparatively short and often bifid spinous processes. The transverse processes arise near the junctional zone of the pedicle and lamina. Between the transverse processes at each vertebral level lies a sulcus for the spinal nerves.

The spinal nerves are composed of a dorsal root and a ventral root (Fig. 21–1). The dorsal root arises from sensory fibers emanating from the dorsal root ganglia that lie outside the spinal cord. These dorsal root fibers enter the posterolateral aspect of the spinal cord and into the dorsal horn. Along the anterior aspect of the spinal cord, two or as many as 12 individual rootlets, fila radicularia, arising from anterior horn cells fuse forming the ventral root. Just distal to the dorsal root ganglion, the ventral and dorsal roots merge to form the spinal nerve. In the cervical region, there are eight cervical spinal roots on each side but only seven cervical vertebrae (Fig. 21–2). The first cervical spine nerve arises between the skull and atlas. As a result, each numbered cervical nerve root is related to the bony level immediately inferior to it down to the T1 vertebra. For example, the fifth cervical nerve root exits the spinal column just superior to the fifth cervical vertebrae. The eighth cervical nerve root exits the spinal column superior to the first thoracic vertebra.

At the intervertebral foramina, the spinal nerves are joined by the gray ramus from the cervical sympathetic chain ganglia (Fig. 21–1). The superior cervical ganglion communicates with C1–4 spinal roots, the middle cervical ganglion with the C5 and C6 spinal nerves, and the inferior cervical ganglion with C8 and T1 spinal roots. Importantly, the sympathetic nerves to head and neck arise from the first thoracic segment. Thus, injuries to the T1 nerve root may result in ipsilateral Horner syndrome (miosis, ptosis, and anidrosis). Just distal to the gray ramus, the cervical spinal nerves branch to form an anterior and posterior primary ramus. The nerve fibers in the posterior primary ramus innervate the paraspinal muscles, while the anterior primary rami of C5–T1 cervical spinal nerves form the brachial plexus (Fig. 21–3).

A dermatome refers to the cutaneous region supplied by a specific spinal nerve root segment (Fig. 21–4). Notably, there is some overlap of the cutaneous innervation by individual spinal nerves. The motor fibers emanating from the anterior horn cells, which course through the ventral root, spinal root, brachial plexus, and finally individual nerves, innervate specific muscle groups. Most muscle groups are supplied by motor nerves arising from at least two spinal cord segments (e.g., the deltoid muscle is innervated by motor fibers within the C5 and C6 spinal roots).

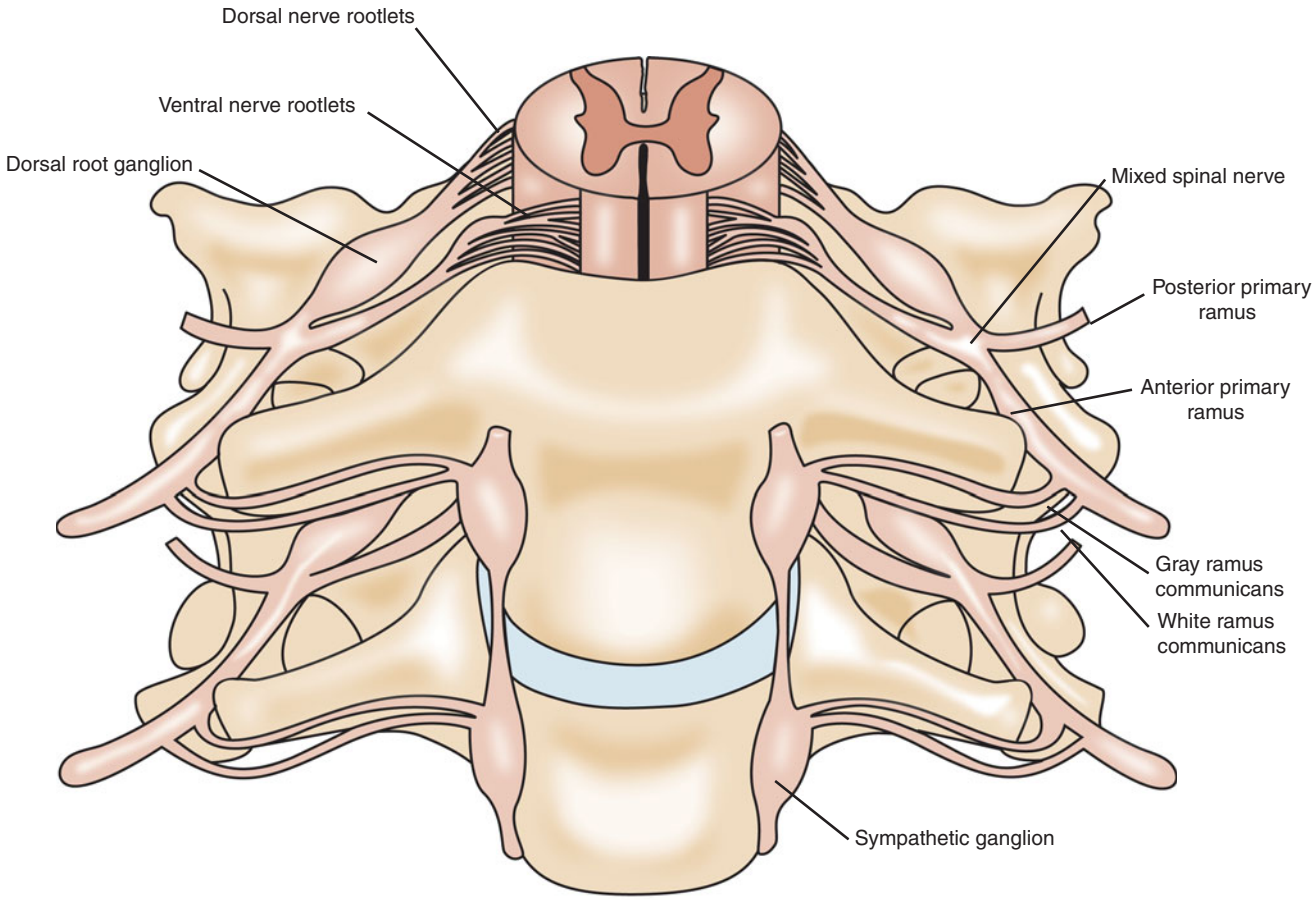


Figure 21–1. The spinal cord is depicted with multiple ventral and dorsal rootlets joining to form the mixed spinal nerve root. Communications between the sympathetic ganglia and the spinal nerves are appreciated, and the gray and white rami are seen as well. (Reproduced with permission from Ferrante MA. Brachial plexopathies: Classification, causes, and consequences. Muscle Nerve 2004;30(5):547–568. Fig. 2, p. 550.)

BRACHIAL PLEXUS

The brachial plexus is composed of three trunks (upper, middle, and lower), with two divisions (anterior and posterior) per trunk. Subsequently, the trunks divide into three cords (medial, lateral, and posterior), and from these arise the multiple terminal nerves innervating the arm (Table 21–1, Fig. 21–4).[1–3] More specifically, the anterior primary rami of C5 and C6 fuse to form the upper trunk; the anterior primary ramus of C7 continues as the middle trunk, while the anterior rami of C8 and T1 join to form the lower trunk. Of note, in approximately 62% of anatomic dissections of the brachial plexus, the C4 spinal nerve contributes to the upper trunk.[1,4] In this situation, the brachial plexus is said to be a "prefixed plexus" in which all of the spinal nerve contributions usually are shifted up one level. As a result, the contribution from the T1 spinal segment to the lower trunk of the brachial plexus may be minimal. In contrast, in approximately 7% of anatomic dissections of the brachial plexus C5 contributes minimally to the brachial plexus, a so-called "postfixed plexus."[1] In such cases, the spinal nerve contributions may be shifted down by one level; thereby, C7 contributes to the upper trunk while the lower trunk might receive nerves from the T2 spinal segment. However, the frequency of contributions of C4 and T2 to the brachial plexus is controversial, based on surgical explorations in patients following trauma.[1,5]

The anterior divisions of the upper and middle trunks fuse to form the lateral cord, while the anterior division of the lower trunk continues as the medial cord. The three posterior divisions of the upper, middle, and lower trunks join forming the posterior cord. The designations medial, lateral, and posterior cords refer to their respective anatomic positions relative to the axillary artery. The cords constitute the longest subsections of the brachial plexus.[6] There are some anatomic variation and communication between nerve fibers running between the different cords.[1,4] For example, some nerve fibers may exit the lateral cord and join the medial cord. Thus, the ulnar nerve may have contributions from the C7 spinal.

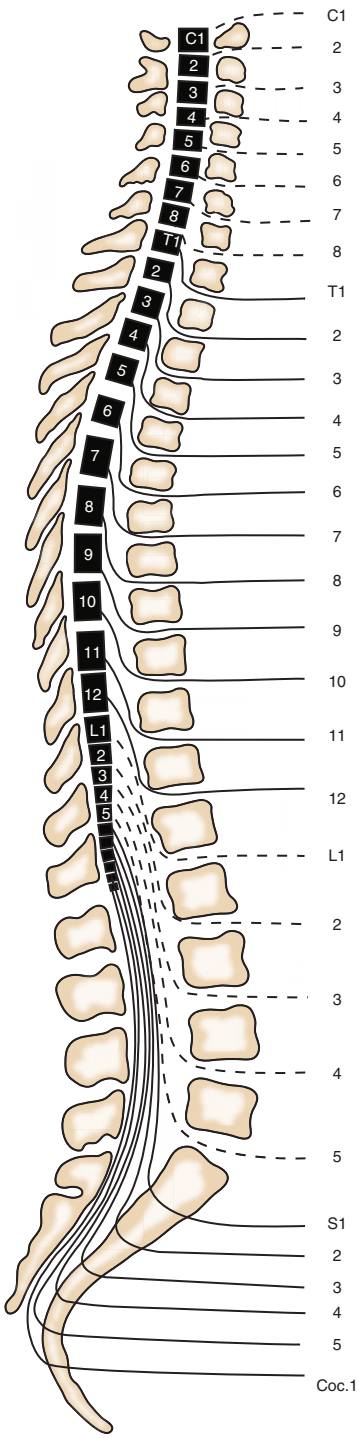


Figure 21–2. A sagittal section of the adult spinal column is depicted with the spinal cord demarcated by individual neural segments. Note the anatomic discrepancy between the termination of the spinal cord and vertebral column. The disparity between the spinal cord's neural segment and associated bony level with respect to spinal nerve exit is also shown. (Modified with permission from Haymaker W, Woodhall B: Peripheral Nerve Injuries: Principles of Diagnosis. Philadelphia, WB Saunders, 1953, Fig. 25, page 32.)

TERMINAL NERVES

From the spinal nerves and subsegments of brachial plexus rise the terminal nerves, which may be purely sensory, motor, or mixed sensorimotor (Fig. 21–3). The dorsal scapular nerve, long thoracic nerve, and a branch to the phrenic nerve arise directly from the spinal roots. The only two terminal nerves arising from the trunks are the subclavian and suprascapular nerves, and these both leave from the upper trunk. No terminal nerves come directly from the middle and lower trunk. The upper and lower subscapular and thoracodorsal nerves depart from the posterior cord, while the posterior cord terminates as the axillary and radial nerves. From the proximal aspect of the medial cord arises a single motor branch innervating the pectoral muscle, the medial pectoral nerve. The purely sensory medial brachial and medial antebrachial cutaneous nerves originate from the distal aspect of the medial cord. The medial cord terminates by sending a medial branch to the median nerve with the remnant continuing as the ulnar nerve. The lateral pectoral nerve comes off the proximal portion of the lateral cord. The lateral cord terminates as the musculocutaneous nerve and a lateral branch that joins a branch mentioned above from the medial cord to form the median nerve. Individual terminal nerves are discussed in more detail below.

Spinal Accessory Nerve

Although not a nerve arising from the brachial plexus, the spinal accessory nerve or cranial nerve XI courses through the neck and shoulder region and is often affected with brachial plexus injuries and therefore is discussed here. The nerve consists of a bulbar or accessory component that arises from the medulla and a spinal portion that arises from the anterior horn cells in the cervical cord down to C6. The nerves from the bulbar origin supply the soft palate and contribute to the recurrent laryngeal and possibly parasympathetic fibers, which then merge into the vagal nerve to the heart. The spinal component ascends between the ligamentum denticulatum and posterior spinal nerve roots, enters the cranium through the foramen magnum, and then exits the skull via the jugular foramen. The nerve descends posterior to the diagastric and stylohyoid muscles to the sternocleidomastoid muscle, which it innervates, and terminates in the trapezius muscle, which it also supplies.

Terminal Nerves Arising from Cervical Roots (Fig. 21–3)

Phrenic Nerve

The phrenic nerve is derived primarily from the C4 spinal nerve, but C3 and C5 roots may also contribute. The

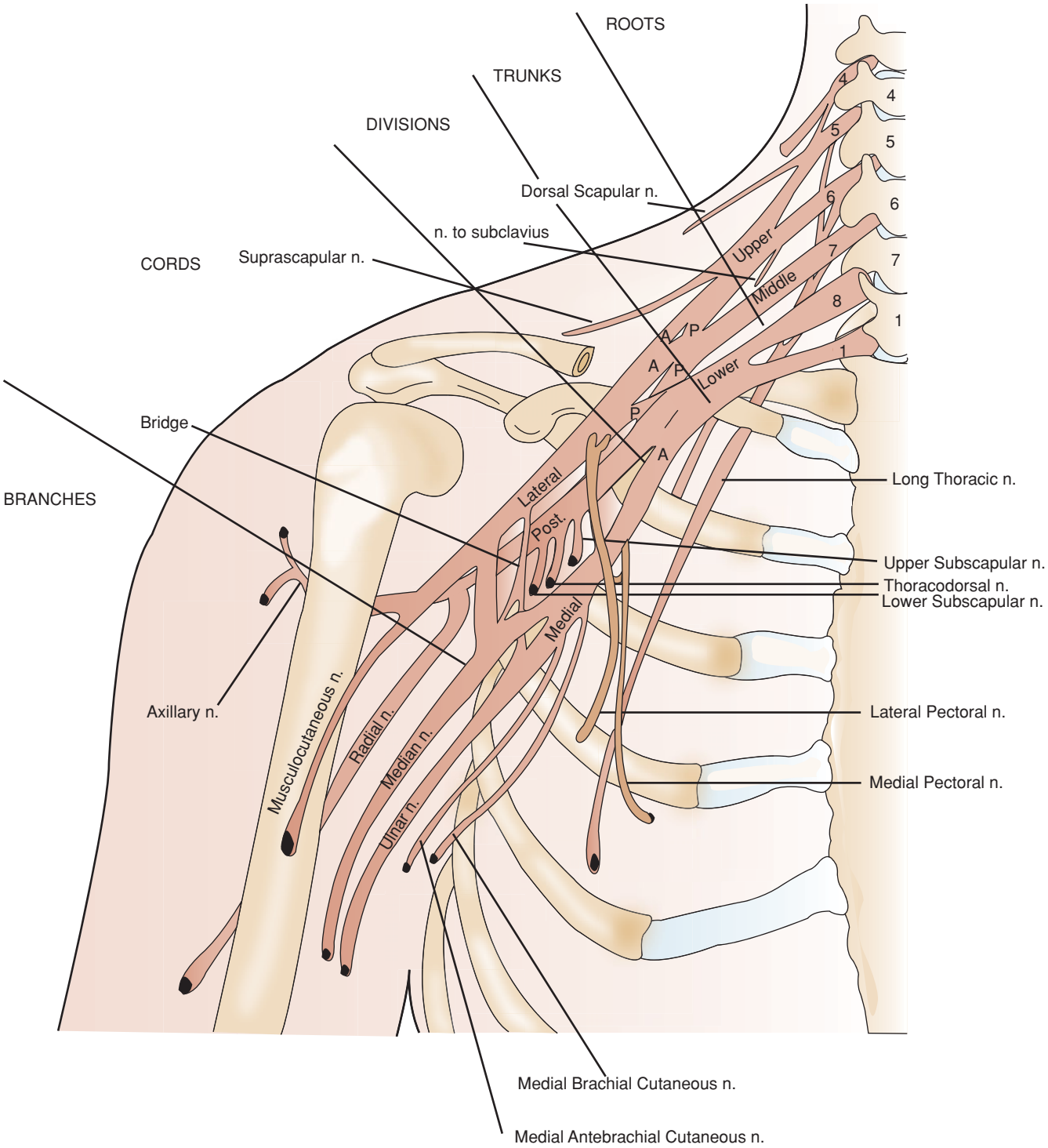


Figure 21–3. Diagrammatic representation of the brachial plexus (trunks, cords, and divisions) as well as its terminal nerves are depicted. (Modified with permission from Dumitru D, Zwarts MJ. Brachial plexopathies and proximal mononeuropathies. A, anterior division; P, posterior division; n, nerve. In Dumitru D, Amato AA, Zwarts MJ, eds. Electrodiagnostic Medicine, 2nd edn. Philadelphia: Hanley & Belfus, 2002, Fig. 19.1, p. 778.)

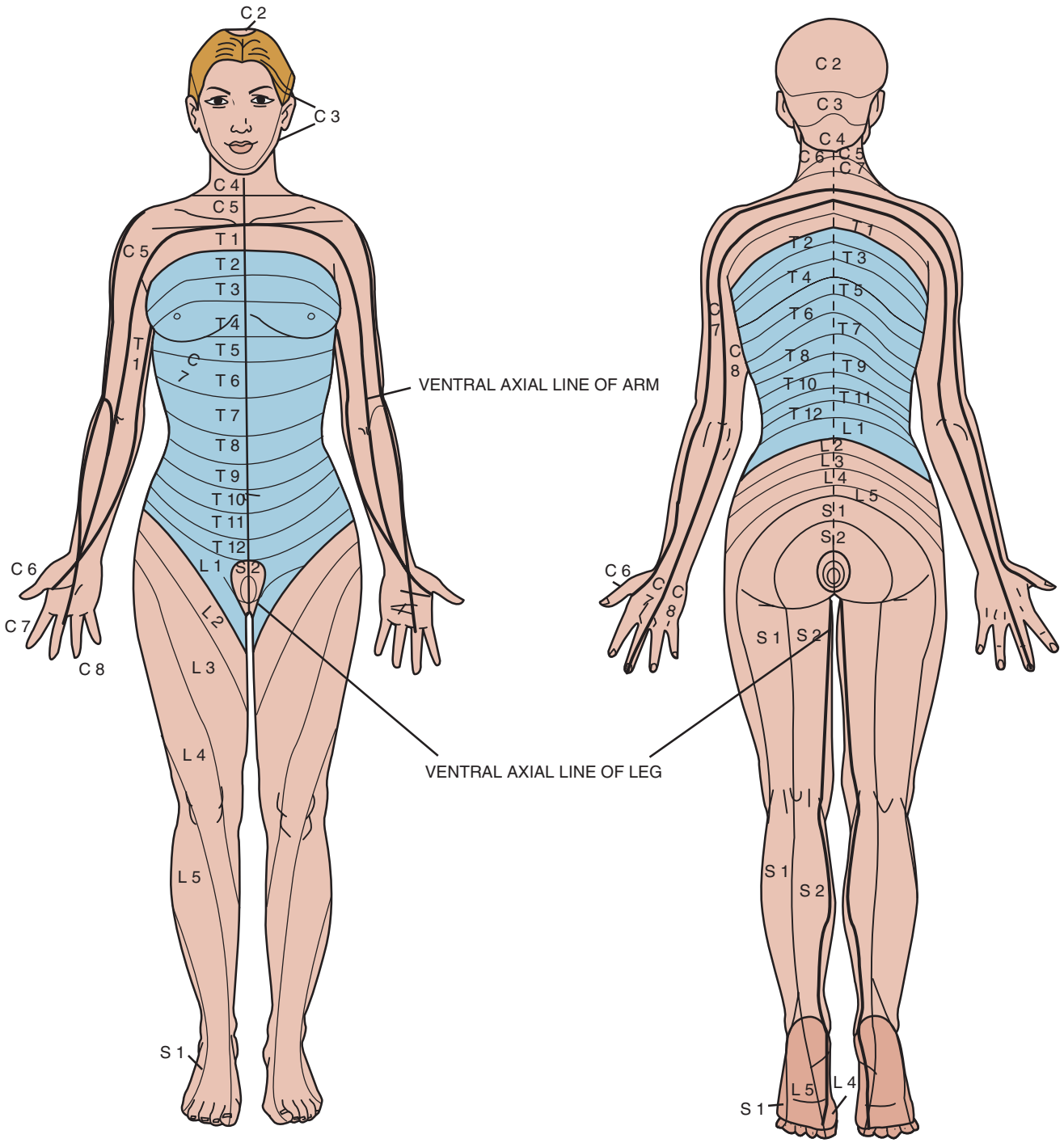


Figure 21–4. Dermatomal representation. (Modified with permission from Keegan JJ, Garret FD. Segmental distribution of the cutaneous nerves in the limbs of man. Anat Rec 1948; Dec 102(4):409–437, Fig. 2, page 411.)

phrenic nerve crosses the anterior scalene and enters the thorax where it innervates the diaphragm.

Dorsal Scapular Nerve

The dorsal scapular nerve usually arises directly from the C5 spinal nerve shortly after it exits the intervertebral foramen (Fig. 21–5). The nerve courses between the middle and posterior scalene musculature and innervates the major and minor rhomboid muscles and the levator scapulae.

Long Thoracic Nerve

Branches arising from the C5, C6, and C7 spinal nerves join forming the long thoracic nerve. The nerve descends to the lateral chest wall, where it innervates the serratus anterior muscle.

▶ **TABLE 21–1. INNERVATION OF THE MUSCLES IN THE UPPER LIMB**

Muscle	Root(s)	Trunk	Cord	Nerve
Trapezius				Spinal accessory (cranial nerve XI)
Rhomboid major and minor	C4, C5			Dorsal scapular
Serratus anterior	C5–7			Long thoracic
Supraspinatus/infraspinatus	C5, C6	Upper		Suprascapular
Pectoralis major	C5, C6	Upper	Lateral	Lateral pectoral
Pectoralis major and minor	C7, C8, T1	Middle/lower	Medial	Medial pectoral
Latissimus dorsi	C6–8	Upper/middle/lower	Posterior	Thoracodorsal
Teres major	C5–7	Upper/middle	Posterior	Lower subscapular
Teres minor	C5, C6	Upper	Posterior	Axillary
Deltoid	C5, C6	Upper	Posterior	Axillary
Brachioradialis	C5, C6	Upper	Posterior	Radial
Biceps brachii	C5, C6	Upper	Lateral	Musculocutaneous
Brachialis	C5, C6	Upper	Lateral/(posterior)	Musculocutaneous/(radial)
Triceps	C6–8	Upper/middle/lower	Posterior	Radial
Anconeus	C7, C8	Middle/lower	Posterior	Radial
Supinator	C7, C8	Middle/lower	Posterior	Posterior interosseous
Extensor carpi radialis	C6, C7	Upper/middle	Posterior	Radial
Extensor carpi ulnaris	C6–8	Upper/middle/lower	Posterior	Posterior interosseus
Extensor digitorum communis	C7, C8	Middle/lower	Posterior	Posterior interosseus
Extensor indicis proprius	C7, C8	Middle/lower	Posterior	Posterior interosseus
Extensor pollicis	C7, C8	Middle/lower	Posterior	Posterior interosseus
Pronator teres	C6, C7	Upper/middle	Lateral/medial	Median
Flexor digitorum superficialis	C7, C8, T1	Middle/lower	Lateral/medial	Median
Flexor digitorum profundus I and II	C7, C8, T1	Middle/lower	Lateral/medial	Anterior interosseus (median)
Flexor digitorum; profundus III and IV	C7, C8, T1	Middle/lower	Lateral/medial	Ulnar
Flexor carpi radialis	C6, C7, (C8)	Upper/middle/(lower)	Lateral/medial	Median
Flexor carpi ulnaris	C7, C8, T1	(Middle)/lower	(Lateral)/medial	Ulnar
Flexor pollicis longus	(C7), C8, T1	(Middle)/lower	(Lateral)/medial	Anterior interosseus (median)
Pronator quadratus	C8, T1	Lower	Medial	Anterior interosseus (median)
Abductor pollicis brevis	C8, T1	Lower	Medial	Median
Adductor pollicis	C8, T1	Lower	Medial	Ulnar
Opponens pollicis	C8, T1	Lower	Medial	Median
FBP	C8, T1	Lower	Medial	Median
FPB	C8, T1	Lower	Medial	Ulnar
Abductor digiti minimi	C8, T1	Lower	Medial	Ulnar
Dorsal and volar interossei	C8, T1	Lower	Medial	Ulnar
First and second lumbrical	C8, T1	Lower	Medial	Median
Third and fourth lumbrical	C8, T1	Lower	Medial	Ulnar

In parentheses are roots, trunks, cords, or nerves that may have mild contribution to innervation of the muscle group in some patients.
FPB, flexor pollicis brevis.

Terminal Nerves Arising from Trunks (Fig. 21–3)

Suprascapular Nerve

The suprascapular nerve arises from the upper trunk shortly after it is formed. The nerve descends posteriorly between the omohyoid and the trapezius muscles. In the posterior shoulder, it courses through the scapular notch under the scapula's superior transverse ligament and innervates the supraspinatus muscle and then the infraspinatus muscle (Fig. 21–5).

Nerve to the Subclavius

This is a small nerve that arises from the C5 root or upper trunk, which innervates the small subclavius muscle that runs between the clavicle and first rib.

Terminal Nerves Arising from Cords (Fig. 21–3)

Medial Pectoral Nerves

The medial pectoral nerve arises from the medial trunk. The nerve innervates both the pectoralis major and the

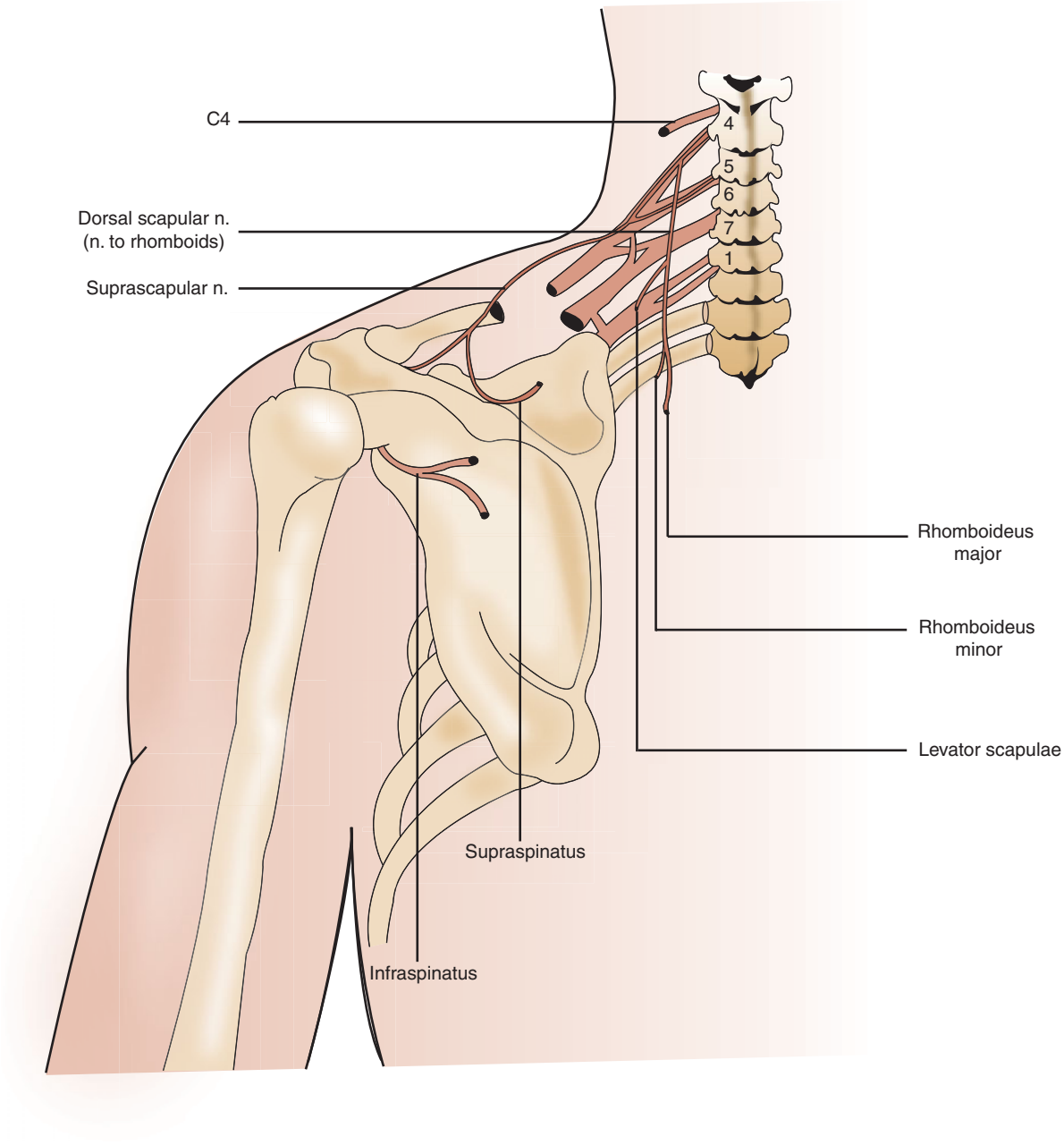


Figure 21–5. The posterior aspect of the thorax is shown, with the dorsal scapular and suprascapular nerves coursing to their respective muscles. The suprascapular nerve passes beneath the suprascapular notch (not depicted) as well as around the spinoglenoid notch, which are two potential areas of compromise. (Modified with permission from Haymaker W, Woodhall B. Peripheral Nerve Injuries: Principles of Diagnosis. Philadelphia: WB Saunders, 1953.)

pectoralis minor muscles. The major spinal contributions to this nerve are C8 and T1.

Lateral Pectoral Nerves

The lateral pectoral nerve usually comes from the lateral cord, but, occasionally, it arises from the anterior division of upper and middle trunks just prior to the formation of the lateral cord. This anatomic variation may explain the observation that in plexus injuries affecting the medial and lateral cords resulting in a flail arm, strength of the pectoralis major muscle, which the nerve innervates is relatively preserved. The major spinal contributions of this nerve are C5–7.

Subscapular Nerves

The upper and lower subscapular nerves originate from the posterior cord in the axilla. The upper subscapular nerve innervates the subscapularis muscle, while the

lower subscapular nerve supplies subscapularis and the teres major muscle. The major spinal contributions to this nerve are from C5 and C6.

Thoracodorsal Nerve

The thoracodorsal nerve comes off the posterior cord and innervates the latissimus dorsi muscle. This nerve can also arise in some cases from the radial and axillary nerves.[4] The major spinal nerves contributing to the thoracodorsal nerve are C5–7, particularly C7.

Medial Cutaneous Nerve of the Arm

The medial cutaneous nerve of the arm (medial brachial cutaneous nerve) originates from the medial cord and supplies sensation to the medial aspect of the upper arm above the elbow.

Medial Cutaneous Nerve of the Forearm

The medial cutaneous nerve of the forearm (medial antebrachial cutaneous nerve) usually projects from the medial cord, but it may arise from the medial cutaneous nerve of the arm.[4] The nerve supplies sensation from the medial forearm down to the wrist.

Musculocutaneous Nerve

The lateral cord terminates as the musculocutaneous and the lateral branch that combines with a branch from the median cord to form the median nerve (Fig. 21–6). In about 5% of individuals, the musculocutaneous nerve originates from the anterior division of the upper trunk in which case the lateral root to the median nerve arises from the middle trunk only.[4] The major spinal nerves contributing to the musculocutaneous nerve are from C5 and C6. In addition, C7 contributes to this nerve in at least half but less than two-thirds of cadavers examined.[4] The musculocutaneous nerve innervates the coracobrachialis, biceps brachii and brachialis muscles. It terminates as the lateral cutaneous nerve of the forearm, supplying sensation to the lateral aspect of the forearm from the elbow to the wrist.

Axillary Nerve

The axillary nerve contains portions of the spinal nerves arising from C5 and C6 and is one of the terminal branches of the posterior cord (Fig. 21–7). The nerve usually originates near the subscapularis muscle posterior to the pectoralis minor muscle and then traverses the quadrangular or quadrilateral space formed inferiorly by teres major, laterally by the long head of the triceps brachii, medially by the humerus, and superiorly by the teres minor. Upon exiting this space, the axillary nerve innervates the teres minor and deltoid muscles. The axillary nerve also sends cutaneous branches that supply sensation to the lateral aspect proximal arm overlying the deltoid muscle.

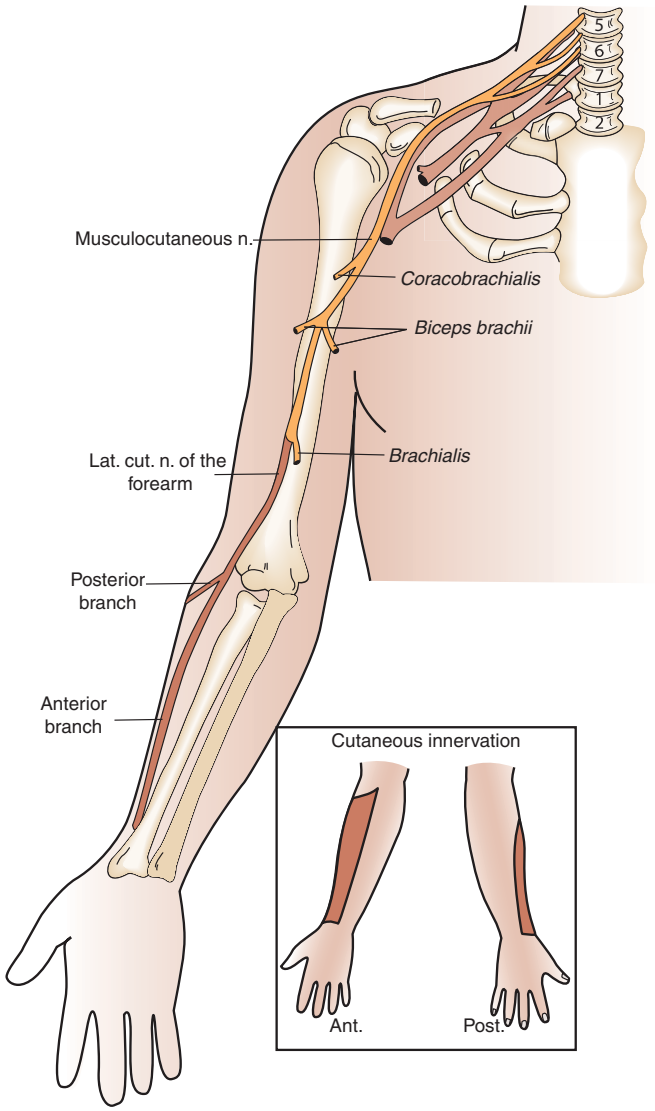


Figure 21–6. The musculocutaneous nerve is the termination of the lateral cord and supplies the coracobrachialis, biceps brachii, and brachialis muscles. It terminates as the lateral antebrachial cutaneous nerve, which splits into two cutaneous branches to supply the radial aspect of the forearm. (Modified with permission from Haymaker W, Woodhall B. Peripheral Nerve Injuries: Principles of Diagnosis. Philadelphia: WB Saunders, 1953.)

Radial Nerve

The radial nerve contains contributions from mainly C5–8 (T1 as well in approximately 10% of individuals) and, in essence, is a continuation of the posterior cord after the axillary nerve branches off (Fig. 21–8).[1,7] While still in the axillary region, a posterior cutaneous nerve branches off the radial to provide sensation to the posterior aspect of the upper arm to the elbow. In the proximal upper arm, the radial nerve travels medial to the humerus and descends between the medial and long heads of the triceps muscle along the spiral groove.

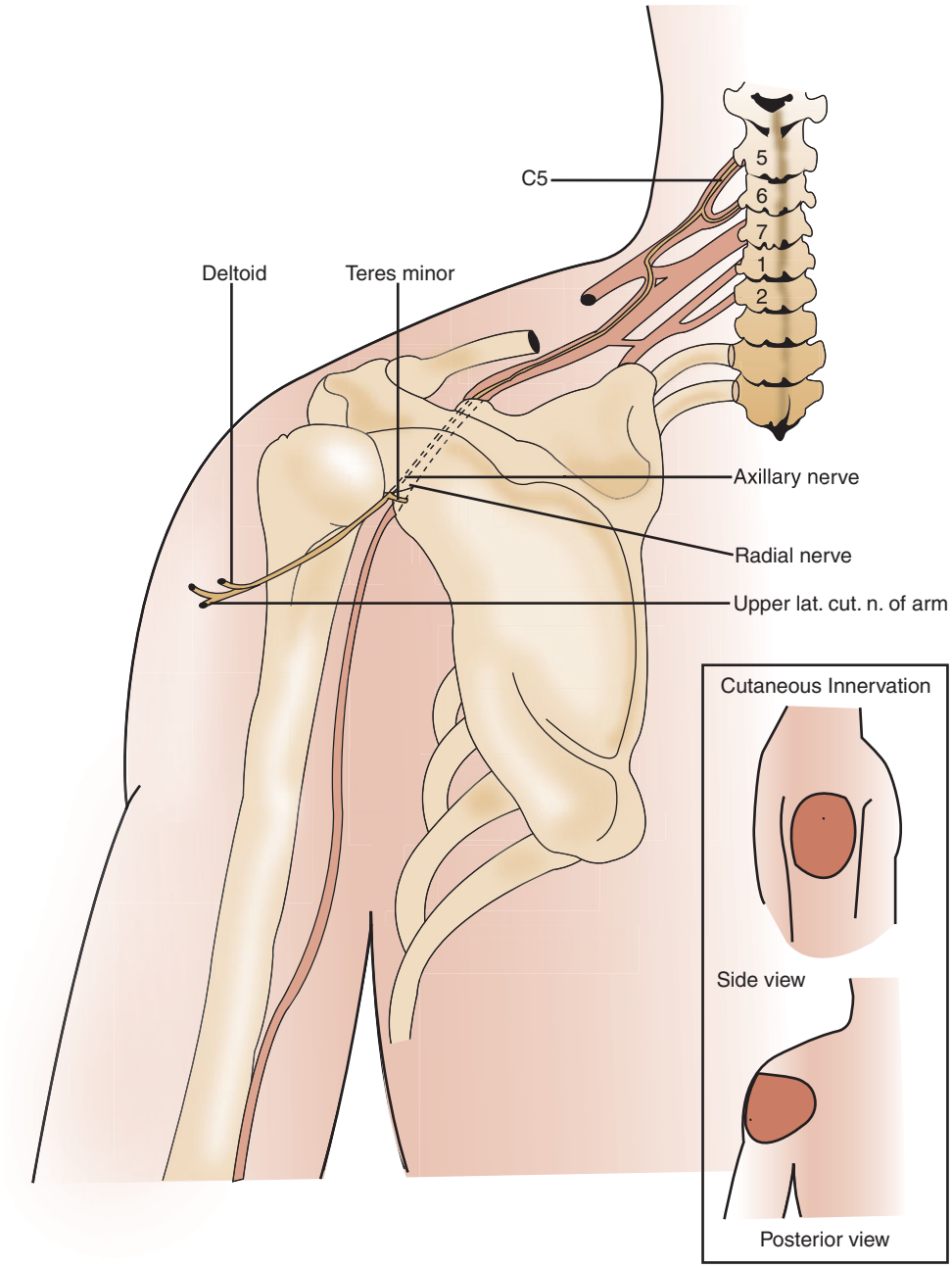


Figure 21–7. One of the terminal branches of the posterior cord is the axillary nerve. It supplies both the teres minor and the deltoid muscles as well as providing cutaneous sensation to the skin overlying the deltoid muscle (upper lateral cutaneous nerve of the arm). (Modified with permission from Haymaker W, Woodhall B. Peripheral Nerve Injuries: Principles of Diagnosis. Philadelphia: WB Saunders, 1953.)

In the upper arm, the radial nerve innervates the long, medial, and lateral heads of the triceps brachii and the anconeus muscles. Upon leaving the spiral groove, the radial nerve courses down to the lateral aspect of the upper arm and innervates the brachioradialis muscle and extensor carpi radialis longus as well as a small branch the brachialis muscle, the latter receiving its main contribution from the musculocutaneous nerve. Additionally, the posterior antebrachial cutaneous nerve supplies sensation to the posterior aspect of the forearm.

In the elbow region, the radial nerve splits to form the purely sensory, superficial radial nerve and the purely motor, posterior interosseous nerve. In this area is the so-called radial tunnel bound by the radius, the

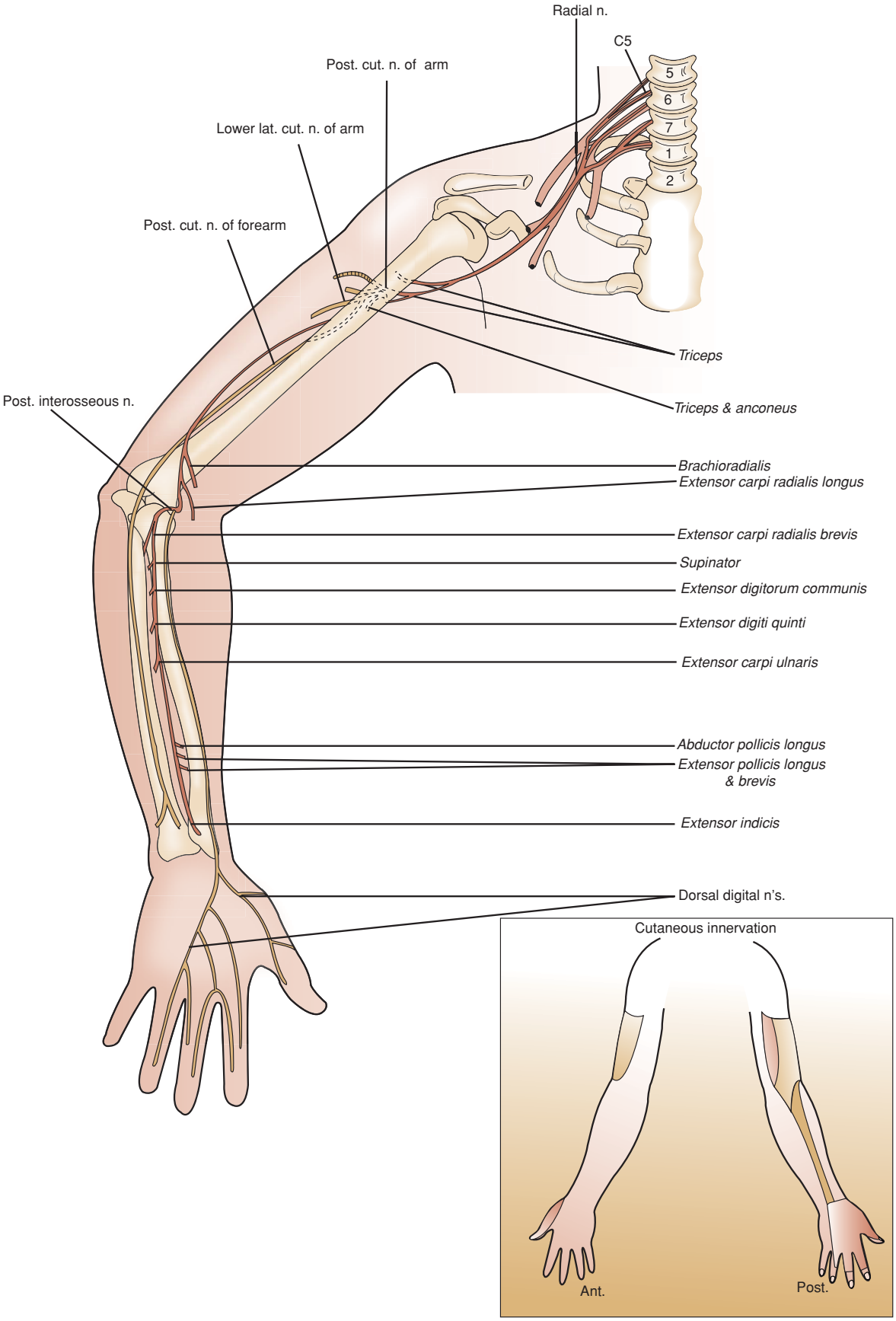


Figure 21–8. The course and muscular innervation of the radial nerve is depicted. In the axilla and proximal arm, the triceps muscle is innervated as well as three sensory branches originate. The sensory branches can be of assistance in localizing a lesion at or proximal to the spiral groove. (Modified with permission from Haymaker W, Woodhall B. Peripheral Nerve Injuries: Principles of Diagnosis. Philadelphia: WB Saunders, 1953.)

capsule of the radiocapitular joint, the brachialis and the biceps brachii tendons (forming the medial walls), and the brachioradialis, extensor carpi radialis, and extensor carpi ulnaris muscles (forming the lateral and anterior walls). The radial tunnel ends at the fibrous band around the superficial head of the supinator muscle, which is known as the arcade of Fröhse. The superficial radial nerve travels on the undersurface of the brachioradialis outside the radial tunnel into the forearm. Around the mid-forearm, the nerve moves more superficially along the extensor aspect of the distal forearm. After the superficial radial nerve passes the wrist, it supplies sensation to the extensor surface of the hand and fingers (except the distal aspects of the fingertips, which are supplied by the median and ulnar nerves, and the dorsum of the medial aspect of the hand and medial fingers that are supplied by the dorsal ulnar cutaneous nerve). The posterior interosseus nerve traverses the radial tunnel and then descends under the arcade of Fröhse. The posterior interosseus nerve continues down the extensor aspect of the forearm. Along the way it innervates the supinator, extensor digitorum communis, extensor digiti minimi, extensor carpi ulnaris, abductor pollicis longus, extensor pollicis longus and brevis, and the extensor indicis proprius.

Median Nerve

The median nerve is formed by the fusion of branches from the lateral and medial cords (Fig. 21–9). The main spinal nerve contributions to the median nerve are C6–T1. Motor fibers arise from C6–T1 spinal segments, while sensory fibers are derived primarily from the C6 and C7 segments. Occasionally, C5 can also contribute to the median nerve.[1] The sensory fibers travel through the upper and middle trunks to the lateral cord into the median nerve, while the motor fibers pass through all the trunks as well as the medial and lateral cords.

The median nerve descends in the anterior compartment of the upper arm to the antecubital fossa region. Past the elbow, the median nerve courses through the two heads of the pronator teres muscle and then between the flexor digitorum superficialis and profundus muscles to the wrist. In the forearm, the median nerve innervates the pronator teres, flexor carpi radialis, palmaris longus, and flexor digitorum superficialis muscles. In the proximal to mid-forearm level, the anterior interosseous nerve branches from the main median nerve. This is a pure motor nerve that supplies the flexor digitorum profundus 1 and 2, flexor pollicis longus, and pronator quadratus muscle. The main median nerve trunk continues distally down the forearm to the wrist. Just prior to entering the carpal tunnel, the palmar cutaneous branch arises to supply sensation over the thenar eminence. The nerve then enters the carpal tunnel bounded by the carpal bones with the transverse ligament serving as the roof. Also within the carpal tunnel lie the nine flexor tendons to the fingers. Within or just distal to the carpal tunnel, the recurrent branch of the median nerve arises and innervates the abductor pollicis brevis, opponens pollicis, and the superficial head of the flexor pollicis brevis. The terminal branches of the median nerve supply the first and second lumbrical muscles, while the digital branches provide sensation to the volar aspects (and the tips of the dorsal aspects) of the thumb, index, and middle fingers and the lateral half the ring finger.

Ulnar Nerve

The ulnar nerve arises as the termination and continuation of the medial cord distal to the medial cutaneous nerves of the arm and forearm and the medial branch of the median nerve (Fig. 21–10). The spinal nerve contributions are mainly C8 and T1, but C7 fibers may also be present in 43–92% of cases, as suggested by brachial plexus dissections.[1,4] The C7 contribution derives from a branch off the lateral cord and innervates the flexor carpi ulnaris muscle. The ulnar nerve descends anterior to the teres major and latissimus dorsi muscles into the upper arm. Then the nerve travels down the posterior compartment of the upper arm to the ulnar groove at the elbow. The ulnar groove is formed by the medial epicondyle of the humerus and the olecranon process of the ulna, with the ulnar collateral ligament serving as the floor. Approximately 1.0–2.5 cm distal to the ulnar groove, the nerve traverses under a fibrous aponeurotic arch connecting the humeral and ulnar heads of the flexor carpi ulnaris muscle. The area encompassing the ulnar groove and aponeurotic arch is commonly referred to as the cubital tunnel. Of note, the ulnar nerve yields no branches in the arm proximal to the elbow.

Distal to the elbow, the ulnar nerve travels between the flexor carpi ulnaris and flexor digitorum profundus muscles down to the wrist. In the forearm, it innervates the flexor carpi ulnaris and the flexor digitorum profundus III and IV muscles. The dorsal ulnar cutaneous nerve originates in the mid or distal forearm to provide sensation to the dorsum of the medial aspect of the hand and fourth and fifth digits. Just prior to entering Guyon's canal at the wrist, the palmar branch arises to provide sensation to the hypothenar eminence and innervation of the palmaris brevis muscle. The remaining ulnar nerve travels into Guyon's canal formed by the hook of the hamate bone (on the radial aspect), the pisiform bone (on the ulnar aspect), the pisiohamate ligament (serves as the floor), and the transverse carpal ligament (serves as the roof). Within or just distal to Guyon's canal, the ulnar nerve terminates into its terminal branches. A superficial terminal branch supplies sensation to the palmar aspect of the little finger and half of the ring finger plus some of the distal aspects of these digits dorsally. A deep motor branch innervates the hypothenar muscles and then turns and continues across the hand to innervate the third and fourth lumbricals, interossei, adductor pollicis, and deep head of the flexor pollicis brevis muscle.

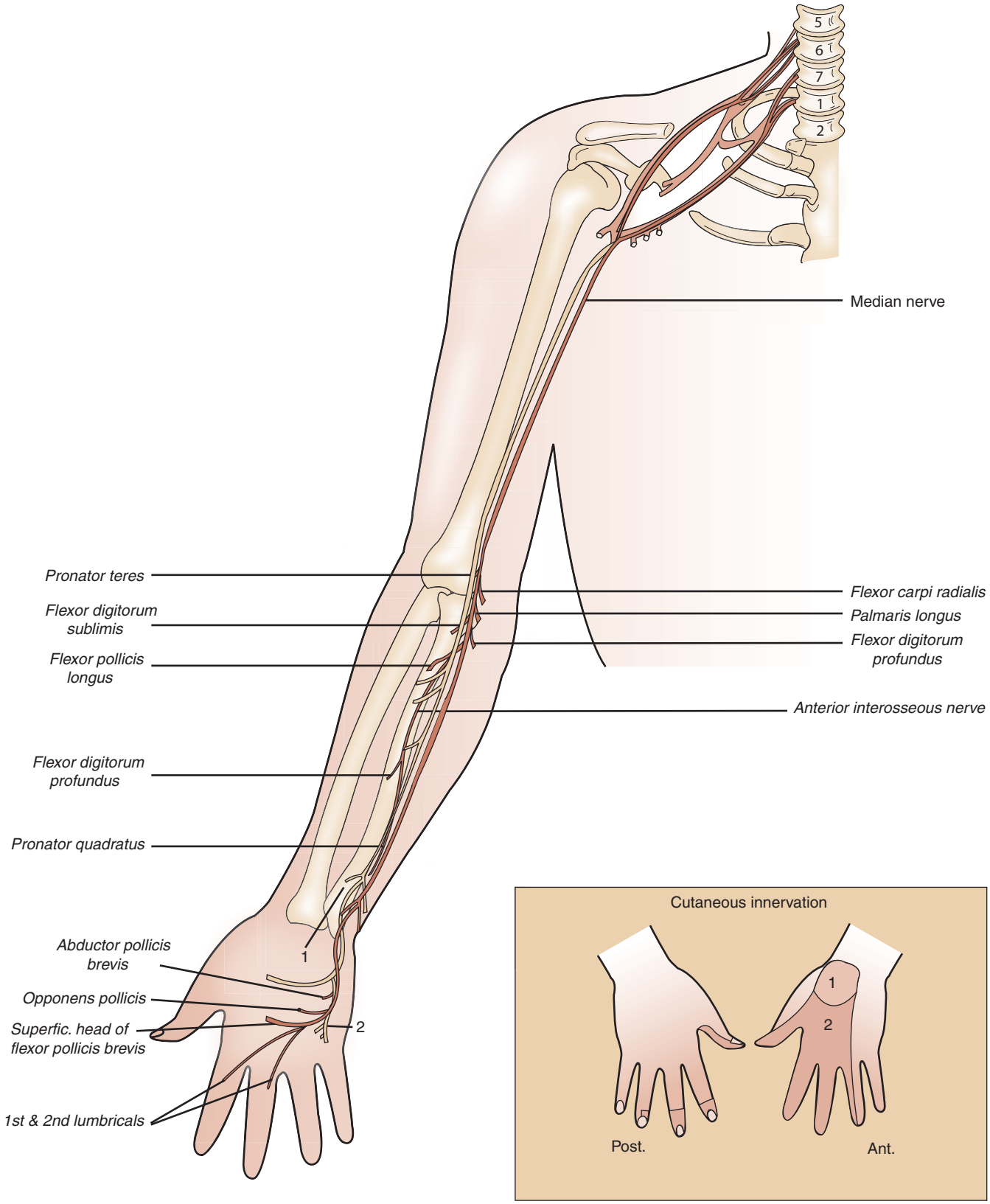


Figure 21–9. There are no muscular or cutaneous branches arising from the median nerve in the axillary region or arm. The first branch originating from the median nerve is to the pronator teres in the proximal forearm. (Modified with permission from Haymaker W, Woodhall B. Peripheral Nerve Injuries: Principles of Diagnosis. Philadelphia: WB Saunders, 1953.)

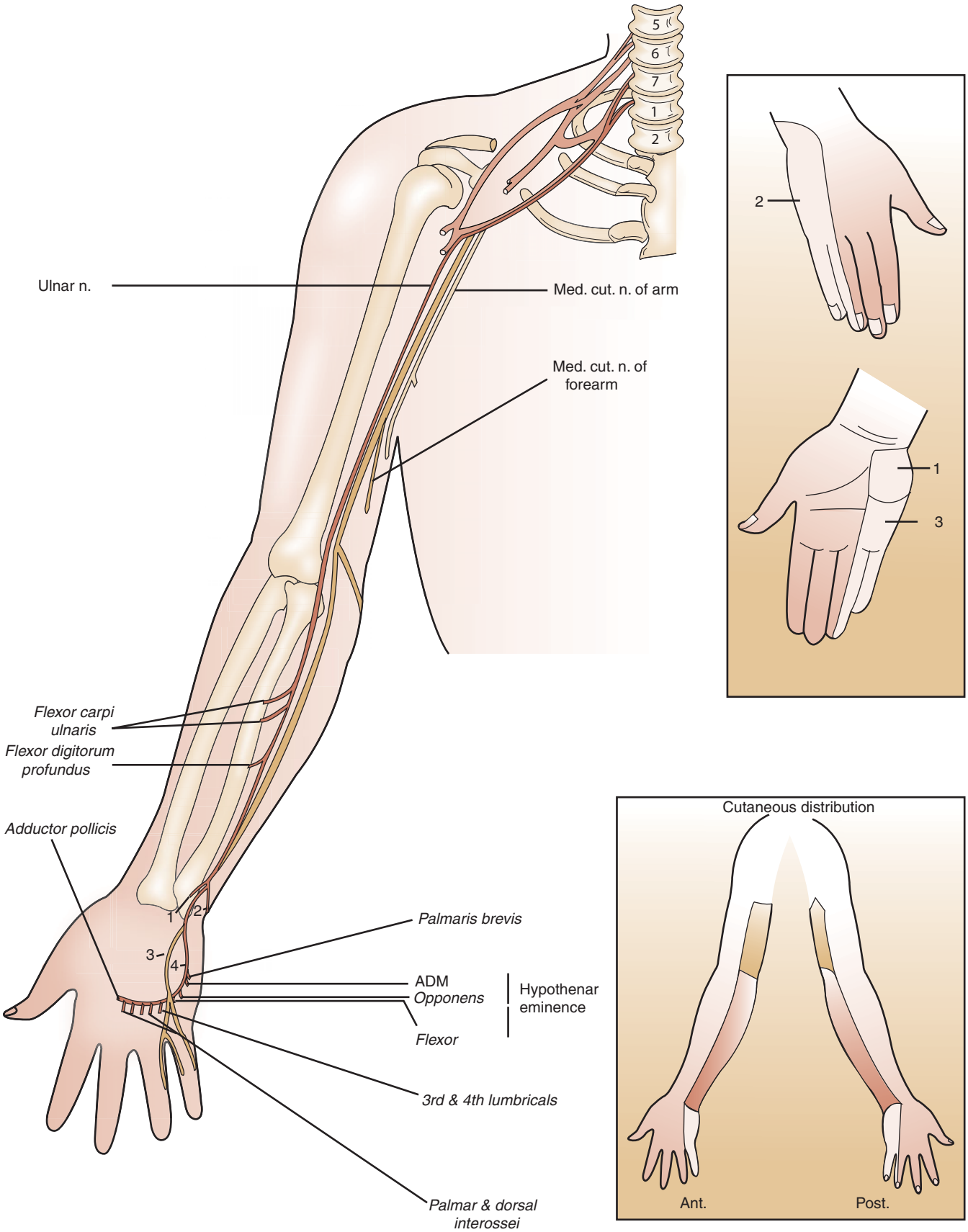


Figure 21–10. The ulnar nerve does not have any motor or cutaneous branches in the arm. ADM, abductor digiti minimi. The cutaneous branches of the medial cutaneous nerves of the arm and forearm are depicted. (Modified with permission from Haymaker W, Woodhall B. Peripheral Nerve Injuries: Principles of Diagnosis. Philadelphia: WB Saunders, 1953.)

▶ PATHOPHYSIOLOGY OF RADICULOPATHIES, PLEXOPATHIES, AND MONONEUROPATHIES

Prior to discussing the approach to patients with focal nerve lesions in the arm, it is important to understand the possible pathophysiological bases of these neuropathies. Clinicians need to be aware of the mechanisms of nerve injury so that they can plan the appropriate electrodiagnostic evaluation and the timing of these studies, interpret the findings, and offer reasonable prognoses and treatment options. The pathophysiological bases of nerve injury are limited: conduction block with or without demyelination or axonal degeneration. The method by which an individual injured the nerve (e.g., gun shot wound to upper arm, prolonged hyperextension of the arm during surgery, and falling asleep on arm) often provides insight into the underlying pathophysiology.

TYPES OF NERVE FIBER DAMAGE

Neuropraxia

The term "neuropraxia," also known as first-degree injury, refers to neuronal dysfunction due to transient conduction block.[1,8–10] In regard to focal peripheral nerve lesions, neuropraxia may arise from ischemia or demyelination. Compression of a nerve can result in segmental ischemia, which if of only short duration, results in a rapidly reversible physiologic conduction block lasting minutes or perhaps a few hours. However, experimental studies suggest that pressure related to compression on the nerve results in a distortion of the underlying nerve segment with paranodal and then segmental demyelination.[11] Neuropraxia due to demyelination may resolve after several weeks following remyelination of the nerve segment. Thus, prognosis in lesions associated with only conduction block without secondary axonal loss is excellent.

Axonotmesis

Axonotmesis or second-degree injury refers to nerve injuries in which the axon is interrupted but the epineurium is intact.[1,8–10] Following this type of nerve injury the axon distal to the lesion will degenerate over the next 7–10 days. Subsequently, regenerating nerve sprouts emerge from the proximal stump of the sectioned nerve to attempt reinnervation of previously denervated tissues (e.g., muscle or cutaneous skin). Because the endoneurium is preserved, there is a greater likelihood that the regenerating axons can grow back and reinnervate denervated tissues. Axons grow back at a rate of 1 mm/d, so restoration of function can take many months to over a year, depending on the site of the lesion and length of the nerve.

Neurotmesis

Neurotmesis refers to severe nerve injuries in which the axon and the supporting epineurium are interrupted.[1,8–10] It is impossible to distinguish between axonotmesis and neurotmesis unless there is exploratory surgery and direct inspection of the nerve. Because the endoneurium is also interrupted, it is more difficult for regenerating nerve sproats to reinnervate the target tissues. Scarring secondary to the disruption of the overlying connective tissue can also impede reinnervation. Regenerating nerves may become entwined with the scar tissue creating a neuroma. Thus, the prognosis for spontaneous recovery following this type of lesion is poor.

▶ APPROACH TO PATIENTS

As with other neuromuscular disorders, the most important step is trying to localize the site of the lesion based on the history and physical examination. Following this, electrodiagnostic studies are performed to confirm the localization or try to localize the exact site of the lesion more accurately if not apparent by the clinical examination. Often radiologic studies are done to further assist in identifying the site of the lesion and the possible cause. We begin the discussion of the approach of such patients with a review of electrodiagnostic studies that can be helpful.

ELECTRODIAGNOSTIC STUDIES

The evaluation of the arm for possible cervical radiculopathy, brachial plexopathy, or mononeuropathy requires performing sensory, motor, and mixed sensorimotor nerve conduction studies (NCS) along with electromyography (EMG) (Table 21–2). This text is not meant to be a "how-to book" on EMG and NCS, and for this we refer the reader to several excellent reference books regarding electrodiagnostic medicine (more details can also be obtain in Chapter 2 of this book).[6,12–15] However, clinicians taking care of patients with neuromuscular disorders need to be aware of the utility and limitations of these studies. The electrodiagnostic studies also need to be tailored to the individual patients depending on their symptoms and signs and as the results of the ongoing EMG and NCS are being analyzed.

Sensory NCS

Evaluating the sensory nerve action potentials (SNAPs) is important in distinguishing a radiculopathy from a more distal process. The lesion in most radiculopathies is proximal to the dorsal root ganglia. Because the cell bodies and distal axons are intact in cervical radiculopathies, the SNAPs should be normal. In contrast, in brachial plexopathies and mononeuropathies in which the lesion

▶ TABLE 21–2. BRACHIAL PLEXUS CLASSIFICATION: NATURE OF INJURY

Closed	Open
Idiopathic brachial plexus neuropathy	Trauma
Traction injuries (obstetric, postsurgical)	e.g., gunshot wound, shrapnel, and lacerations
Closed trauma	
Radiation related	
Tumor (primary/secondary)	
Neurogenic thoracic outlet syndrome	
Rucksack palsy	
Genetic (HNA and HNPP)	

HNA, hereditary neuralgia amyotrophy; HNPP, hereditary neuropathy with liability to pressure palsy.
Modified from Wilbourn AJ. Brachial plexus disorders. In Dyck PJ, Thomas PK, Griffin JU, et al. (eds). Peripheral Neuropathy, 3rd edn. Philadelphia: W.B. Saunders, 1992, pp. 911–950.

is distal to the dorsal root ganglion, one would expect to see reduced amplitudes of SNAPs in the distribution of the affected nerve, provided there is significant axonal injury. In cases of a demyelinating lesion or conduction block (as the case in neuropraxic injuries), the SNAP distal to the site of the lesion is usually normal. When the injury to the plexus or peripheral nerve is axonal in nature, one also needs to remember that it takes several days from the time of the injury for Wallerian degeneration of the axons to occur distally. Thus, it takes approximately 7–10 days for the SNAPs to disappear even if the nerve is completely severed. After this period of time there is sufficient degeneration of axons to begin to distinguish postganglionic axonal loss from conduction block/demyelination or a preganglionic lesion. However, an abnormal SNAP does not imply that the spinal root is normal as there may be a concurrent injury more proximal. For example, in traumatic brachial plexopathies, one may also see avulsion of nerve roots.

It is very important to compare the SNAPs in the affected arm with ones in the contralateral arm. It is possible that the SNAP amplitude(s) in an affected arm may still fall "within normal limits" for that electrodiagnostic laboratory. However, if the SNAP amplitude(s) is reduced compared to the normal extremity (usually want to see it less than half the size), this would be considered abnormal. This of course is not helpful if the symptoms are bilateral.

The specific sensory studies performed are again dependent on the possibilities for the site of the lesion (Table 21–3).[16] If one is evaluating a patient with sensory symptoms affecting the thumb, the possibilities include a C6 radiculopathy, upper trunk, lateral cord, median neuropathy, or radial neuropathy. Thus, the sensory studies

▶ TABLE 21–3. NERVE CONDUCTION STUDIES

Sensory Studies			
	Brachial Plexus		
Spinal Root	Trunk	Cord	Peripheral Nerve
C6	Upper	Lateral	Lateral antebrachial cut.
C6	Upper	Lateral	Median to first/second digit
C6	Upper	Posterior	Radial to base of first digit
C6	Upper	Lateral	Median to second digit
C7	Middle	Lateral	Median to third digit
C8	Lower	Medial	Ulnar to fifth digit
C8	Lower	Medial	Dorsal ulnar cutaneous
T1	Lower	Medial	Medial antebrachial cut.

Motor Studies				
	Brachial Plexus			
Spinal Root	Trunk	Cord	Peripheral Nerve	Muscle
C5, C6	Upper	Lateral	Musculocutaneous	Biceps
C5, C6	Upper	Posterior	Axillary	Deltoid
C5, C6	Upper		Supracapular	SS, IS
C7, C8	Middle/lower	Posterior	Radial	EIP
C8, T1	Lower	Medial	Median	APB
C8, T1	Lower	Medial	Ulnar	ADM and FDI

Cut., cutaneous; SS, supraspinatus; IS, infraspinatus; EIP, extensor indicis proprius; APB, abductor pollicis brevis; FDI, first dorsal interosseous; ADM, abductor digiti minimi.
Modified with permission from Wilbourn AJ. Electrodiagnosis of plexopathies. Neurol Clin 1985;3:511–529.

most helpful would be a median SNAP from the thumb or index finger, a superficial radial SNAP from the thumb, median and ulnar mixed nerve palmar studies, and perhaps the lateral antebrachial cutaneous SNAP along with comparison to the asymptomatic side. Additionally, it is important to assess a nerve that is not felt to be clinically affected (e.g., an ulnar SNAP in this situation). If the patient has symptoms involving little finger, then the investigator needs to conduct studies to differentiate a C8/T1 radiculopathy, lower trunk, medial cord, and ulnar neuropathy from one another.

Motor NCS

Evaluation of a motor nerve is performed by stimulating the nerves at several locations and recording the compound muscle action potential (CMAP) from distally located muscles, as discussed in Chapter 2 (Table 21–3).[16] As with sensory studies, the majority of routine motor stimulation sites are remote from the proximally located lesions associated with a radiculopathy or plexopathy. Thus, it is technically very difficult to assess for a demyelinating/conduction block lesion in these proximal sites. Further, most electrodiagnostic laboratories only routinely perform median, ulnar, and radial CMAPs. These motor studies are most useful in lower trunk and medial cord injuries as well as median, ulnar, or radial neuropathies. These can assist in localizing the site and nature of the lesion (e.g., axonal or demyelinating/conduction block) involving these nerves. Again, in an axonal lesion one needs to wait about 7–10 days until Wallerian degeneration has occurred and CMAP amplitudes become reliably reduced. Further, in demyelination/conduction block, one would have to assess the CMAP by stimulating the nerve proximal and distal to the site of the lesion. Importantly, routine median and ulnar CMAPs are not abnormal in patients with C5–7 radiculopathies and upper trunk plexopathies. An axillary CMAP recorded from the deltoid or musculocutaneous CMAP recorded from the biceps brachii can be performed in such cases, but again it would be important to study the contralateral asymptomatic side as a comparison. Radiculopathies are not usually associated with an abnormal CMAP even if an affected muscle is studied unless there has been severe end-stage neurogenic atrophy of the muscle. Remember that most muscle groups are supplied by more than one nerve root, and thus detecting reduced CMAP amplitudes in cervical radiculopathies is not particularly common unless it is severe or there are multiple roots affected.

F-Waves

F-wave studies have limited value in the evaluation of most radiculopathies and entrapment neuropathies. The reason for this is clear if one understands the pathogenesis of most of these focal neuropathies. The length of a possible compressive/demyelinating lesion is small in most radiculopathies and even mononeuropathies due to entrapment/compression (e.g., ulnar neuropathy at the elbow or median neuropathy at the wrist). Remember, the F-wave latency takes into account the time for the stimulus to travel antegrade through the motor nerve, stimulate a pool of anterior horn cells, and then travel back down the motor axon to stimulate the muscle. Thus, even if there were focal slowing across a small site of demyelination, this may be obscured by the normal conduction to and from the spine across the majority of the nerve. Further, most criteria regarding F-waves use the shortest latencies of multiple responses to define if the study is abnormal. Thus, one only needs to have one normal axon for the F-wave study to be deemed normal. However, if one is looking for a large proximal demyelinating lesion, as can be seen in some focal forms of chronic inflammatory demyelinating neuropathy, then F-waves are of some value.

H-Reflex

The only reliable H-reflex in the arm is from the flexor carpi radialis muscle following median nerve stimulation at the antecubital fossa.[17] This study is not routinely performed, as it usually does not assist in localizing the lesion apart from what is gained from the clinical examination, routine motor and sensory NCS, and the EMG. Nevertheless, the H-reflex for the flexor carpi radialis muscle may be abnormal in C6 or C7 radiculopathies, upper or middle trunk plexopathies, lateral cord lesions, or proximal median neuropathies.

Somatosensory-Evoked Potentials

Somatosensory-evoked potentials have limited utility in radiculopathies and most neuropathies for much the same reason as discussed with F-waves. However, somatosensory-evoked potentials may be of value in assessment of brachial plexopathies because routine sensory NCS will not pick up a demyelination or conduction in the plexus.[18–21]

Needle EMG

The EMG examination is absolutely essential in the evaluation of patients for radiculopathy, plexopathy, and mononeuropathy. In combination with the clinical examination and carefully performed motor and sensory NCS, the EMG of muscles supplied by different spinal roots, trunks, divisions, and cords of the brachial plexus, and different terminal nerves solidifies the localization of the site of the lesion. As discussed in Chapter 2, with EMG we assess the presence of abnormal insertional and spontaneous activity, the morphology of motor unit action potentials (MUAPs), and the recruitment properties

of these units. Abnormal insertional or spontaneous activity in the form of positive sharp waves or fibrillation potentials implies membrane instability, which in neurogenic processes is typically due to axonal degeneration. Irritation of the nerve with or without axonal degeneration may result in fasciculation potentials, complex repetitive discharges, or myokymic discharges. The detection of myokymic discharges in a patient with history of cancer and radiation, who is now presenting with focal deficits in an arm, would strongly suggest radiation-induced injury to the roots or plexus as opposed to tumor infiltration. The demonstration of abnormal spontaneous activity in the paraspinal muscles suggests that there is at least some injury to the anterior horn cells or spinal nerves but also does not exclude an injury more distally (e.g., double crush).

Importantly, fibrillation potentials and positive sharp waves may not be present for up to 1 week in a paraspinal muscle and 3 weeks or following an axonal injury to a nerve root. However, voluntary recruitment of MUAPs is affected immediately. Thus, any injury to the nerve that results in a significant loss of muscle strength should be accompanied by reduced recruitment (e.g., fast-firing) MUAPs. In neuropraxic injuries in which there is demyelination or conduction block without axonal degeneration, fibrillation potentials and positive sharp waves are not seen and the only abnormality apparent on the EMG is reduced recruitment of MUAPs.

Following an axonal injury, muscle fiber may be reinnervated and thus no longer are fibrillation potentials and positive sharp waves evident. Reinnervation is more complete in muscles closer to the site of axonal injury (e.g., paraspinal muscles in a radiculopathy). Muscle groups more distal to the site of the lesion (e.g., hand intrinsic muscles in a cervical radiculopathy) may be less likely to be completely reinnervated, and thus fibrillation potentials and positive sharp waves may persist indefinitely.

Another important point is that because of fascicular arrangement of axons running through various segments of the nerve trunk from the spine to the target muscle, unless the nerve is completely severed the EMG does not necessarily demonstrate an abnormality in every muscle group innervated by an affected spinal nerve root, trunk, cord, or terminal nerve.

RADIOLOGICAL STUDIES

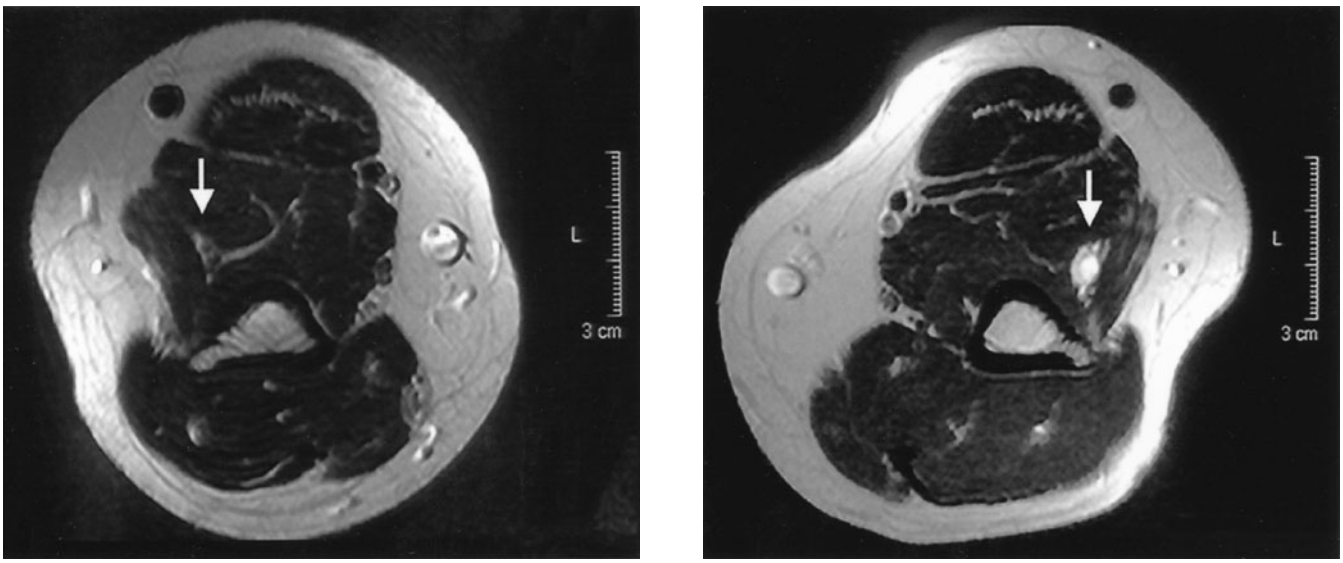
Imaging studies such as a myelogram or magnetic resonance imaging (MRI) of the cervical spinal and brachial plexus are extremely valuable and complement the clinical examination and electrodiagnostic medicine study. MRI has, for the most part, replaced myelogram and computerized axial tomographic (CT) scans except in individuals in whom MRI is contraindicated (e.g., those with magnetic implants) for evaluation of radiculopathies. CT scans with and without contrast agent can be useful,[22,23] but high-resolution MRI is much more sensitive for radiculopathies, plexopathies, and focal neuropathies (Fig. 21–11).[23–29] Several studies have investigated the utility of ultrasound in focal neuropathies (Fig. 21–12).[30–36]

▶ SPECIFIC DISORDERS

CERVICAL RADICULOPATHIES

Recall the disparity between the number of cervical vertebrae (seven) and nerve roots (eight) (Fig. 21–2). As a result, each numbered cervical nerve root is related to the immediate inferior bony level. For example, the C5 spinal root exits the spinal column between the fourth and fifth cervical vertebra, and it is vulnerable to compression from a herniated disk (herniated nucleus pulposus or HNP) between C5 and C6. The C6 spinal root exits the spinal column between the fifth and the sixth cervical vertebrae and may be injured from an HNP between C5 and C6. In the same manner, an HNP between C6 and C7 levels may damage the C7 root, while an HNP at the C7 and C8 vertebral may impinge the C8 nerve root. The T1 spinal nerve exists between the eighth cervical and first thoracic vertebrae and may be damaged by an HNP at this level.

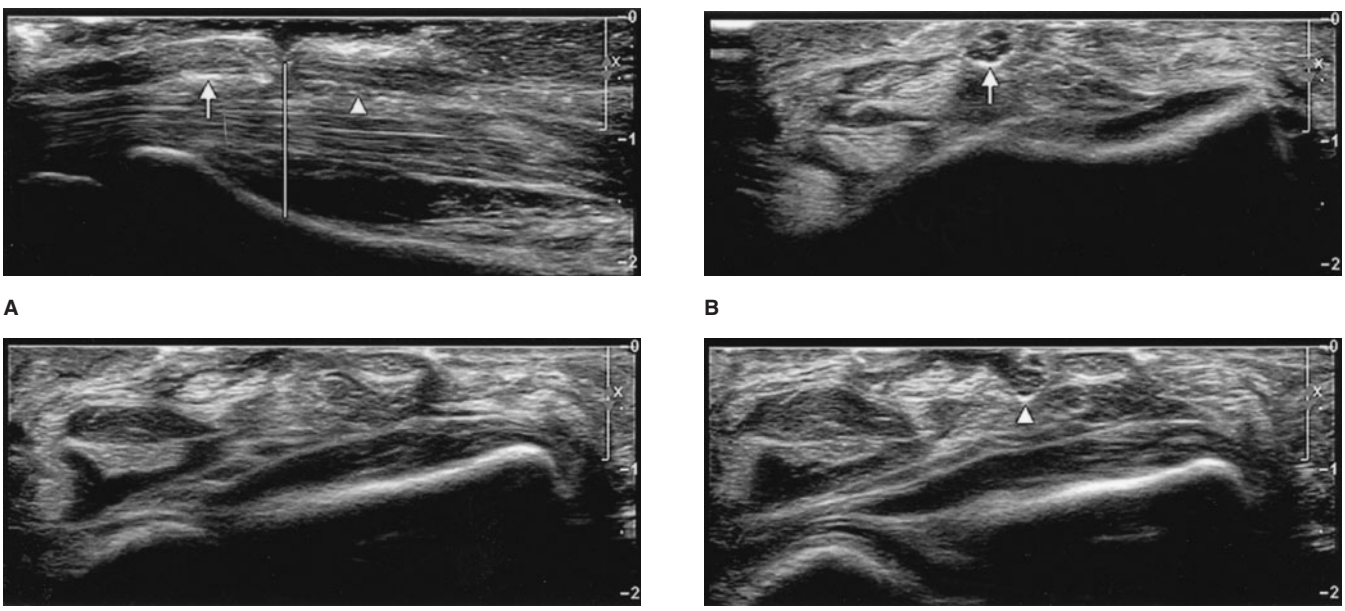
Most cervical radiculopathies involve the C5–8 spinal nerve roots (C7 occurring in 31–81%, C6 in 19–25%, C8 in 4–10%, and C5 in 2–10%).[13,37–42] Causes of cervical radiculopathy are multiple (Table 21–4) and most commonly involve compression of nerve root by an HNP or osteophytes in the case of degenerative spine disease. Individuals with a cervical radiculopathy typically present with neck or posterior shoulder pain that radiates down the affected arm. Turning the head toward the painful arm, particularly with neck extension, can narrow the neuroforamen further compressing the nerve root and thus exacerbates the pain as can putting pressure on top of an affected individual's head. The patient may have weakness in the distribution of the affected myotome and sensory loss in the dermatome that is involved. The deep tendon reflexes of affected muscles may also be reduced. Because there is much overlap in the territories supplied by individual spinal roots, symptoms and signs can be similar to a plexopathy or even focal neuropathy. Therefore, as previously discussed, EMG and NCS combined with imaging studies are extremely valuable in localization. Imaging studies are also important to assess structural etiology (e.g., HNP, osteophyte impinging on root, tumor of the nerve or extrinsic tumor/mass compression of the nerve, or inflammatory process). Further, nerve root avulsion may accompany nearly 80% of severe brachial plexopathies due to trauma.[42]



Right radial nerve

Left radial nerve

Figure 21–11. MRI (T2) forearms in a patient with multifocal motor neuropathy affecting the left radial nerve demonstrates focal enlargement and enhancement of the radial nerve (arrows) in the forearm on the left side. (Photo courtesy of Steven A. Greenberg. M.D. Reproduced with permission from Greenberg SA, Amato AA. EMG Pearls. Philadelphia: Hanley & Belfus, 2004, Fig. 2, p. 208.)



A

B

C

D

Figure 21–12. Ultrasound images depicting transection of the median nerve in the forearm. (A) Sagittal view showing the distal nerve stump (arrow), proximal stump (arrowhead), and the transection (line). Cross-sectional views at the level of the distal nerve (B), site of transection (C), and proximal nerve (D). The median nerve is seen in images (B) and (D), but it is not present in image (C) at the site of transection. (Reproduced with permission from Cartwright MS, Chloros GD, Walker FO, Wiesler ER, William W, Campbell WW. Diagnostic ultrasound for nerve transaction. Muscle Nerve 2007;796—799, Fig. 1, p. 797.)

▶ TABLE 21–4. CAUSES OF RADICULOPATHY

Herniated nucleus proposus
Degenerative joint disease
Rheumatoid arthritis
Trauma
Vertebral body compression fracture
Pott's disease
Compression by extradural mass (e.g., meningioma, metastatic tumor, hematoma, and abscess)
Primary nerve tumor (e.g., neurofibroma, schwannoma, and neurioma)
Carcinomatous meningitis
Perineurial spread of tumor (e.g., prostate cancer)
Acute inflammatory demyelinating polyradiculopathy
Chronic inflammatory demyelinating polyradiculopathy
Sarcoidosis
Amyloidoma
Diabetic radiculopathy
Infection (Lyme disease, herpes zoster, cytomegalovirus, syphilis, schistosomiasis, and strongyloides)

C5 Radiculopathy

People with a C5 radiculopathy may have weakness of shoulder abduction and external rotation, elbow flexion, and supination of the wrist along with sensory loss in the shoulder region. The biceps brachii and brachioradialis deep tendon reflexes may be asymmetrically reduced compared to the unaffected limb. Routine median and ulnar motor and sensory NCS are normal, as these do not carry any fibers emanating from the C5 spinal root. Electrodiagnostic localization is dependent on the EMG examination (Table 21–1). Abnormalities in the mid-cervical paraspinal, supraspinatus, infraspinatus, deltoid, biceps brachii, supinator, and brachioradialis muscles are seen in C5 radiculopathies. However, these muscles are also innervated by C6. The rhomboids are primarily innervated by C5, so abnormalities in this group strongly support a C5 radiculopathy. Further, if one sees membrane instability in the triceps brachii, pronator teres, extensor carpi radialis, or flexor carpi radialis that are innervated by C6 but not by C5, the above findings are more consistent with a C6 nerve root lesions or multiple root involvement.

C6 Radiculopathy

Individuals with a C6 radiculopathy can present in a similar manner to that described above with a C5 radiculopathy. However, weakness may also involve extension of the elbow (triceps), pronation, extension, and flexion of the wrist (pronator teres, extensor carpi radialis, or flexor carpi radialis). In a patient with suspected C6 radiculopathy, one needs to consider an upper trunk or lateral cord lesion, median neuropathy, or radial neuropathy. Therefore, at the very least, we usually perform median and radial SNAPs and median CMAP. In addition, we obtain lateral antebrachial cutaneous SNAPs if we are suspicious of a brachial plexopathy affecting the upper trunk. As discussed, these NCS should be normal in a C6 radiculopathy, but the flexor carpi radialis H-reflex may be abnormal. However, localization hinges on the EMG study (Table 21–1). There is significant overlapping of findings in C6 and C5 as well as C7 radiculopathies. Needle EMG may demonstrate abnormalities in the mid to low cervical paraspinals, supraspinatus, infraspinatus, deltoid, biceps brachii, triceps brachii, pronator teres, brachioradialis, supinator, extensor carpi radialis, and flexor carpi radialis muscles.

C7 Radiculopathy

People with a C7 radiculopathy often have pain or sensory symptoms radiating down the arm into the middle digit. Weakness of elbow extension and wrist and finger flexion or extension may be evident along with a diminished triceps reflex. In patients with suspected C7 radiculopathy, median CMAPs, median SNAP to the third digit, and radial SNAPs can be done to assess for a more distal lesion. But again, one should expect routine NCS to be normal in a C7 radiculopathy except for perhaps the flexor carpi radialis H-reflex. On EMG, abnormalities may be detected in the triceps brachii, anconeus, pronator teres, flexor carpi radialis, extensor digitorum communis, extensor digitorum indicis, extensor pollicis longus and brevis, and flexor pollicis longus muscles (Table 21–1).

C8/T1 Radiculopathy

It is often very difficult to distinguish a C8 from a T1 radiculopathy, so these are discussed together. Individuals who are affected have sensory disturbance affecting the medial aspect of the hand and forearm along with hand weakness. The differential diagnosis included a lower trunk plexopathy, a medial cord lesion, and an ulnar neuropathy. In cases of ulnar neuropathy, the site of the lesion may be at the wrist, elbow, or elsewhere. The NCS are very helpful in terms of localization. It is important to perform ulnar and median CMAPs and SNAPs as well as a medial antebrachial cutaneous SNAP, if one is really suspicious for a plexus lesion (Table 21–3). The SNAPs should be normal in a radiculopathy, but in a lower trunk or medial cord injury the ulnar and medial antebrachial cutaneous SNAP amplitude may be reduced. A reduction in the median CMAP amplitude with a normal median SNAP would further support a lower trunk or medial cord injury (Table 21–3). On EMG, one may see abnormalities in any of the median- or ulnar-innervated hand muscles, as these are all innervated by C8 and T1 spinal roots (Table 21–1). The thenar eminence may be predominantly innervated by T1, so the median CMAP amplitude may be disproportionately

reduced compared to the ulnar CMAP in a T1 radiculopathy. Most of the radial-innerved muscles supplying the fingers originate from the C7 and C8 spinal segments but not T1. Therefore, EMG of these muscle groups can help distinguish a C8 from a T1 radiculopathy.

Multiple Cervical Radiculopathies

Most cervical radiculopathies involve only one root, but approximately 12–30% may involve multiple levels.[38,40] The presence of EMG abnormalities suggesting a polyradiculopathy must raise the suspicion of other diseases, particularly motor neuron disease. In such cases, it is important to study the lower extremity, thoracic paraspinals, and even selected cranial nerves (e.g., the tongue and sternocleidomastoid).

THORACIC RADICULOPATHIES

For the sake of completeness, we will briefly discuss thoracic radiculopathies although these are relatively uncommon. HNPs in the thoracic region account for only 0.22–5.3% of all disc protrusions.[43–46] Approximately 75% occur between T8 and T12, with most occurring between T11 and T12. Central and centrolateral HNPs can compress the spinal cord, leading to symptoms and signs of a myelopathy. At the T11–12 region, the conus medullaris or cauda equina may be affected with ensuing bowel/bladder and lower extremity deficits. Thoracic cord compression at higher levels produces signs and symptoms consistent with a myelopathy. Patients may present circumferential chest or abdominal pain, leg pain or weakness, or bowel or bladder difficulties (e.g., constipation, urinary retention, and incontinence).

Trauma is the most common cause of a herniated thoracic disc accounting for 14–63% of cases.[47,48] Degenerative changes of the spine account for a minority of cases. Other structural causes for thoracic radiculopathies that need to be considered include compression due to metastatic disease, vertebral collapse, Pott's disease, and primary nerve tumors. Perhaps, the most common etiology of thoracic radiculopathy is diabetes mellitus (e.g., diabetic radiculoneuropathy). Additional nonstructural causes of thoracic radiculopathies include Lyme disease, herpes zoster, sarcoidosis, and carcinomatous meningitis. Of note, thoracic disk herniations on imaging are far more common than causally related clinical syndromes, and clinicians needs to be cautious before attributing non-specific clinical symptoms to an imaging abnormality.

The electrodiagnostic evaluation of thoracic radiculopathies is limited. NCS are not helpful. EMG may demonstrate abnormal insertional and spontaneous activity in the thoracic paraspinal muscles. Care must be taken not to insert the needle too far so as to avoid a pneumothorax. EMG of abdominal muscles may be of value, as one can also assess for MUAP morphology and recruitment abnormalities.

TREATMENT OF RADICULOPATHIES

Treatment is dependent on the etiology of the radiculopathy. For the sake of discussion, we will focus here on treatment of radiculopathies related to HNPs or spondylotic disease, as radiculoneuropathies related to other entities (e.g., Lyme disease, diabetes) are discussed in other chapters in this book. It is difficult to make evidence-based medical decisions regarding the best therapeutic approach to patients with cervical radiculopathies due to the lack of well-designed, prospective, controlled, and blinded trials. That said, it is important to realize that the natural history of radiculopathies related to compression from HNPs is favorable. In a large series of patients with cervical radiculopathy followed for up to 5 years, 90% were asymptomatic or had only slight pain at last follow-up; however, 26% underwent surgery.[49]

Treatment of acute radiculopathy is focused on relief of pain. Injections of corticosteroids or local anesthetic agents have been employed, but again there is no strong medical evidence that these are beneficial. Likewise, there is no proven efficacy for bed rest, traction of the neck, nonsteroidal anti-inflammatory drugs, or muscle relaxants. Commonly used medications for neuropathic pain such as antiepileptic agents or tricyclic antidepressants can be tried, as can short courses of narcotics. In patients with intractable pain or those with significant weakness, decompressive surgery may be warranted. A randomized, controlled trial of patients with cervical radiculopathy demonstrated that those who had surgery had more rapid pain relief, but functional recovery was similar to conservatively treated patients after 1 year.[50]

BRACHIAL PLEXOPATHY

Brachial plexopathies can be classified on the basis of the nature of the injury (i.e., an open or closed brachial plexopathy), the anatomic location of the lesion, or the mechanism of injury (Table 21–2).[1–3] From a clinical perspective, the way we approach patients is to first localizing the site of the lesion and then trying to identify the etiology (although in cases of trauma the cause is often obvious). Therefore, we will begin by reviewing clinical and electrodiagnostic features that one may expect to see with lesions affecting various trunks and cords of the brachial plexus.

Upper Trunk (Fig. 21–3)

Individuals with upper trunk lesions have weakness in the deltoid and biceps brachii muscles. Therefore, they

commonly complain of difficulty lifting their arms. Sensory loss involves the lateral arm and forearm down to the lateral aspect of the hand and fingers. The biceps brachii and brachioradialis reflexes are typically reduced. Injuries in isolation are relatively common when compared to lone middle or lower trunk lesions.

EMG and NCS are useful in differentiating an upper trunk lesion from a C5 or C6 radiculopathy. Remember that upper trunk lesions are distinguished from C5–6 injuries in that the posterior primary rami are spared, as are the nerve branches to the rhomboid and serratus anterior muscles. Also, trunk lesions are distal to the dorsal root ganglion. Therefore, if the nature of upper trunk injury is axonal damage and not just neuropraxia (i.e., conduction block and/or demyelination), the radial, median, and lateral antibrachial cutaneous SNAPs may have reduced amplitudes, particularly when compared to an asymptomatic contralateral arm (Table 21–3). These SNAPs would be normal in a cervical radiculopathy or in a neuropraxic or demyelinating process affecting the trunk. Routine median and ulnar CMAPs are not particularly helpful other than excluding involvement of other trunks or nerves. A musculocutaneous CMAP can be done by recording from the biceps brachii, but this is usually not useful in distinguishing a C5 or C6 radiculopathy from an upper trunk lesion. However, the EMG can be localizing in combination with the sensory studies. Recall that the posterior primary rami to the paraspinal muscles, the dorsal scapular nerve to the rhomboid, and long thoracic nerve to the serratus anterior come off the cervical roots before the formation of the upper trunk. So EMG of these muscles may show evidence of denervation in a C5 or C6 radiculopathy but would be spared if the lesion only involved the upper trunk. One should do extensive EMG to ensure that abnormalities are restricted to muscles innervated by the upper trunk, with sparing of muscles innervated by the middle and lower trunk (Table 21–3).

Middle Trunk (Fig. 3)

Isolation of middle trunk lesions is extremely rare and is most often affected in combination with other lesions in the plexus. Symptoms and signs would resemble a C7 radiculopathy. Affected people may experience weakness of elbow, wrist, and finger extension and sensory loss or pain in the posterior forearm and the dorsal and palmar aspect of the middle finger. The triceps reflex may be reduced.

Provided the injury is axonal in nature, a diminished amplitude of the median SNAP to the third digit may be evident as the cutaneous fibers that supply this finger usually traverse the middle trunk (Table 21–3). Also, the radial CMAP recorded from the extensor indicis proprius may have a reduced amplitude, if there is sufficient axon loss. However, the EMG is most important in delineating the extent of motor involvement. Remember that the middle trunk contains the C7 spinal nerves and after passing through the middle trunk these diverge and traverse the posterior and lateral cords (Table 21–1, Fig. 21–3). Thus, all the muscles innervated by the radial nerve would be affected in addition to some median-innervated forearm muscles (e.g., those muscles with C6 and C7 and lateral cord innervation). Additionally, EMG abnormalities may be appreciated in the pectoralis major, latissimus dorsi, and teres major muscles, as these muscles are, in part, innervated by the C7 spinal nerves and middle trunk via the medial and posterior cords. However, the serratus anterior muscle, which has C7 innervation in common but not the middle trunk, would be spared with a middle trunk lesion (recall the long thoracic nerve branches directly off the roots). There are no nerve branches arising directly from the middle trunk, and so it can be difficult to distinguish a lesion involving the middle trunk from those affecting portions of the lateral and posterior cords.

Lower Trunk (Fig. 21–3)

Lesions affecting the lower trunk present symptoms similar to a C8/T1 radiculopathy, medial cord, and ulnar neuropathy. Individuals who are affected often have sensory loss on the medial aspect of the forearm (more extensive than that seen with an ulnar neuropathy) and hand along with weakness of ulnar-, median-, and radial-nerve-innervated wrist/hand muscles. Involvement of radial-nerve and posterior cord innervated C8/T1 muscles puts the lesion more proximal than a medial cord.

NCS are valuable in localizing the lesion (Table 21–3). With axonal lesions, one would expect to see reduced amplitudes of ulnar and medial antebrachial cutaneous SNAPs in both lateral trunk and medial cord lesions but not in a C8 or T1 radiculopathy. A reduction in the amplitude of the median and ulnar CMAPs may be seen in a severe radiculopathy, lower trunk, or medial cord axonopathies. EMG should show signs of denervation in radial-, median-, and ulnar-innervated distal arm muscles, as the nerves supplying these muscles all course through the upper trunk (Table 21–1). However, the lower cervical paraspinal muscles should be spared in lower trunk lesions. Compared to other plexus nerve injuries, the prognosis for recovery is comparatively poor because of the long distance a regenerating nerve must cover to reinnervate the muscles in the distal arm.[1,51]

Posterior Cord (Fig. 21–3)

The nerves originating from the posterior cord include the thoracodorsal, the upper and lower subscapular, axillary, and radial nerves. Depending on where the lesion is in the cord, individuals who are affected may have weakness of shoulder abduction, shoulder extension, supination of the wrist, and elbow/wrist/finger

extension along with sensory disturbance in shoulder area, posterior upper and lower arm, and the dorsum of the hand.

Provided the lesion is axonal in nature and involves nerves emanating from the C6 spinal segment, the superficial radial SNAP amplitude may be reduced in a posterior cord lesion (Table 21–3). However, the sensory studies of the lateral antebrachial cutaneous nerves, which also course through the upper trunk but the lateral cord as opposed to the posterior cord, would be normal. A radial CMAP recording from the extensor indicis proprius would be expected to show reduced amplitude when there has been significant axonal loss involving the C7 and C8 spinal nerve fibers coursing through the posterior cord. EMG would be expected to demonstrate abnormalities of the latissimus dorsi, teres major (though difficult to study), deltoid, and the radial-innervated muscles (Table 21–1).

Lateral Cord (Fig. 21–3)

The lateral cord is the continuation of the anterior division of the upper trunk. Individuals with a lateral cord lesion may experience weakness of shoulder flexion and abduction, elbow flexion, pronation, and flexion of the wrist. In addition, sensory disturbance would involve the lateral aspect of the upper arm and forearm along with the lateral and palmar aspect of the hand and fingers. The biceps brachii reflex should be reduced.

Median SNAPs to the first three digits, superficial radial nerve to the thumb, and the lateral antebrachial cutaneous nerve should be studied to help localize pathology to the lateral cord (Table 21–3). With axonal lesions to the lateral cord, the median and lateral antebrachial SNAPs are expected to have decreased amplitude but the radial SNAP should be normal as this arises from the posterior cord. A musculocutaneous CMAP recording from the biceps brachii muscles may have a reduced amplitude. EMG can demonstrate evidence of denervation in the biceps brachii, pronator teres, flexi carpi radialis muscles, and perhaps the infraclavicular and midsternal fibers of the pectoralis major (Table 21–1). These findings coupled with normal EMG of the cervical paraspinal, supraspinatus, infraspinatus, deltoid, and triceps muscles localize the lesion distal to the upper trunk and out of the territory of the posterior cord.

Medial Cord (Fig. 21–3)

The medial cord is a continuation of the anterior division of the lower trunk. A medial cord injury clinical resembles a lower trunk lesion except that radial-nerve-innervated wrist/hand muscles would be spared. Remember that nerves to radial-innervated muscles in the forearm course through the lower trunk and then the posterior cord rather than the medial cord. Therefore, the ulnar-, median-, and radial-innervated muscles to the fingers are affected in a lower trunk lesion; only the ulnar- and median-innervated muscles will be abnormal with medial cord damage.

The medial antebrachial cutaneous and ulnar SNAPs may be reduced in amplitude provided that there is axonal injury but does not help distinguish a medial cord from a lower trunk lesion (Table 21–3). Similarly, decreased amplitudes of median and ulnar CMAPs to the thenar and hypothenar muscles are seen in injuries to both locations. One way to try to differentiate a medial cord from a lower trunk lesion would be by assessing the radial CMAP recorded from the extensor indicis proprius muscles. EMG is more helpful in distinguishing between a lower trunk and a medial cord injury. Again, if EMG demonstrates signs of denervation in radial- as well as median- and ulnar-innervated musculature, then a lower trunk as opposed to medial cord injury should be considered (Table 21–1).

SPECIFIC BRACHIAL PLEXUS DISORDERS

In the following section, we will go into more detail about the common types of brachial plexopathy.

Immune-Mediated Brachial Plexus Neuropathy

Immune-mediated brachial plexus neuropathy (IBPN) goes by various terminologies including acute brachial plexitis, neuralgic amyotrophy, and Parsonage–Turner syndrome.[2,3,52–56] IBPN usually presents with an acute onset of severe pain in the shoulder region often described like a hot poker jammed into the upper arm. Sometimes the pain involves the forearm or may be restricted to this segment of the arm (as often seen in individuals with anterior interosseus syndrome as a forme fruste of IBPN). The pain is often exacerbated by movement of the arm. The intense pain usually lasts several days to a few weeks, but a dull ache can persist for 3 years or more.[56] Individuals who are affected may not appreciate weakness of the arm early in the course because the pain limits movement. However, as the pain dissipates, weakness and often sensory loss are appreciated. Attacks can occasionally recur.[56]

Clinical findings are dependent on the distribution of involvement (e.g., specific trunk, divisions, cords, or terminal nerves). Occasional mild abnormalities of the cerebrospinal fluid (increased protein or pleocytosis) is found indicative of presumed inflammatory process also extending to the roots.[54] One large study suggested that 36% of patients recovered most functions within the first year, 75% by the second year's end, and 89% by the end of the third year.[54] However, another recent large

study of 246 cases found that approximately two-thirds of patients still had persistent pain and weakness after 3 years and <8% had a full recovery according to the patients.[56] Mild paresis was still evident in 69%, with severe weakness in 3%.

The most common pattern of IBPN involves the upper trunk or a single or multiple mononeuropathies primarily involving the suprascapular, long thoracic, or axillary nerves.[1,55–59] Additionally, the phrenic [60,61] and anterior interosseous [56,62–64] nerves may be concomitantly affected. Any of these nerves may also be affected in isolation as a forme fruste of IBPN. In most IBPNs, the paraspinal muscles are not abnormal on EMG, suggesting that the lesion is distal to the root/spinal nerve level, but occasionally signs of active denervation are apparent, suggesting root involvement. Rarely, multiple cranial nerves (IX, X, XI, and XII) can be involved.[65] In this regard, an isolated spinal accessory neuropathy presenting as acute unilateral suboccipital and neck pain and weakness of the trapezius muscle may also represent a forme fruste of IBPN.[66]

The pathogenic basis of IBPN is unknown but presumed to be immunologic. Circumstantial evidence of an inflammatory basis is that IBPN may develop following an infection and vaccination and when the immune system has been modified as after bone transplantation and with treatment with immune-modulating agents (e.g., interferons, interleukin-2, and tumor necrosis-alpha blockers).[54,67–71] In addition, some series have reported antibodies directed against peripheral nerve myelin and soluble terminal complement complexes.[72] Biopsies of the brachial plexus are not typically performed for IBPN, but there are few descriptions of such biopsies revealing perivascular epineurial and endoneurial inflammatory cell infiltrates. The antigen(s) of which the autoimmune attack is directed is not known but the electrodiagnostic abnormalities suggest a primary insult against the axons of the nerves as opposed to the myelin.

The electrodiagnostic findings are dependent on the site(s) of involvement. Nerve damage can be rather multifocal and usually associated with axonal damage.[1–3,52,57,] The upper trunk is primarily involved in most patients. Thus, it is not surprising that median and ulnar motors studies are abnormal in only about 15% of patients with IBPN.[57] Median and radial SNAPs are more likely to be abnormal. Also, when CMAPs are recorded from the deltoid, biceps, and serratus anterior muscles and SNAPs of the lateral and antebrachial cutaneous and median sensory nerves are performed, about 50% of patients demonstrate abnormalities. Other laboratory abnormalities include slightly increased cerebrospinal fluid protein with or without mild pleocytosis in a little over 10% of patients.[54,56] MRI scan of the plexus may demonstrate increased T2 signal suggestive of inflammation or edema.[28,29,56]

We often treat patients presenting acutely who continue to have severe pain with a short course of corticosteroids (e.g., prednisone 50 mg daily tapering by 10 mg every 4–5 days), although there are very few evidence-based studies that have demonstrated any efficacy. However, in our anecdotal experience, corticosteroids seem to help alleviate the pain, which can be useful in allowing the patient to proceed with physical therapy. If the pain has already resolved by the time we see them, we do not treat with corticosteroids. The mainstay of treatment is physical and occupational therapy to prevent contractures in an immobilized arm, improve function, and maintain strength in unaffected muscles.

Other Immune-Mediated Neuropathies

Rarely, a painless brachial plexopathy may be the sole manifestation of an asymmetric form of chronic inflammatory demyelinating neuropathy or multifocal acquired motor and sensory demyelinating neuropathy.[73] In addition, it is possible that multifocal motor neuropathy may likewise present with the conduction block or demyelinating lesion affecting a trunk or cord within the brachial plexus. Diagnosis of either of these entities requires demonstration of conduction block or focal slowing localized to the brachial plexus, which is often technically difficult. The importance of identifying multifocal acquired motor and sensory demyelinating neuropathy or multifocal motor neuropathy is that these disorders require immunotherapy. See Chapter 12 on "Chronic Inflammatory Demyelinating Polyneuropathy and Related Disorders" for more details.

Obstetrically Related Plexopathies

The annual incidence of obstetrically related plexus injuries ranges between 0.38 and 2.0 per 1000 live births.[1–3,74–80] Three types of brachial plexus injury complicate childbirth: (1) diffuse plexopathy, (2) upper trunk plexopathy (Erb palsy), or (3) lower trunk plexopathy (Klumpke paralysis). The plexus can be damaged during childbirth due to traction on the arm and thereby the nerves. Increased risk is associated with heavy birth weight of the infant, mothers with short stature, breech presentation, long and difficult labor, and heavily sedated mothers (resulting in diminished muscle tone during delivery).[1,75,76,81–83] In addition, forceful downward traction applied to the head after the fetal third rotation is a risk factor of obstetric brachial plexus palsy in vaginal deliveries in cephalic presentation.[84]

Erb palsy, the most common type of obstetric paralysis, results from stretch of the nerves of the upper trunk of the brachial plexus.[18,75,77] Severe traction injury may also lead to avulsion of the C5 or C6 spinal nerves. Traction of the upper trunk can occur with shoulder dystocia in a vertex presentation or difficulty delivering

the aftercoming head in a breech presentation. Upper trunk lesion leads to weakness of the supraspinatus, infraspinatus, deltoid, biceps brachii, teres minor, brachioradialis, extensor carpi radialis longus/brevis, and supinator muscles. An infant who is affected typically lie with their arm adducted and internally rotated (unopposed pull of the sternal portion of the pectoralis major and latissimus dorsi muscles), elbow extended and forearm pronated (unopposed triceps and pronator teres/quadratus muscles), and wrist/fingers flexed (weak wrist extensors—the so-called "waiter's tip position").[1] Diaphragmatic or serratus anterior weakness suggests the possibility of root avulsion, as the nerves to these muscles derive proximal to the upper trunk.

Rarely, the lower trunk or C8 or T1 roots are injured during childbirth (Klumpke paralysis).[79] These usually occur in the setting of face presentation and hyperextension of the neck but can also complicate breech deliveries with hyperabduction of the arm. Infants will have good proximal arms strength, but weakness of hand muscles is evident. Finally, the entire plexus can also be affected to varying degrees.[85,86]

Radiological imaging is essential to assess for the possibility of associated humeral or clavicular fractures as well as diaphragmatic paralysis. In addition, MRI should be done to assess for nerve root avulsion.[2,87,88]

Electrodiagnostic studies are useful to determine the site and severity of injury and prognosis and to decide about the appropriateness and timing of any operative intervention.[1,2,75,76,81] Abnormalities in SNAPs and CMAPs may be evident in 7–10 days. Electrodiagnostic studies are typically performed 4–6 weeks following delivery, as it can take this long for active signs of denervation to be evident on EMG. However, detection of voluntary MUAPs at any time even before the 4–6-week period demonstrates that there is at least partial continuity between the anterior horn cells and the target muscle, if not clinically evident. Prognosis is better if the nerve is not completely severed. If SNAPs or CMAPs are low or absent and there is initially no MUAP on EMG, serial studies can be performed every 6–8 weeks to assess for evidence of reinnervation.

The natural history is not well defined, but patients with upper trunk lesions often have significant improvement within 3 months, but those with lower trunk lesions are more likely to have a more prolonged course and incomplete recovery. Unfortunately, there is no chance for regeneration of the nerves following a root avulsion. Reconstructive surgical procedures may be employed in order to help restore elbow flexion and shoulder abduction in patients with severe axonal injury.[61,89–91]

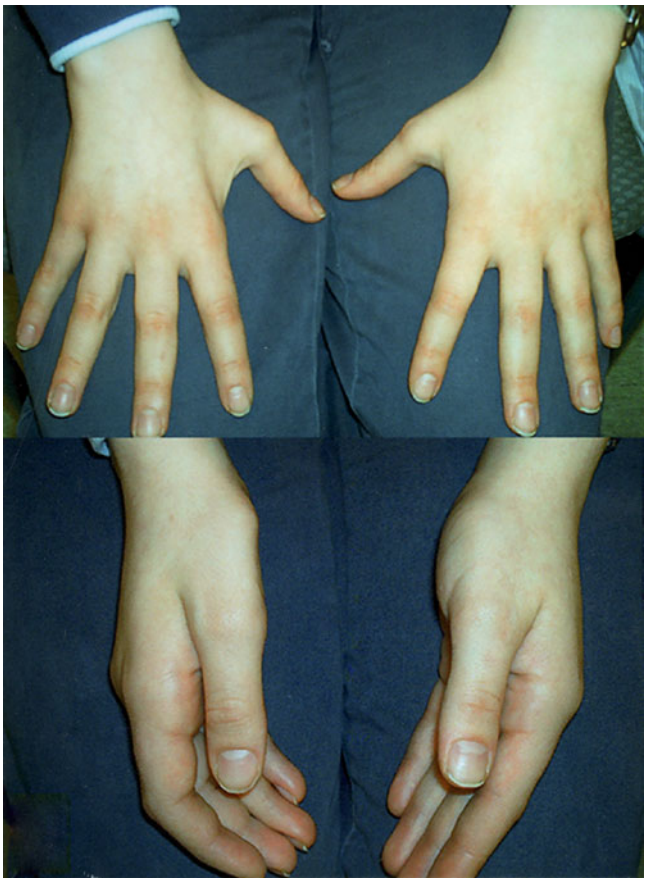
Neurogenic Thoracic Outlet Syndrome

The term "thoracic outlet syndrome" has been ascribed to a group of disorders attributed to compromise of blood vessels or nerves at any of several points between the base of the neck and the axilla.[1–3] Our discussion is here limited to the rare neurogenic form of thoracic outlet syndrome, which, in essence, is a lower trunk plexopathy. Most individuals who are affected are women with a prominent C7 transverse process or true cervical rib that can be appreciated on plain films of the cervical spine (Fig. 21–13). These cases are often associated with a sharp fibrous band extending from the tip of the elongated C7 transverse process or cervical rib to the first thoracic rib. This band usually cannot be visualized on imaging studies, including MRI scans. The proximal aspect of the lower trunk becomes angulated or stretched as it passes over this fibrous band. Because the T1 fibers lie below the C8 fibers, these are usually distorted and thus are more likely to be damaged. Thus, individuals who are affected present with muscle atrophy and weakness that is often greater in the thenar muscles, which have more T1 innervation than the hypothenar muscles, which have more C8 innervation. In addition, patients complain of numbness, paresthesia, and pain along the medial aspects of the arm, forearm, and hand. Electrodiagnostic studies demonstrate that the median CMAP and medial antebrachial cutaneous SNAP amplitudes are reduced to a greater extent than the ulnar SNAP and CMAP because the former studies assess (i.e., studies that primarily assess T1 fibers while ulnar studies that primarily assess C8 fibers. [2,59,92–95] Neurogenic thoracic outlet syndrome is typically treated by surgical resection of the taut band.

Plexopathies Associated with Neoplasms

Neoplasms involving the brachial plexus may be primary nerve tumors, local cancers expanding into the plexus (e.g., Pancoast lung tumor or lymphoma), and metastatic tumors.[96,97] Primary brachial plexus tumors are less common than the secondary tumors and include schwannomas, neurinomas, and neurofibromas.[25,43,98–100] These primary tumors may present as mass lesions in the supraclavicular fossa region or axilla. Pain and paresthesias are early symptoms, while motor and sensory losses occur later as the tumor may initially distort the nerve fibers but do not result in conduction block, demyelination, or axon loss right away.

Schwannomas are commonly benign and well encapsulated, affect the proximal segments of the plexus, and may be surgically removed with minimal damage to the nearby nerve fibers.[98,100,101] However, malignant schwannomas do rarely occur.[102] Neurofibromas are the most common form of peripheral nerve tumor and are typically benign. However, when seen in the context of neurofibromatosis, these are often multiple and affect a larger portion of the brachial plexus.[98] Additionally, neurofibromas interdigitate more with nerve fibers within the nerve fascicle and are more commonly associated with neurological deficits than schwannomas. Further, it



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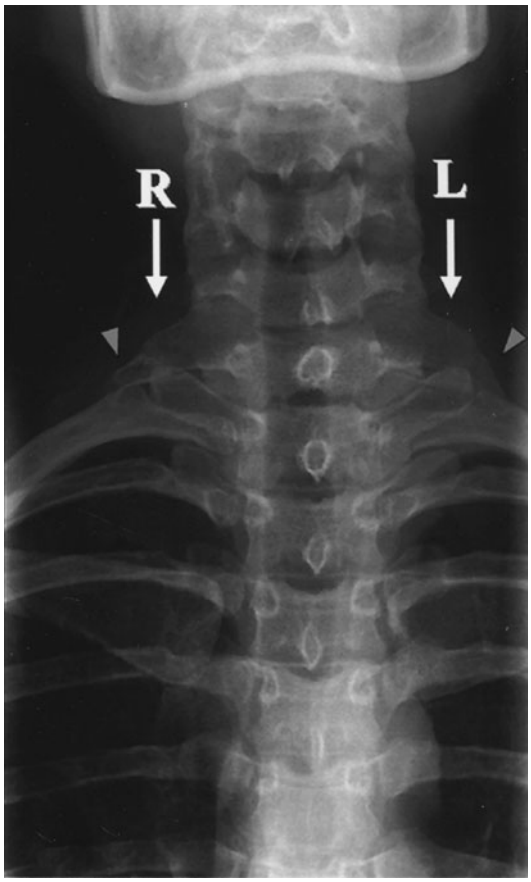

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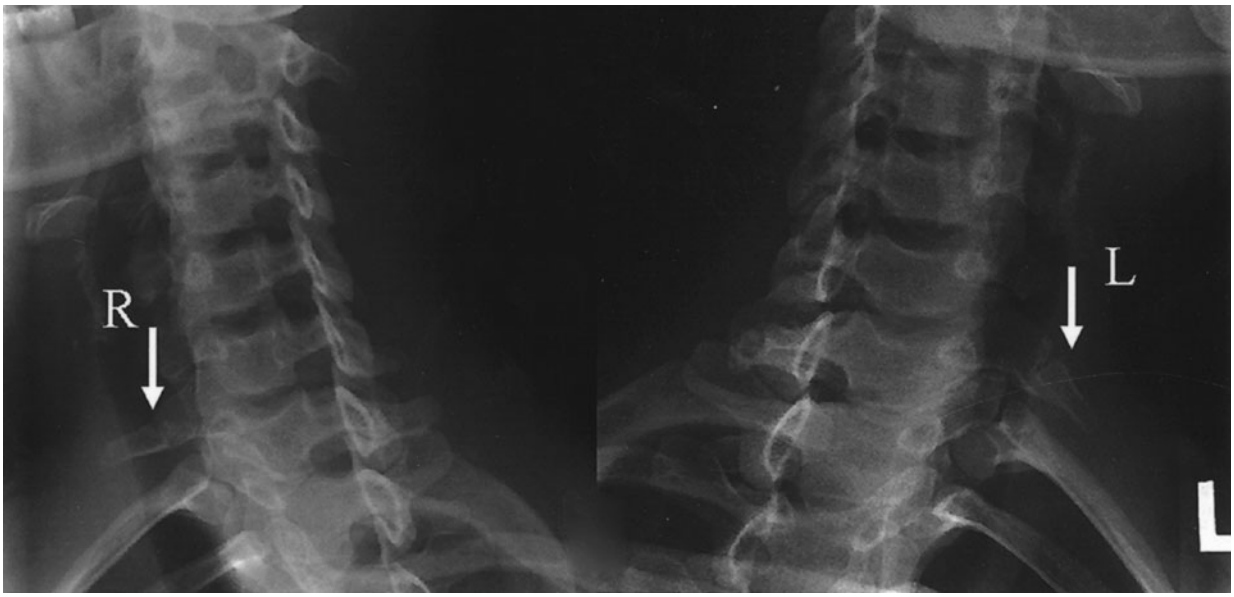

C

Figure 21–13. Neurogenic thoracic outlet syndrome. Atrophy of the right thenar eminence and first dorsal interosseus muscles are evident (A). Plain cervical spine films demonstrate small cervical ribs (arrows) bilaterally on AP (B) view and oblique view (C). (Photo courtesy of Steven A. Greenberg. M.D. Reproduced with permission from Greenberg SA, Amato AA. EMG Pearls. Philadelphia: Hanley & Belfus, 2004, Fig. 1A and B, p. 46 and Fig. 3, p. 50.)

is difficult to remove these surgically without damaging the affected nerve. These tumors can also convert to a more malignant form, particularly in neurofibromatosis.

Secondary tumors affecting of the brachial plexus are more common and are always malignant. These may arise from local tumors expanding into the plexus. For example, a Pancoast tumor of the upper lobe of the lung may invade or compress the lower trunk, while a primary lymphoma arising from the cervical or axillary lymph nodes may also infiltrate the plexus).[96,97] Pancoast tumors typically present as an insidious onset of pain in the upper arm, sensory disturbance in the medial aspect of the forearm and hand, and weakness and atrophy of the intrinsic hand muscles along with an ipsilateral Horner syndrome. Chest CT scans or MRI can demonstrate extension of the tumor into the plexus. Metastatic involvement of the brachial plexus may occur with spread of breast cancer into the axillary lymph nodes with local spread into the nearby nerves. Pain is usually the presenting manifestation due to spread of the cancer into the plexus and is accompanied by widespread paresthesias. Weakness and sensory loss conform to the distribution of the affected nerves. Likewise, electrodiagnostic abnormalities are dependent on the nerves that are involved as previously discussed.[14,21]

Recurrent Neoplastic Disease or Radiation

The treatment for various malignancies (e.g., lung, breast, and lymphoma) is often radiation therapy, the field of which may include parts of the brachial plexus. It can be difficult in such situations to determine if a new brachial plexopathy is related to tumor within the plexus or from radiation-induced nerve damage. Radiation can be associated with microvascular abnormalities and fibrosis of surrounding tissues, which can damage the axons and the Schwann cells.[1,103] Radiation-induced plexopathy can develop months or years following therapy and is dose dependent.[7,97,104]

Tumor invasion is usually painful and more commonly affects the lower trunk, while radiation injury is often painless and affects the upper trunk.[97] Imaging studies such as MRI and CT scans are useful but can be misleading with small microscopic invasion of the plexus. EMG can be informative if myokymic discharges are appreciated, as this finding strongly suggests radiation-induced damage.[105,106] However, absence of myokymic discharges does not rule out radiation as the cause of the plexopathy.

Backpack or Rucksack Palsy

This condition refers to paresis of the arms occurring in soldiers or civilians wearing heavy backpacks or rucksacks strapped around the shoulders.[1,2,3,107,108] Motor and sensory losses most typically are in the distribution of the upper trunk but can be more widespread. The injury is usually neuropraxic in nature, although secondary axonal degeneration may occur. If one sees electrophysiological features of generalized demyelination, particularly in sites of common compression (e.g., at the carpal tunnel, across the elbow, and across the fibular head) then hereditary neuropathy with liability to pressure palsy needs to be considered.

Perioperative Plexopathies (Median Sternotomy)

The most common surgical procedures associated with brachial plexopathy as a complication are those that involve median sternotomies (e.g., open heart surgeries and thoracotomies). Brachial plexopathies occur in as many as 5.0% of patients following a median sternotomy and typically affects the lower trunk.[1–3,109–111] Thus, individuals manifest with sensory disturbance affecting the medial aspect of forearm and hand along with weakness of the intrinsic hand muscles, as discussed previously. Because of the location of the sensory symptoms, these lesions are often incorrectly blamed on ulnar neuropathies resulting from poor intraoperative elbow positioning or padding. The mechanism of this plexopathy is felt to be related to the stretch of the lower trunk. These injuries are usually neuropraxic in nature, so most individuals who are affected recover in a few months.[110,112] However, some patients with more severe damage may have a longer recovery, and it may not be complete. Neurophysiological features are those previously discussed for lower trunk lesions.

Burners/Stingers

Burners and stingers refer to brachial plexus injuries caused by impact to shoulder region usually in the course of contact sports (e.g., football).[1,2] Usually, the affected athlete notes severe pain and sensory disturbance in the arms without any motor loss. The symptoms typically resolve after a few minutes. The mechanism is unclear, but the rapid recovery in most cases suggests a neuropraxic injury to the cervical roots or plexus, particularly the upper trunk.

Hereditary Neuropathies Manifesting as Brachial Plexopathy

Hereditary neuralgic amyotrophy (HNA) is an autosomal-dominant disorder characterized by recurrent attacks of pain, weakness, and sensory loss in the distribution of the brachial plexus often beginning in childhood.[56,113] The clinical and electrophysiological features of HNA resemble those of IBPN. HNA should be considered in patients with recurrent attacks of brachial plexitis even though the nonhereditary, idiopathic cases can recur.[56] In addition, hereditary neuropathy with liability to pressure palsies can present as painless brachial plexopathy. This may be one etiology of backpack palsy that was discussed in a previous section. In

contrast to HNA, hereditary neuropathy with liability to pressure palsy (HNPP) is a generalized or multifocal process, which is demyelinating in nature. HNA can be caused by mutations in the gene septin 9 (SEPT9), while HNPP is usually caused by deletions in chromosome 17p11.2, resulting in a loss of function of peripheral myelin protein 22 (PMP-22). See Chapter 9 regarding "Charcot–Marie–Tooth Disease and Related Disorders" for more details.

SURGICAL TREATMENT OF BRACHIAL PLEXOPATHIES

The treatment of traumatic brachial plexopathies and timing of any surgical intervention are dependent on the type and severity of the injury, the location, and the time frame.[91] Most closed injuries result in neuropraxic or axonotmesis that may recover spontaneously. As a result, they are initially treated conservatively with physical and occupational therapy. Patients are followed closely with serial clinical and electrodiagnostic assessments to assess for recovery. If patients show no signs of recovery after 2–3 months in upper trunk lesions or 4–5 months for middle or lower trunk lesions, surgical intervention should be considered.[91] Injuries associated with high-energy trauma or those associated with near-total paralysis may be observed for a shorter period of time (3 weeks to 3 months) prior to surgery.[114] Injuries associated with sharp penetrating trauma are more likely associated with severing of nerves and should be repaired within 72 hours, if possible.[17,90,98,115] Worsening neurological function, hematoma formation, concomitant bone or vascular injuries, and compartment syndrome are other indications for more acute surgical intervention.[91] Various surgical techniques including neurolysis, nerve grafting, neurotization, and free muscle transfer are performed in order to assist in regaining shoulder abduction and elbow flexion and some use of the hand function.[114,116–118]

▶ TERMINAL NERVE LESIONS

In this section, we discuss mononeuropathies of the upper limb mainly due to trauma, compression, or entrapment, or those that are idiopathic in nature. Any of these nerves may be affected alone or in combination with other nerve lesions in other settings such as vasculitis (isolated or systemic), infection (e.g., Lyme disease, leprosy, HIV, cytomegalovirus, and hepatitis), immune-mediated demyelination (e.g., multifocal motor neuropathy and multifocal acquired demyelinating motor and sensory neuropathy), and other inflammatory neuropathies (e.g., perineuritis and sarcoidosis), as discussed in other chapters in this book.

SPINAL ACCESSORY

As discussed previously, the spinal accessory nerve does not arise from the brachial plexus. Since it is often damaged with trauma to the neck and shoulder region with or without brachial plexus involvement, we discuss spinal accessory neuropathy in this chapter. Lymph node biopsy and other surgical procedures in the posterior triangle are very common etiologies for spinal accessory neuropathies. The nerve can also be involved in IBPN. Injury of the nerve results in drop of the ipsilateral shoulder and lateral winging of the scapula (Fig. 21–14). Winging from a spinal accessory nerve lesion is accentuated by shoulder abduction to

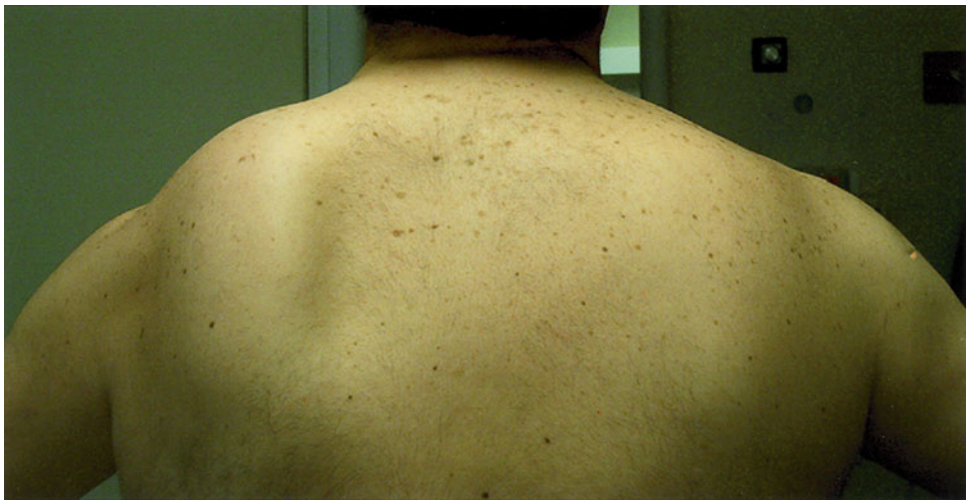

Figure 21–14. Spinal accessory neuropathy. Winging of the left scapula is appreciated and is brought out by abduction of the shoulder. (Photo courtesy of Steven A. Greenberg. M.D. Reproduced with permission from Greenberg SA, Amato AA. EMG Pearls. Philadelphia: Hanley & Belfus, 2004, Fig. 1A, p. 37.)

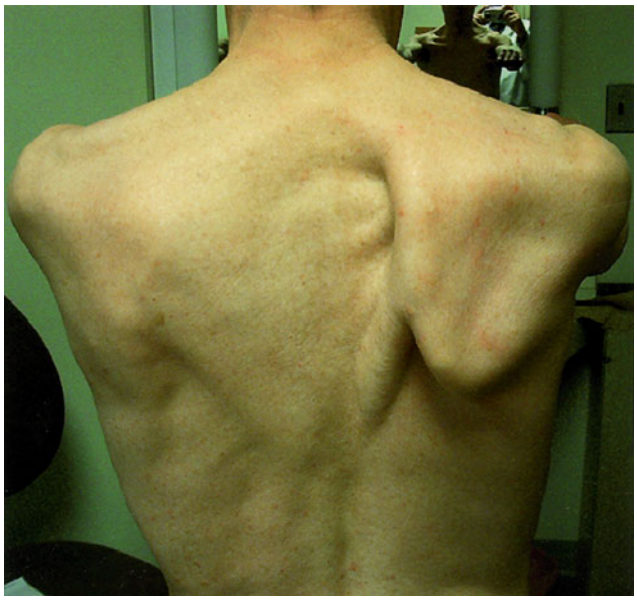

Figure 21–15. Long thoracic neuropathy. Winging of the right scapula is appreciated and is enhanced by having the patient flex the arm forward at the shoulder. There is also atrophy of the infraspinatus secondary to a superimposed suprascapular nerve injury. (Photo courtesy of Steven A. Greenberg. M.D. Reproduced with permission from Greenberg SA, Amato AA. EMG Pearls. Philadelphia: Hanley & Belfus, 2004, Fig. 2, p. 42.)

90°. Most lesions are distal to the innervation of the sternocleidomastoid muscles; however, proximal damage may result in weakness of turning the head to the contralateral side. CMAPs recorded from the trapezius muscle may demonstrate reduced amplitude compared to the contralateral side, but electrodiagnosis usually relies on demonstrating denervation changes in this muscle.

DORSAL SCAPULAR NERVE

The dorsal scapular arises mainly from C5 spinal root but may have contributions from the C4 segment (Fig. 21–15). The nerve innervates the rhomboid major and minor along with the levator scapula, which assist in retraction, elevation, and medial inferior angle rotation of the scapula. Therefore, damage to the dorsal scapular nerve leads to scapular winging, with the inferior angle rotated laterally. Elevation of the arm overhead will accentuate the scapular winging. It is very unusual to have an isolated dorsal scapular nerve injury. NCS are not particularly helpful. Electrodiagnostic confirmation requires demonstration of EMG abnormalizes isolated to the rhomboid and levator scapula muscles.

LONG THORACIC NERVE

The long thoracic nerve originates from the fusion of branches from the C5, C6, and often C7 spinal roots,

▶ TABLE 21–5. CONDITIONS ASSOCIATED WITH PROXIMAL LONG THORACIC NEUROPATHY

Trauma
Surgical injury (post-thoracotomy, radical mastectomy, axillary surgery, and rib resection)
Immune-mediated brachial plexus neuropathy

and it innervates the serratus anterior muscle (Fig. 21–3). This muscle stabilizes the scapula and helps hold it tight against the posterior thoracic trunk during movement of the shoulder girdle. A long thoracic neuropathy manifests as scapular winging with the scapula as a whole and the inferior angle rotated medially (Fig. 21–15). This winging is accentuated by having the patient flex the arm forward at the shoulder.

The long thoracic nerve may be damaged from trauma [119–121] or during surgical procedures, particularly mastectomies and thoracotomies (Table 21–5).[122,123] Most often, we see long thoracic neuropathies either isolated or in combination with other neuropathies in the setting of IBPN.[54] Motor NCS of the long thoracic nerve is not typically performed, and electrodiagnostic confirmation of a long thoracic neuropathy requires demonstration of EMG abnormalities isolated to the serratus anterior muscle. Needle EMG of this muscle should be done cautiously due to risk of pneumothorax.

Long thoracic neuropathies are usually managed conservatively depending on etiology. Open injuries due to trauma may require surgery. Otherwise, in most instances we start with physical and occupational therapy along with bracing. Braces can be used to help keep the shoulder abutted against the thorax. If the shoulder function does not improve over time, surgery can be considered to stabilize the scapula.[124,125]

SUPRASCAPULAR NERVE

The suprascapular nerve arises from the upper trunk and innervates the supraspinatus and infraspinatus muscles (Fig. 21–5). The supraspinatus muscle assists in shoulder abduction, while the infraspinatus muscle is used to externally rotate the arm at the shoulder. Thus, these movements are limited, depending on the location of the suprascapular nerve injury.

The nerve may be damaged with trauma to the shoulder region, particularly if there is a dislocation or fracture of the shoulder.[126–130] The branch to the infraspinatus muscle might rarely become compressed within the spinoglenoid notch.[131,132] More commonly, this suprascapular nerve is affected in the setting of IBPN and involvement may be isolated to this nerve.[54,55]

Motor conduction studies to this nerve are technically limiting, so electrodiagnosis relies on EMG demonstration of denervation changes in the supraspinatus and

infraspinatus muscle if the lesion is proximal to the suprascapular notch or limited to the infraspinatus muscle if the lesion occurs in the region of the spinoglenoid.

Management is dependent on the etiology of the neuropathy. Surgery is warranted for open lesions related to trauma, otherwise conservative therapy with pain control is recommended. Local injections of corticosteroids can be tried if the cause is felt to be related to compression of the nerve in the suprascapular or supraglenoid notch, and some even advocate surgery; however, entrapment of the nerves at this site remains a controversial etiology.[133,134]

MEDIAL/LATERAL PECTORAL NERVES

The medial and lateral pectoral nerves are discussed together as both innervate the pectoralis minor and major muscles (Fig. 21–3). The large pectoralis major muscle assists in medial rotation, anterior flexion, and adduction of the upper arm, while the pectoralis minor assists in scapula stabilization during shoulder extension. These nerves may be damaged during surgical procedures in the anterior chest and axillary region. Again, motor conduction studies of these nerves are not routinely performed and electrodiagnostic confirmation requires demonstration of EMG abnormalities in the pectoralis minor and major muscles.

SUBSCAPULAR NERVES

Injuries to the subscapular nerves have not been described in detail and rarely occur in isolation but may be involved in more generalized plexopathy. As the lower subscapular nerve innervates the teres major muscle, damage to this nerve may result in weakness of internal rotation and adduction of the upper arm. There are no motor NCS for this nerve, and needle EMG of the muscle is difficult given its deep location.

THORACODORSAL NERVE

The thoracodorsal nerve arises form the posterior cord and innervates the latissimus dorsi muscle (Fig. 21–3). Weakness of this muscle results in impaired ability to adduct, medially rotate, and extend the upper arm. Slight winging of the inferior margin of the scapula may be observed when the patient is asked to place the dorsum of the hand of the affected arm on the buttock.[10,122]

The nerve is usually affected in association with posterior cord or more proximal brachial plexus injuries. NCS are not routinely done on this nerve, but EMG of the latissimus dorsi muscle is easy to perform and helps in localizing the lesion to C5–7 nerve fibers at or proximal to the posterior cord.

TABLE 21–6. CONDITIONS ASSOCIATED WITH MUSCULOCUTANEOUS NEUROPATHY

Trauma (fracture or dislocation of shoulder, fracture of humerus, missile injuries, stab wounds, and blunt force injuries)
Injection injury
Immune-mediated brachial plexus neuropathy
Soft-tissue or peripheral nerve tumor
Ischemia (e.g., vasculitis)
Multifocal motor neuropathy or multifocal acquired demyelinating motor and sensory neuropathy
Compression within hypertrophied biceps brachii muscle after vigorous exercise
Compression by sharp free margin of biceps aponeurosis

MUSCULOCUTANEOUS NERVE

The musculocutaneous nerve represents a continuation of the lateral cord and innervates the coracobrachialis, biceps brachii, and to some extent the brachialis (Fig. 21–6). After innervating these muscles, it terminates as the lateral antebrachial cutaneous nerve to supply sensation to the lateral aspect of the forearm from the elbow to the wrist. Damage to the musculocutaneous nerve may therefore result in sensory loss in this distribution and weakness of elbow flexion accompanied by reduced deep tendon reflex of the biceps brachii. The musculocutaneous nerve may be damaged by anterior dislocations of the shoulder and prolonged hyperextension of the arm, secondary to weight lifting (perhaps compressed within hypertrophic muscle) (Table 21–6).[8,122,135–137] It is also often affected in IBPN.[54]

The lateral antebrachial cutaneous SNAP is easy to obtain and would be expected to be reduced in axonal lesions affecting the musculocutaneous nerve (Table 21–3). This is nonlocalizing in and of itself as the SNAP could also be reduced with lateral cord or upper trunk lesions; however, it would be normal in C6 radiculopathy. A musculocutaneous CMAP can be obtained by stimulating the brachial plexus in the supraclavicular fossa and recording from the biceps brachii. The study should be compared to the contralateral side in order to assess the degree of possible axon loss or conduction block. EMG may show denervation abnormalities in the coracobrachialis, biceps brachii, and brachialis muscles (Table 21–1). Again abnormalities in the supraspinatus, deltoid, biceps brachii, and pronator teres muscles but not in serratus anterior, rhomboids, or paraspinal regions would imply an upper trunk injury, while denervation changes in the latter three regions would suggest a radiculopathy. On the other hand, only finding abnormalities in the biceps brachii and pronator teres is more consistent with a lateral cord injury.

Initial management depends on the etiology of the neuropathy. Those caused by severe trauma may require

TABLE 21–7. CONDITIONS ASSOCIATED WITH AXILLARY NEUROPATHY

Trauma (e.g., fracture or dislocation of shoulder, fracture of humerus, missile injuries, stab wounds, and blunt force injuries)
Stretch injury (e.g., hyperabduction during sleep and surgery)
Injection injury
Immune-mediated brachial plexus neuropathy
Soft-tissue or peripheral nerve tumor
Ischemia (e.g., vasculitis)
Multifocal motor neuropathy or multifocal acquired demyelinating motor and sensory neuropathy

surgical treatment. However, in most cases a conservative approach is warranted.

AXILLARY NERVE

The axillary nerve originates from the posterior cord and innervates the teres minor and deltoid muscle (Fig. 21–7). In addition, the lateral cutaneous nerve of the upper arm arises from the axillary nerve. Thus, axillary neuropathies may manifest with weakness of abduction of the upper arm and sensory loss in the region of skin overlying the deltoid muscle.

Axillary neuropathies may occur in the setting of IBPN, trauma to the shoulder or fractures of the upper humerus, or stretch injury (Table 21–7).[8,9,105,122,138,139] Axillary CMAPs may be recorded from the deltoid muscle following supraclavicular stimulation of the brachial plexus to see if there is asymmetrical loss of amplitude on the affected site. A superficial radial SNAP would be expected to be normal in an axillary neuropathy and can help distinguish an axillary neuropathy from a posterior cord lesion or upper trunk lesion (Table 21–3). Further, EMG should show evidence of denervation in the deltoid muscle with sparing of radial-innervated muscles in an isolated axillary neuropathy (Table 21–1). In addition, a normal EMG of the supraspinatus, infraspinatus, biceps brachii, pronator teres, and brachioradialis suggests that the lesion is distal to the C5/C6 roots or upper trunk when combined with denervation of the deltoid.

Axillary neuropathies related to penetrating injuries should be surgically explored. Otherwise, these are managed conservatively with pain management and PT/OT. If there is no improvement within 6 months, surgical treatment and grafting can be considered.[140]

RADIAL NERVE

The radial nerve is one of the major terminations of the posterior cord and is comprised of fibers from spinal segments C5–8 and occasionally contains T1 fibers (Fig. 21–8). The radial nerve is quite long and provides innervation to upper arm and forearm muscles as well as for cutaneous sensation of large aspects of the arm. The clinical and electrodiagnostic features of a radial neuropathy depend on the site of the lesion. The superficial radial SNAP should be abnormal, if there is significant axonal nerve injury, except with posterior interosseous nerve damage, as this is a purely motor nerve. Radial CMAP to the radial-innervated muscles such as the extensor indices proprius should be performed with stimulation below and above the spinal groove to assess for focal conduction block or slowing across this site. With significant axonal injury the amplitude should be reduced. EMG is more helpful in localizing the site and nature of the lesion. Evidence of active denervation in the form of fibrillation potentials and positive sharp waves would be expected in an axonal nerve injury, provided there has been substantial time for Wallerian degeneration to occur. In a neuropraxic injury, only reduced recruitment of MUAPs would be appreciated on EMG.

Proximal Radial Neuropathy

Damage to the nerve in the axilla or proximal upper arm is uncommon but can result from compression (e.g., crutches, patients who are intoxicated falling asleep with outstretched arm and upper arm pressed against a hard surface, missile injuries, and other trauma to the axilla) (Table 21–8).[8,9,122] Of course, a radial neuropathy can also occur in the setting of a more widespread multifocal process (e.g., vasculitis, IBPN). Proximal radial nerve injuries can result in weakness of elbow, wrist, and finger extension as well as supination of the forearm. In addition, sensory disturbance may be evident in the posterior aspect of the forearm and back of the hand and fingers. Provided there is sufficient axon loss, the superficial radial SNAP and radial CMAP recorded from the extensor indicis proprius may have reduced amplitudes (Table 21–3). EMG should demonstrate signs of

TABLE 21–8. CONDITIONS ASSOCIATED WITH PROXIMAL RADIAL NEUROPATHY

Trauma
Fracture of humerus
Improper use of crutches (e.g., compression in axilla)
Stretch injury (e.g., hyperabduction of arm during surgery and sleep)
Saturday night palsy (external compression by arm being compressed against firm edge at the spiral groove—usually in individuals who are intoxicated)
Other external compression (partner falling asleep on arm)
Immune-mediated brachial plexus neuropathy
Soft-tissue or peripheral nerve tumor
Ischemia (e.g., A-V fistulas and vasculitis)
Multifocal motor neuropathy or multifocal acquired demyelinating motor and sensory neuropathy

denervation in the triceps as well as more distal radial-innervated forearm muscles (Table 21–1).

Radial neuropathy in the upper arm distal to the branches innervating the triceps arises from various mechanisms. One of the most common radial neuropathies is the so-called "Saturday night palsy" and is usually the result of prolonged compression of the radial nerve in the spiral groove in an individual who is intoxicated. Proximal radial nerve lesions have also been speculated to be the result of anomalous muscle compression or damage secondary to triceps muscle contraction.[141,142] On clinical examination, one would expect to find weakness of the radial-innervated muscles distal to the triceps in addition to sensory loss in the posterior aspect of the forearm and back of the hand and fingers. Again, a superficial radial SNAP and a radial CMAP may have reduced amplitudes. EMG should demonstrate signs of denervation of radial-innervated forearm muscles but sparing of the more proximal triceps muscles.

Proximal radial neuropathies caused by penetrating trauma should be surgically explored and treated with end-to-end anastomosis or grafting. Closed traumas, including humerus fractures, are often due to neuropraxia and recover gradually on their own, so a trial of conservative therapy is employed prior to any surgery. Proximal radial neuropathies related to pressure or stretch injuries (e.g. Saturday night palsy) or IBPN are also treated conservatively. Finger and wrist splints, pain control, and physical and occupational therapy are employed.

Posterior Interosseus Neuropathy

Damage to the posterior interosseus nerve will result in weakness of wrist and finger extensors with sparing of sensation. The posterior interosseus nerve can be damaged from multiple mechanisms (Table 21–9). Although some have speculated that the nerve can be entrapped within the supinator muscle, this is quite rare in our opinion. Many such cases probably represent a forme fruste of an IBPN or another immune-mediated neuropathy (e.g., multifocal motor neuropathy). On NCS, the superficial radial SNAP should be normal, but the radial CMAP recorded from the extensor indicis proprius may reveal a reduction in amplitude, provided there is significant axon loss (Table 21–3). EMG should demonstrate signs of denervation in muscles innervated by the posterior interosseus nerve.

Unless the posterior interosseus neuropathy is related to open trauma, it is managed conservatively as discussed with proximal radial neuropathies. Rare cases of the so-called radial tunnel syndrome with compression of the posterior interosseus nerve may improve with surgery.[143] Again, we feel that such entrapment is quite rare and the existence is controversial.

▶ TABLE 21–9. CONDITIONS ASSOCIATED WITH POSTERIOR INTEROSSEUS NEUROPATHY

Immune-mediated brachial plexus neuropathy
Trauma
Compression by tumors, ganglion cysts, lipoma, and bursitis
Compression by the arcade of Frohse
Compression by facial bands connecting the brachialis to the brachioradialis muscle at the radial head
Compression by edge or fibrous bands within the supinator muscle
Compression by a bifid extensor carpi radialis brevis muscle
Rheumatoid arthritis
Soft-tissue or peripheral nerve tumor
Ischemia (e.g., A-V fistulas and vasculitis)
Multifocal motor neuropathy or multifocal acquired demyelinating motor and sensory neuropathy

Superficial Radial Neuropathy

The superficial radial nerve is a pure sensory branch of the radial nerve that provides sensation to the dorsum of the hand. It can be damaged by various means (Table 21–10). In particular, compression by tight bands, watches, and handcuffs can lead to a superficial radial neuropathy. The superficial radial SNAP is usually decreased in amplitude, while motor studies and EMG would be normal. This type of neuropathy is usually due to neuropraxia and improves spontaneously. Cases related to laceration or other trauma may require surgery.

MEDIAN NERVE

As previously discussed, the median nerve contains fibers originating from spinal segments C6–T1, which then course through all three trunks and the medial and lateral cords. The median nerve is then formed by the merging of branches from the medial and lateral cords (Fig. 21–9). Axons from spinal segments and C7 that course through the upper and middle trunks and lateral cords are responsible for providing cutaneous sensation to the palmar aspect of the hand and digits 1–3 and usually the lateral half of digit 4. In addition, these segments also innervate several forearm muscles including

▶ TABLE 21–10. CONDITIONS ASSOCIATED WITH SUPERFICIAL RADIAL NEUROPATHY

External compression (handcuffs, tight wrist bands, and casts)
De Quervain tenosynovitis
Trauma
Soft-tissue or peripheral nerve tumor

▶ TABLE 21–11. CONDITIONS ASSOCIATED WITH PROXIMAL MEDIAN NEUROPATHY

Improper use of crutches (e.g., compression in axilla)
Trauma (e.g., dislocation of shoulder, fracture of humerus, missile injuries, stab wounds, and tourniquets)
Compression by ligament of Struthers
Pronator teres syndrome
Thickened lacertus fibrosum
Fibrous arch of the flexor digitorum superficialis
Tendonous band or hypertrophied pronator teres muscle
Sleep palsies
Compartment syndrome
Ischemia (e.g., A-V fistulas and vasculitis)
Immune-mediated brachial plexus neuropathy
Soft-tissue or peripheral nerve tumor
Multifocal motor neuropathy or multifocal acquired demyelinating motor and sensory neuropathy

the pronator teres and flexor carpi radialis. On the other hand, C8 and T1 nerve fibers course through the lower trunk and medial cord and innervate muscles controlling finger movements and provide no sensory input.

Proximal Median Neuropathy

Proximal median neuropathies in the axilla and upper arm may result from misuse of crutches, missile injuries, and laceration of the nerve by trauma (Table 21–11).[8,9,144,145] Compression of the nerve can also occur due to an awkward sleeping position—often in individuals who are intoxicated. Ischemic damage to the median nerve can occur as a complication of shunt blood from the nerve via therapeutic fistula (e.g., for dialysis).[146] The median nerve can be affected as well in the setting of IBPN. Proximal median neuropathies have been reported to be caused by compression by the ligament of Struthers, but this is controversial.[147–150] Compression by the lacertus fibrosis or bicipital aponeurosis at the elbow have also been implicated as possible etiologies.[151]

Individuals with proximal median neuropathies present with weakness of the median-innervated forearm and hand muscles and reduced sensation in the palmar aspect of the hand, digits 1–3, and the lateral aspect of digit 4. Median SNAPs to any of these digits would be expected to show reduced amplitudes again, provided there is sufficient axonal injury. The distal latency or conduction velocity of the median SNAP would be expected to be normal or only slightly impaired compared to the loss of amplitude. Similarly, the median CMAP amplitude recorded from the abductor pollicis studies may be reduced. It is important in these proximal median neuropathies to look for evidence of slowing of CV, temporal dispersion, or focal conduction block (discussed in Chapters 2 and 12). EMG would be expected to demonstrate abnormalities in median-innervated muscles in the forearm and hand (Table 21–1).

A controversial entity is the so-called pronator teres syndrome. In this disorder, the median nerve is thought to be compressed where it passes under the fibrous arch connecting the two heads of the pronator teres muscle. The major clinical manifestation is pain and tenderness in the volar aspect of the forearm and paresthesias in the distribution of the median nerve. These symptoms are exacerbated by having the patient actively trying to pronate the forearm against resistance. We remain rather skeptical of this diagnosis, as there is usually no objective evidence of weakness in median-innervated muscles. Further, median and ulnar NCS and EMG are typically normal.

Proximal median neuropathies carry a poor prognosis if there is significant axonal degeneration. The reason is the long distance the nerve must grow in order for complete reinnervation to occur. As long as there are some voluntary MUAPs in the forearm and hand muscles, there is potential for recovery.

The proximal median neuropathies are usually treated conservatively unless trauma is involved. Decompression surgeries have not been adequately studied in a scientific fashion, owing in part to the rarity of proximal median compressive neuropathies.

Anterior Interosseous Syndrome

The anterior interosseous nerve can be damaged from multiple mechanisms (Table 21–12). Most commonly, in our experience, an anterior interossesseus neuropathy arises either in conjunction with or as a forme fruste of an IBPN. As the anterior interosseous nerve is a pure motor nerve, patients do not have sensory loss. However, severe pain in the forearm for several days or weeks is typical in cases related to IBPN. Individuals have weakness in the flexor digitorum profundus I and II, flexor hallicis longus, and pronator quadratus muscles. This leads to difficulty with pinching maneuvers or forming the letter "O" with their thumb and index or middle fingers, as they have weakness of flexion of the distal aspects of these digits. Most cases should be managed conservatively. However, if there is no improvement in function after 4–6 months, surgical exploration to assess for compression can be considered.[139,152]

▶ TABLE 21–12. CAUSES OF ANTERIOR INTEROSSEUS NEUROPATHY

Immune-mediated brachial plexus neuropathy
Trauma
Fibrous band within the pronator teres
Compartment syndrome
Soft-tissue or peripheral nerve tumor
Ischemia (e.g., A-V fistulas and vasculitis)
Multifocal motor neuropathy

▶ TABLE 21–13. CONDITIONS ASSOCIATED WITH MEDIAN NEUROPATHY AT THE WRIST

Idiopathic
Flexor tenosynovitis
Degenerative joint disease
Rheumatoid arthritis
Sarcoidosis
Space-occupying lesions (e.g., ganglion cysts, lipomas, hemangiomas, giant cell tumors, and osteomas)
Trauma (e.g. Colle fracture and dislocation/fracture of carpal bones)
Pregnancy
Endocrine (e.g., hypothyroid, acromegaly, and diabetes mellitus*)
Amyloidosis (familial and primary)
Hereditary neuropathy with liability to pressure palsies
Soft-tissue or peripheral nerve tumor

* It is unclear if individuals with typical generalized diabetic polyneuropathy may be predisposed to focal mononeuropathies related to compression.

Median Neuropathy at the Wrist or Carpal Tunnel Syndrome

Median neuropathy at the wrist or carpal tunnel syndrome (CTS) is the most common mononeuropathy. There are multiple causes of median neuropathy at the wrist, although the vast majority are thought to be related to tenosynovitis of the flexor tendons which also occupy the carpal tunnel along with the median nerve. (Table 21–13).[8,9] Some clinicians restrict the term "CTS" only to those median neuropathies at the wrist caused by tenosynovitis. People with median neuropathy at the wrist usually complain of numbness and tingling of their fingers particularly at night or if they are doing activities with their hands. Sometimes the numbness and tingling as well as the pain patients describe extend beyond the territory of the median nerve (e.g., these may describe sensory symptoms in the little finger and aching in the forearm as well). The symptoms may be exacerbated by repetitive activity. However, the discomfort often occurs at rest and frequently wakes people up at night. The painful paresthesiae may be briefly alleviated by shaking the hands, the so-called 'flick sign."[106]

Clinical examination may reveal loss of sensation in the median nerve distribution to the fingers. Motor function is generally spared unless the injury is severe at which point weakness of atrophy of the thenar muscles is appreciated. Tapping over the wrist may elicit increased paresthesias in the fingers (Tinel sign), but this is not very specific. Having the persons maintain their wrists in the flexed posture may also exacerbate the discomfort in the fingers (Phalen sign), and this is more specific for CTS.

Sonography of the median nerve at the wrist may demonstrate flattening of the median nerve at the wrist

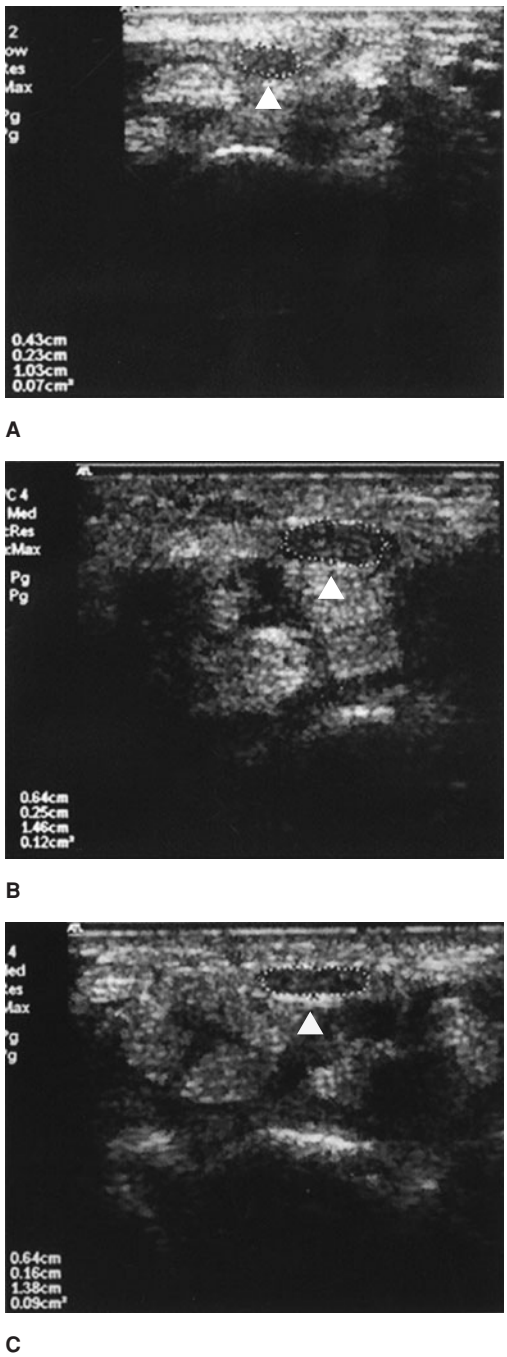

Figure 21–16. Sonograms of a patient with symptomatic carpal tunnel syndrome. (A) The median nerve of normal size at the proximal level (7 mm^2). (B) At the pisiform level the size of the median nerve was larger (12 mm^2) compared with the proximal level. (C) Increased flattening of the median nerve at distal level. (Reproduced with permission from Altinok T, Baysal O, Karakas HM, et al. Ultrasonographic assessment of mild and moderate idiopathic carpal tunnel syndrome. Clin Radiol 2004;59(10):916–925, Fig. 6, p. 923.)

(Fig. 21–16).[30,31,36] Likewise, MRI of the wrist may show reduction of the cross-sectional diameter of the carpal tunnel.[25,26] Swelling of the tendons, boney and cystic lesions, as well as compression of the nerve may be visualized by MRI. The major drawback of MRI is that it is very expensive. Despite the potential benefits, imaging of the carpal tunnel is not routinely applied by most clinicians.

There are various NCS that can be performed to confirm the clinical impression of a median neuropathy at the wrist. It should be recognized that NCS like all tests are imperfect, and it is estimated that approximately 10% of patients with histories highly suggestive of CTS will have normal NCS. In addition to performing median sensory and motor studies, it is essential to also include motor and sensory studies of other nerves (e.g., ulnar or radial) to ensure that the neuropathy is not more generalized. The studies should also be tailored according to the individual's symptoms. If a patient complains of sensory disturbance mainly in the third digit, then a median SNAP to the third digit should be performed as opposed to doing the median SNAP to the thumb or second digit. Median SNAPs are more sensitive than CMAPs in detecting abnormalities associated with CTS. Mixed compound nerve action potentials (CNAPs), which are obtained by stimulating the median and ulnar mixed nerves in the palm and recording over the respective nerves at the wrist, are often even more sensitive as they are usually performed across a shorter distance. Significantly prolonged distal latencies of the median palmar mixed CNAP compared to the ulnar study would support the clinical impression of CTS.

In addition to stimulating at the wrist and recording at the digit, it is sometimes useful to do a mid-palm stimulation (half-way between site of wrist stimulation and the recording electrodes) when performing the median SNAPs. If one sees a prolonged distal latency/slow CV and reduced amplitude following wrist stimulation, this should be compared to latency/CV and amplitude after stimulation in the palm to see if there was more focal slowing or conduction block across the wrist. This is particularly valuable in people who have a baseline generalized polyneuropathy in order to see if there is a superimposed median neuropathy at the wrist.

The earliest electrodiagnostic abnormalities on NCS in CTS are prolonged distal latencies or slowing of the median SNAP or palmar mixed CNAP across the palm. Subsequently, there may be a reduction in SNAP or mixed CNAP amplitude due to either axon loss or conduction block. Subsequently, distal latencies of the median CMAP become prolonged. Amplitudes of the median CMAP are usually affected much later in the course. In severe cases of CTS, median SNAPs and median CMAPs recorded from the abductor pollicis brevis may be unobtainable. Thus, from an NCS standpoint, one cannot localize the site of the median neuropathy, as a lesion may be anywhere from the hand to the origin of the median nerve in the plexus. In such cases, it is useful to perform median CMAP to the second lumbrical and ulnar CMAP to the second interosseus muscles while stimulating the median and ulnar nerves, respectively, at the wrist. The reason is that the median CMAP from the second lumbrical is often less affected in CTS than the CMAP from the APB. Therefore, a CMAP from this muscle may be obtained when one from the abductor pollicis brevis cannot. Thus, a prolonged distal latency and reduced amplitude of the median CMAP (second lumbrical) compared to the ulnar CMAP (second interosseus) may be appreciated and may confirm the localization of the lesion to the wrist. EMG is often done to further assess the degree of axonal damage and assess the localization of the lesion. Often the EMG is normal in mild CTS, but as it becomes more severe reduced recruitment of CMAPs and later signs of active denervation (e.g., fibrillation potentials) may become evident.

The treatment of CTS has been the subject of several recent reviews.[153–156] Treatments of CTS include modification of activities, splinting of the wrist, corticosteroid injections, nonsteroidal anti-inflammatory drugs, diuretics, and surgery. To complicate matters, there are various surgical techniques that can be employed as well (standard open surgery with exploration and release vs. minimally invasive endoscopic approach). Unfortunately, most studies of CTS have lacked scientific rigor, and thus recommendations for the best therapeutic approach are debatable.

Twenty to seventy percent of patients with CTS treated nonsurgically improve to some extent.[153,157,158] Corticosteroid injections into the carpal tunnel have become an increasingly used alternative to surgery. Risks include cutaneous atrophy, depigmentation, and inadvertent puncture of the median nerve, blood vessels, or tendons within the carpal tunnel.[153] Median nerve injury and tendon rupture are the most severe complications, but each occurs in <0.1% of injections. Approximately 30% of patients have no or only mild improvement following local corticosteroid injection, while 70% have a very good response (complete relief or only minor residual symptoms).[153,159] A study comparing corticosteroid injection vs. surgery demonstrated similar short-term efficacy of both treatments, but the relapse rate was common in the injection group and rare in the surgical group after 1 year.[102] In this regard, there are no good studies assessing the safety and efficacy of repeated corticosteroid injections.

The average success rate from surgery is approximately 75% (range 27–100%), but 8% of patients actually worsen.[153] Failure rates may relate to patients being operated on who do not actually have CTS. In this regard, improvement following surgery is noted in only half of patients who had normal electrodiagnostic testing prior surgery, while success rates are much higher in those with NCS that were abnormal. Another common cause of failed surgery is incomplete division the

transverse carpal ligament, perhaps owing to poor choice of incision and inadequate exposure.[153] Another reason for failed surgery is such end-stage denervation resulting from delayed treatment. There may be a <50% success rate for surgery in patients with marked thenar atrophy and weakness, no recordable median CMAPs and SNAPS, and active denervation on EMG.[153,159] In our opinion, CTS surgery in this population should only be considered for reasons of pain relief, not with the expectation that strength or sensation will return in any meaningful way.

Complications of surgery occur in 1–2% of cases and include injury to the recurrent motor and cutaneous branches of the median nerve, lesions of the main trunk of the median nerve, the main trunk and deep motor branch of the ulnar nerve, postoperative hematoma, wound infection, scarring, and complex regional pain syndrome.[153]

With the above caveats, we initially try conservative management having patients wear neutral angle wrist splints, particularly those individuals with only sensory abnormalities on NCS. In patients with objective motor deficits, we still try a short trial of wrist splints along with corticosteroid injections. However, we refer them for surgery if there is no benefit after a couple of months. We usually do not recommend surgery when NCS are normal.

ULNAR NERVE

The ulnar nerve is the anatomic continuation of the medial cord and contains nerve fibers originating from the C8 and T1 spinal roots, which course through the lower trunk and then median cord (Fig. 21–10). As previously discussed, there may also be a contribution from C7 in some individuals. This is a long nerve and lesions may occur anywhere along its course. Therefore, the clinical and electrophysiological findings are dependent on the site and nature of the lesion.

Proximal Ulnar Neuropathy (Axilla to Upper Elbow Region)

Similar mechanisms that cause proximal median and radial neuropathies can cause a proximal ulnar neuropathy (Table 21–14).[8,9] There are no ulnar-innervated muscles in the upper arm; therefore, any proximal lesion will clinically resemble those caused by more common ulnar neuropathy at the elbow (discussed in next section). Ulnar neuropathies in the upper arm related to open trauma usually require surgical repair.

Provided there is significant axonal loss, the ulnar and dorsal ulnar SNAPs would be expected to have reduced amplitudes while the lateral antebrachial cutaneous SNAP should be normal (Table 21–3). The ulnar CMAP may demonstrate reduced amplitude without focal slowing or conduction block across the elbow. EMG should show abnormalities confined to ulnar-innervated muscles in the hand and forearm (Table 21–1). However, these SNAPs and EMG alterations do not distinguish between a proximal ulnar neuropathy in the upper arm and one across the elbow. Electrophysiologically, the only way one can localize an ulnar neuropathy to the proximal upper arm is by demonstrating focal conduction block or slowing of CV of the ulnar CMAP between axillary and above the elbow stimulation sites.

▶ TABLE 21–14. CONDITIONS ASSOCIATED WITH PROXIMAL ULNAR NEUROPATHY

Trauma
Compression during sleep
Soft-tissue or peripheral nerve tumor
Ischemia (e.g., A-V fistulas and vasculitis)
Multifocal motor neuropathy or multifocal acquired demyelinating motor and sensory neuropathy

Ulnar Neuropathy at the Elbow

This is the second most common mononeuropathy aside from CTS, and it is usually the result of compression of the nerve at this level. As the nerve is superficial around the ulnar groove, it is more susceptible to extrinsic compression (e.g., from leaning on the elbow). There are numerous intrinsic mechanisms by which the ulnar nerve may be injured in this region (Table 21–15).[8,9] The term "tardy ulnar palsy" is applied to ulnar neuropathies that occur following bone injuries at the elbow. It is speculated that the nerve may become stretched or compressed by exuberant callus formation or altered angle of the elbow joint. The nerve may also become entrapped or compressed by the humeroulnar aponeurotic retinaculum or by other anatomic structural variants in and around the ulnar groove and cubital

▶ TABLE 21–15. CONDITIONS ASSOCIATED WITH ULNAR NEUROPATHY AT THE ELBOW

Tardy ulnar palsy (due to deformities of elbow related to previous fractures of humerus or other trauma to the joint)
Subluxation of the ulnar nerve
Compression by arcade of Struthers (medial intramuscular septum)
Compression by aponeurotic band between heads of flexor carpi ulnaris
Compression by ligament/band (retrocondylar)
Trauma
Soft-tissue tumor or masses
Leprosy
Diabetes mellitus*

* It is unclear if individuals with typical generalized diabetic polyneuropathy may be predisposed to focal mononeuropathies related to compression.

tunnel. Also, the nerve can occasionally prolapse out of the ulnar groove.

Regardless of the etiology, the clinical signs and symptoms of an ulnar neuropathy at the elbow are similar. Individuals who are affected often complain of discomfort and perhaps tenderness in the medial elbow. They will typically describe numbness and tingling in the medial aspect of the hand and the fifth digit along with the medial half of the fourth digit (both palmar and dorsal aspects of these fingers). Tapping the nerve in the elbow often exacerbates these symptoms (e.g., positive Tinel sign). Weakness may involve any or all of the ulnar-innervated muscles in the hand and forearm. This can lead to decreased muscle grip and spreading out or bringing fingers closer together. It is not uncommon for an ulnar neuropathy at the elbow to produce detectable hand but not forearm muscle weakness. We have found assessing for weakness of the flexion of little finger at the distal interphalangeal joint to be the most reliable means by which to detect ulnar forearm muscle weakness when it is present. With axonal degeneration, atrophy of the hypothenar and interossei muscles may be seen (most notably appreciated in the first dorsal interosseous).

Imaging studies such as MRI and ultrasound have been used to assist in diagnosis,[32,33] but, in general, electrodiagnostic studies are the primary tool to confirm one's clinical impression. Ulnar and dorsal ulnar cutaneous SNAP amplitudes should be reduced if there is significant axonal damage. However, if there is only a neuropraxic or demyelinating lesion in the elbow these SNAPs are typically normal, as these do not assess slowing of conduction across the elbow. Localization is dependent on the ulnar CMAP and EMG.[6,160–162] We usually perform ulnar CMAPs recording from both the first dorsal interosseous and the abductor digiti minimi muscles with stimulation sites at the wrist, below the elbow, and above the elbow. Because of the fascicular arrangement of nerves destined to innervate these muscles, one may find abnormalities in one but not the other muscle. Most of the lesions in the elbow initially lead to demyelination in this segment. One would expect to see normal distal latencies, amplitudes, and CV between the wrist and below-elbow stimulation sites. However, slowing of CV may be appreciated between the below- and above-elbow sites.[161] As the size of the demyelinating lesion may be small, the shorter the distance between the below- and above-elbow sites, the more likely one will be able to demonstrate focal slowing (we try to keep the distance at most 8–10 cm). In addition, conduction block may be appreciated between these sites of stimulation. To further localize where in the elbow the nerve is damaged and to increase the sensitivity if routine ulnar CMAPs across the elbow are normal one can do inching studies. Perhaps, a more appropriate term is "centimetering" as the nerve is stimulated every 1–2 cm, beginning 5 cm below to 5 cm above the elbow.[6,160,162] Assessing for slowing of the ulnar mixed compound nerve action potentials across the elbow may be informative in some patients.[163] If secondary axonal degeneration occurs then focal slowing of conduction velocity or conduction block may no longer be apparent. In such cases, the ulnar CMAP does not help in differentiating an ulnar neuropathy at the wrist from a more proximal lesion. The dorsal ulnar cutaneous SNAP is thus important, because an abnormality in this study implies a lesion proximal to the wrist as do EMG abnormalities in ulnar-innervated forearm muscles (e.g., flexor carpi ulnar and flexor digitorum III and IV). Again, in neuropraxic or demyelinating lesions, the EMG may just demonstrate reduced recruitment of MUAPs.

There is a lack of randomized, prospective studies aimed at assessing the efficacy of various treatments of the more common ulnar neuropathy at the elbow.[164] Most studies have been retrospective and subject to bias. Individuals with intermittent sensory symptoms may respond to conservative measures.[32,165] Nonsurgical measures include elbow pads, avoidance of leaning on the elbow, splinting the elbow in extention at night, and nonsteroidal anti-inflammatory drugs. Surgical procedures may be more beneficial in patients who have motor signs and symptoms, but not everyone improves.[32] There are various surgical approaches (e.g., simple decompression, medial epicondylectomy, and nerve transposition), and none has been rigorously studied in a scientific fashion. There may be increased risks with nerve transposition including infarction due to devascularization of the nerve and increased scarring. We are particularly reluctant to recommend this procedure to diabetics with their increased risk of microvasculopathy.

Ulnar Neuropathy in the Hand

The ulnar nerve can be damaged at various locations within the wrist or hand and by different mechanisms (Table 21–16). One of the most common etiologies is a compression by a ganglion cyst, which can easily be seen on MRI (Fig. 21–17) or ultrasound of the hand (Fig. 21–18).[35] Other imaging studies such as ultrasound may be useful. The ulnar nerve can be damaged in one of four

▶ TABLE 21–16. CONDITIONS ASSOCIATED WITH ULNAR NEUROPATHY AT THE WRIST

External compression (e.g., bicyclist)
Space-occupying lesions (e.g., ganglion cysts, lipoma, and nerve sheet tumors)
Trauma (fracture to metacarpals, pisiform, hamate, dislocation of distal ulna, and laceration)
Degenerative arthritis
Rheumatoid arthritis
Diabetes mellitus*

* It is unclear if individuals with typical generalized diabetic polyneuropathy may be predisposed to focal mononeuropathies related to compression.

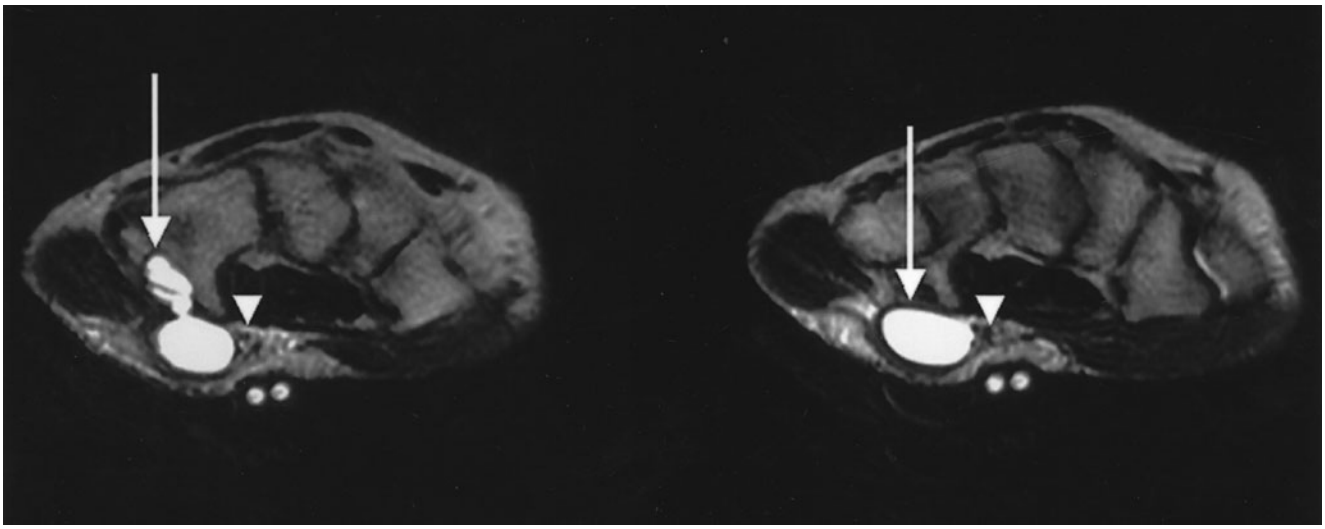

Figure 21–17. Ultrasound of wrist in a patient with ulnar neuropathy. Gray-scale ultrasonography of the wrist in the axial plane from the palmar aspect was performed with a multifrequency LA39 linear probe (LOGIQ 500; General Electric, Yokogawa, Japan) and showed the hypoechoic ganglion (single arrow) lying medial to the echogenic flexor tendons (double arrows). Posteriorly lying carpal bones appear echogenic (triple arrows). (Courtesy of Steven A. Greenberg. M.D. Reproduced, with permission from: Greenberg SA, Amato AA. EMG Pearls. Philadelphia: Hanley & Belfus, Inc, 2004, Fig. 2F, page 30.)

sites within the hand, and the clinical and electrophysiological findings are dependent on the site and nature of the lesion (Fig. 21–19).

1. The entire nerve may be damaged just proximal to or within Guyon's canal. This type of lesion affects the superficial sensory and deep motor branches of the distal ulnar nerve, resulting in sensory loss of the volar aspect of the fifth digit and usually the medial half of the fifth digit and weakness of all ulnar-innervated hand muscles. In contrast to more proximal ulnar lesions (e.g., ulnar neuropathy at the elbow), the dorsal ulnar cutaneous nerve is spared; thus, individuals

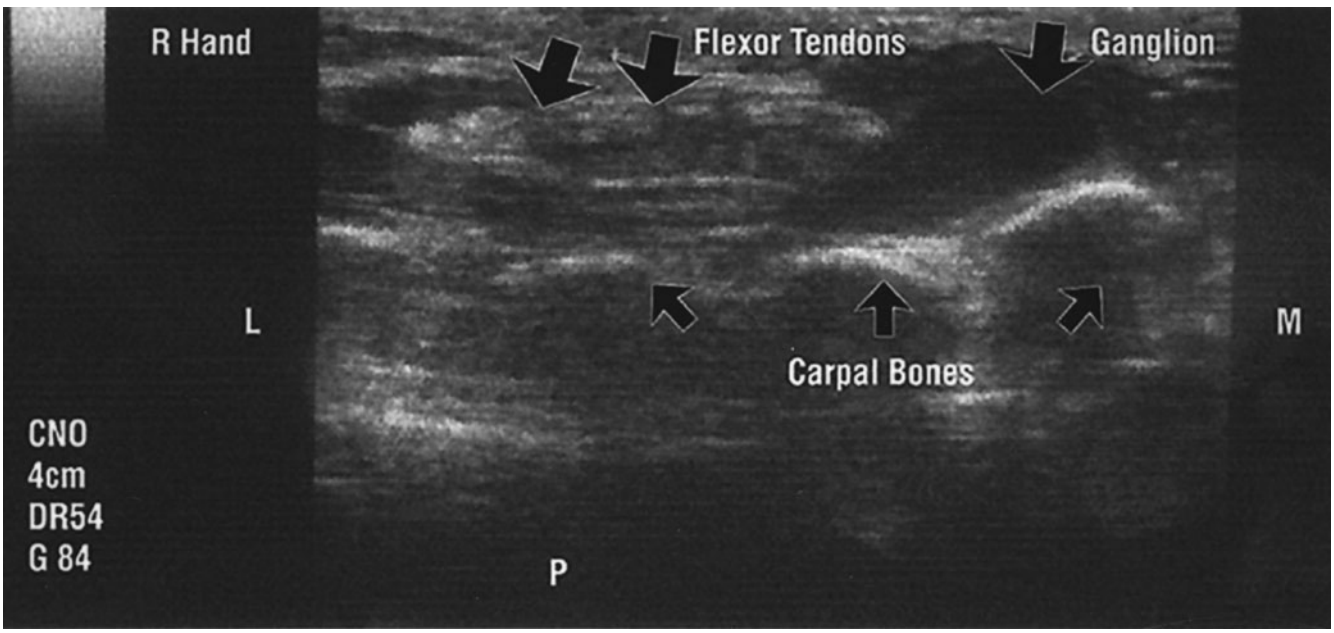

Figure 21–18. There are four main areas in which the ulnar nerve can be damaged at the wrist, and each leads to different clinical and electrophysiological abnormalities as discussed in the text. (Reproduced, with permission, from: Jacob A, Moorthy TK, Thomas SV, Sarada C. Compression of the deep motor branch of the ulnar nerve: an unusual cause of pure motor neuropathy and hand wasting. Arch Neurol. 2005 May;62(5):826–7, Fig. 2, page 827.)

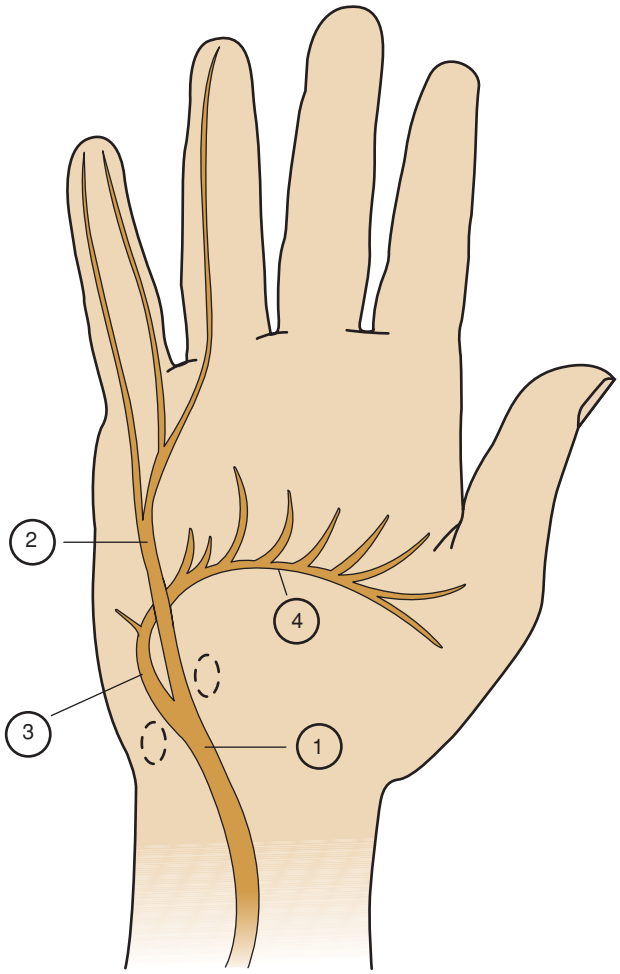

Figure 21–19. MRI of the wrist in a patient with ulnar neuropathy. MRI reveals a ganglionic cyst (arrow) adjacent to the hamate in Guyon's canal that is displacing the ulnar nerve and artery (arrowhead). (Modified with permission from: Stewart JD: Focal Peripheral Neuropathies. New York, Elsevier, 1987, Fig. 10.9, page 180.)

have sensation of the dorsum of the ulnar aspect of the hand. In addition, there is normal strength of the flexi carpi ulnaris and flexor digitorum profundus III and IV. The ulnar SNAP may demonstrate prolonged distal latency or reduced amplitude depending on the degree of axon loss, while the dorsal ulnar cutaneous SNAP should be normal. The ulnar CMAP recorded from both the abductor digiti minimi and the first dorsal interosseous may show prolonged distal latencies or reduced amplitudes, again dependent on the nature and severity of the lesion. EMG may demonstrate evidence of denervation in the first dorsal interosseus and abductor digiti minimi but the flexi carpi ulnaris and flexor digitorum profundus III and IV should be normal.

2. The nerve may be compressed just outside Guyon's canal such that only the superficial sensory branch is affected. In this case, sensation is decreased but all motor functions are spared. Electrodiagnostic studies would only show abnormalities of the ulnar SNAP.
3. The nerve may be damaged distal to the take off of the superficial sensory branch and affect only the deep motor branch. In such cases, sensation is spared, but motor function affecting any or all of the ulnar hand intrinsic muscles in the hand may be affected. The ulnar SNAPs would be normal, but ulnar CMAPs to both the first dorsal interosseus and the abductor digiti minimi should be abnormal, as would EMG of these muscles.
4. Finally, the nerve may be compressed distal to the branch innervating the hypothenar eminence. Thus, only the interossei and adductor pollicis muscles are affected. A lesion may be even more distal such that only the adductor pollicis or perhaps the first dorsal interosseus are abnormal. Ulnar SNAPs and ulnar CMAPs to the abductor digiti minimi would be normal. Only the ulnar CMAP from the dorsal interosseus would show abnormalities. Likewise, on EMG the abductor digiti minimi would be spared and denervation may be appreciated only in the dorsal interossei and adductor pollicis muscles.

Ulnar neuropathy in the hand due to external compression (e.g., bicyclist) may be treated conservatively. If caused by a fracture of the hamate or pisiform bones, exploratory surgery with decompression and neurolysis are often required. Also, ulnar neuropathies in the hand related to open trauma or internal compression (e.g., ganglion cyst) are usually managed with surgery.

▶ CONCLUSION

The multiple etiologies of focal neuropathies affecting the upper extremity (including radiculopathies, plexopathies, and mononeuropathies) can be quite daunting even to the experienced clinician. The key to the evaluation of patients with these types of focal neuropathies begins with localization. This is accomplished by a good physical examination and electrodiagnostic study. Other studies such as various modes of radiological imaging can assist in localizing and identifying an etiology. Prognosis is dependent on the cause and nature of the neuropathy. Neuropraxic lesions secondary to minor compression or stretch usually of the nerve tend to recover well; however, those associated with severe axonal degeneration take much longer to regenerate and recover. Treatment likewise is dependent on the nature of the nerve injury. Most focal neuropathies are initially

managed conservatively, but severe nerve injuries may require surgical intervention.

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CHAPTER 22

Radiculopathies, Plexopathies, and Mononeuropathies of the Lower Extremity

▶ INTRODUCTION

Focal nerve injuries of the lower extremities are among the more common neuromuscular disorders seen by primary physicians, general neurologists, and other healthcare providers in their patients. It is important for clinicians to be familiar with both the diagnosis and the management of these conditions. This emphasis is rooted not only in the application of proper treatment, but also in the avoidance of misdiagnosis and potentially harmful interventions. This latter problem may be escalating due to the widespread availability of imaging and electrodiagnosis (EDX), each of which is more than capable of leading to a false-positive conclusion if not interpreted within the appropriate clinical context. In addition, the pressures placed on the medical system by an aging population may translate to more patients receiving their evaluations by individuals ill prepared to identify cause and effect relationships between abnormal tests and patient signs and symptoms. As an example, it has been estimated that 15% of patients with amyotrophic lateral sclerosis (ALS) have had unnecessary surgeries in the mistaken belief that their neurological deficit was caused by a potentially surgically correctable nerve compression syndrome.[1]

This chapter will review the pertinent and pragmatic peripheral neuromuscular anatomy of the lower extremities. The pathophysiology of nerve injury will be reviewed in only a cursory fashion, as it is covered in significant detail elsewhere (Chapters 2 and 21). The bedside diagnostic strategy that the authors employ when evaluating these patients will be outlined as well as the ancillary testing perspectives we maintain. Finally, a detailed review of the clinical features, etiologies, evaluation, and management of individual mono- and polyradiculopathies, plexopathies, and mononeuropathies of the lower extremities will be provided. As in other chapters in this book, descriptions will rest on a foundation of published data but will be expanded upon by the personal experiences of the authors.

▶ ANATOMY

A basic understanding of the anatomy of the lumbosacral spine is essential for the conceptualization of nerve root disorders (Fig. 22–1).[2] In addition to the intervertebral disks, there are two pairs of synovial joints that form the articular connections between contiguous vertebrae and contribute to both the mobility and the stability of the spinal column. The zygapophyseal or facet joints are formed by extensions of the lamina of two contiguous vertebrae and constitute the posterior aspect of the neural foramina. These joints are innervated by branches of the posterior ramus of the spinal nerve. Diseases affecting these structures are one of many potential sources of nonradiating back pain. The second synovial joint system, the uncovertebral joints of Luschka, arises from the posterior-lateral surfaces of the vertebral bodies. These joints along with the disk itself constitute the anterior boundary of the neural foramina through which nerve roots exit. The superior and inferior boundaries of the neural foramen are formed by the pedicles of the vertebrae immediately above and below the foramen in question. There are two major ligamentous structures within the spinal canal: the posterior longitudinal ligament and the ligamentum flavum. Both are longitudinally oriented, the former running along the anterior aspect of the central canal just posterior to the vertebral bodies and disk spaces. The latter runs along the posterior aspect of the spinal canal just underneath the spinous processes. The posterior longitudinal ligament is only half as broad in the lumbar spinal canal as it is in the cervical region. This may add to an increased risk of paramedian disk herniation. The posterior longitudinal ligament is innervated by the sinovertebral (recurrent meningeal) nerves that arise from the rami communicantes outside the neural foramina. These travel retrograde to innervate the dura and the walls of intraspinal blood vessels as well as the posterior longitudinal ligaments. The ligamentum flavum contains few nocioceptive fibers. Its major clinical significance is its tendency to hypertrophy as part of

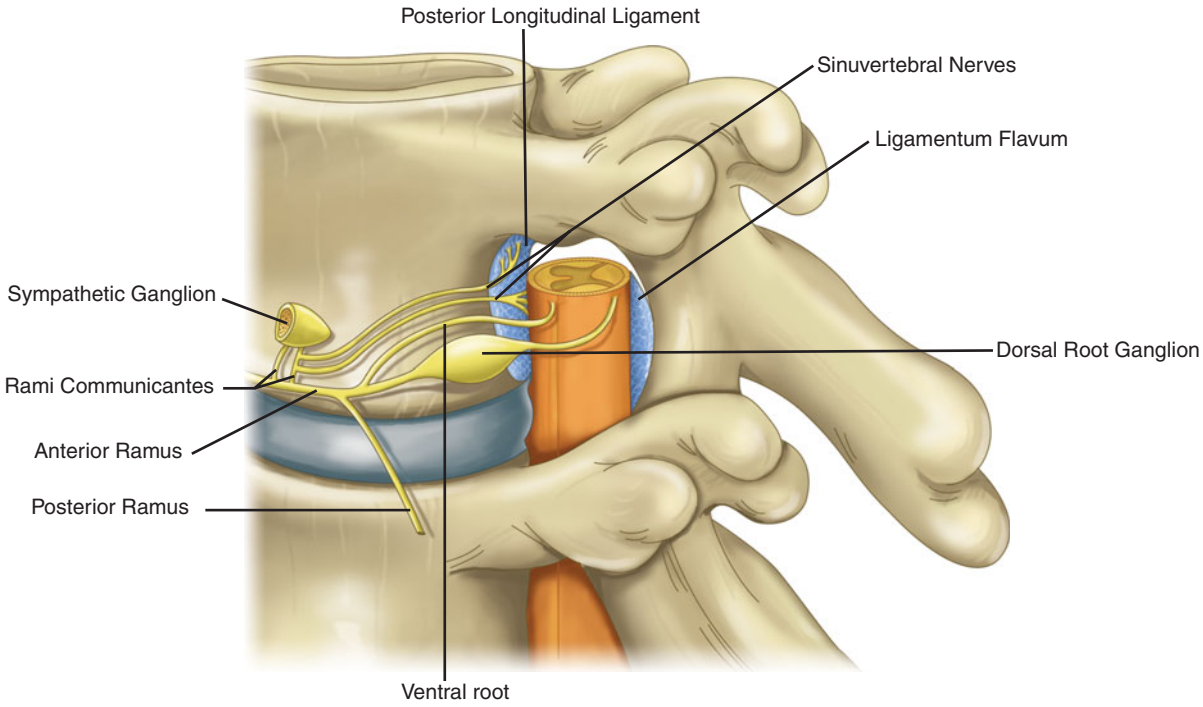

Figure 22–1. Anatomy of the spine.

the spondylitic process and contribute to central canal stenosis. The diameter of the central canal averages 18 mm in most normal adults with a range of between 15 and 23 mm. As in the cervical canal, it widens by a few millimeters when the patient bends forward.

Although this is a text of neuromuscular disorders, it is appropriate to mention potential sources of back, buttock, thigh, and leg pain. It is safe to say that isolated back pain may occur as the initial symptom of disorders, which will eventually affect the peripheral nervous system in the lower extremities. It is equally safe to say that it is difficult to distinguish the uncommon causes of back pain that will evolve into neurological disorders from the far more common "mechanical" and presumed "musculoskeletal" etiologies. In these latter disorders, potential anatomic sources of back pain include the capsules of the facet and sacroiliac joints, the posterior longitudinal ligament, the dura mater and epidural fibro-adipose tissue, epidural veins and arterioles, and the paraspinal muscles. Although it has long been suggested that paraspinal muscle pain originates from muscular spasm promoting constriction of intramuscular blood vessels, the lack of continuous EMG activity in hardened, tender muscles suggests that myoedema rather than continuous muscle activity promotes back stiffness and discomfort. In any event, identifying the anatomic source of back pain in an individual patient is an extremely difficult undertaking. Due to their lack or relative lack of nociceptive nerve endings, neither the annulus of the intervertebral disk nor the ligamentum flavum appear to be likely culprits.

Degenerative spine disease affects a number of different structures, which may individually or collectively narrow the diameter of the neural foramen or the central canal of the spinal column and, as a result, compromise nerve root integrity. Degeneration of the zygapophyseal and uncovertebral joints leads to osteophyte formation and joint enlargement as well as hypertrophy of the nearby ligamentum flavum. Degeneration of the intervertebral disk results in bulging of the annular ring and loss of its vertical height. Both processes contribute to the narrowing of the neural foramina, the former by raising the floor of the foramina while the latter by reducing the rostral–caudal dimensions of the space as the intrapedicular distance diminishes. Spondylolisthesis, the shifting of one vertebral body on another, is another potential consequence of degenerative spine disease and potential contributor to foraminal compromise.

The intervertebral disk consists of a gelatinous center, the nucleus pulposis, and a cartilaginous margin, the annulus fibrosis. As mentioned, the concept of discogenic pain is somewhat nebulous in that there are a paucity of nocioceptive pain fibers innervating the outer annulus and none within the nucleus pulposus itself. Although the pain and pathophysiology of nerve root disease are typically attributed to direct compression of the nerve root and the inflammation that accompanies it,[3–5] it is important to remember that other potentially pain-sensitive structures traverse the neural foramina as well. Both sinuvertebral (recurrent meningeal) nerves that originate from the rami communicantes and radicular arteries and veins may be compromised by foraminal

narrowing. The sinuvertebral nerves innervate the anterior and posterior longitudinal ligaments of the spine, the spinal dura mater, the walls of intraspinal blood vessels, and, to a lesser extent, the outer annular fibers of the intervertebral disks. Compression of these nerves, as well as the structures that these innervate, provides additional potential pain generators. Although there is a rich anastomotic blood supply to the spinal cord and nerve roots, ischemic injury resulting from radicular vascular compression may represent an alternative mechanism of nerve root injury.

The anatomy of the lumbosacral nerve roots varies from both their cervical and thoracic counterparts. A number of these aspects are potentially clinically significant. Correlation between nerve root and disk space involvement is more difficult in the lumbosacral spine than in the cervical spine. The differing anatomy in the lumbosacral region also offers a greater predisposition to multiple and bilateral root involvement than is the case in the cervical region. The reasons for these variations are as follows. Nerve roots in the cervical spine exit the spinal cord in what is essentially a perpendicular vector to the longitudinal trajectory of the spinal cord. In the cervical spine, a disk hernation is exposed to a single nerve root traversing directly over and parallel with the herniated disk. For example, a disk herniation at the fifth and sixth cervical vertebral interspace virtually always compresses the sixth cervical nerve root whose fibers run parallel to and immediately above the C5–6 disk space. The disk herniation may be paramedian, posterolateral, or far lateral in its trajectory, but the sixth cervical root remains in jeopardy in each case.

As the conus medullaris ends between the first and second lumbar vertebrae in the majority of individuals, the nerve roots innervating the lower extremities travel together in an oblique but largely vertical course (Fig. 22–2). Unlike the cervical spine, the nerve root exiting between two vertebral bodies typically shares the numerical label of the upper of the two vertebrae, the numbering scheme having been disturbed by eight cervical nerve roots and only seven cervical vertebrae. It is not this nerve root that exits at that level that typically falls in harms way. For example, the L4 root exits in the foramen created by the L4 and L5 pedicles. As this root approaches this foramen with a largely longitudinal trajectory, it immediately wraps around the L4 pedicle in close proximity in a space that is actually slightly rostral to the actual disk. More typically, an L4–5 disk herniation will affect the L5 root, which is still descending and traveling over the affected disk structure. This correlation is not, however, universal. A far lateral disk herniation at L4–5 may affect the L4 root preferentially, whereas a paramedian disk herniation at L4–5 may actually affect the more medially placed S1 root. In addition, large disk herniations in the lumbosacral region are quite capable of affecting multiple nerve roots, simultaneously affecting one or both lower extremities as well as sphincteric and sexual function.

Radiculopathy occurring as a consequence of spondylosis also differs in its phenotypic expression in the lumbosacral and cervical regions due to differing anatomy. Spondylytic bars in the cervical region are common. Although these may affect the nerve roots bilaterally at that interspace, the phenotype is typically dominated by myelopathic features. In the lumbosacral region, spondylytic narrowing of the central canal typically manifests as a polyradiculopathy, due to the orientation of the cauda equina and the absence of a spinal cord to provide myelopathic signs and symptoms.[6] Spondylosis producing a monoradiculopathy in the lumbosacral spine is most likely to affect the nerve root exiting at that level, rather than the one immediately below. Using the same example as above, narrowing of the lateral recess at L4–5 resulting from any or all of the spondylytic mechanisms listed above puts the L4 root at greatest risk, whereas the L5 root is most likely to be affected by a disk herniation occurring at the same level.

Another implication of lumbosacral nerve root anatomy is its possible effect on electrodiagnostic studies. Sensory nerve action potentials (SNAPs) in the legs may be abnormal in lumbosacral root disease, an apparent contradiction of the general principles of EDX emphasized in Chapter 2.[7] Dorsal root ganglia typically lie in or just lateral to the neural foramina, although there is considerable anatomic variation in this regard.[8] As a result, the dorsal nerve roots within the spinal canal, i.e., the cauda equina, are typically preganglionic. Consequently, Wallerian degeneration most commonly occurs in a centripetal rather than centrifugal direction with resultant SNAP preservation as is the case in the cervical spine. On occasion, the dorsal root ganglia are proximally located, or disk herniations occur sufficiently lateral so that the dorsal root ganglion is affected. Accordingly, SNAPs may be reduced in otherwise typical root disease and serve as an electrodiagnostic confounder.[7]

There is considerable variation in the anatomy of the lumbosacral plexus (Fig. 22–3). It may have contributions from as many as 11 spinal nerves but is typically composed of eight (L1–S3). The lumbar plexus is predominantly composed of branches from L1 to L4, with variable contributions from T11, T12, and L5. Typically, the majority of L4 fibers travel with the lumbar plexus, with a much smaller contribution from L4 joining with L5 to form the lumbosacral trunk. In a "pre-fixed" plexus, the plexus shifts downward so that there is more of an L1 contribution to the lumbar plexus, the femoral and obturator nerves become more L2–3- rather than L3–4-innervated structures, and the majority of L4 fibers end up in the sacral plexus. In the so-called "postfixed" plexus, the plexus is shifted upward so that virtually all

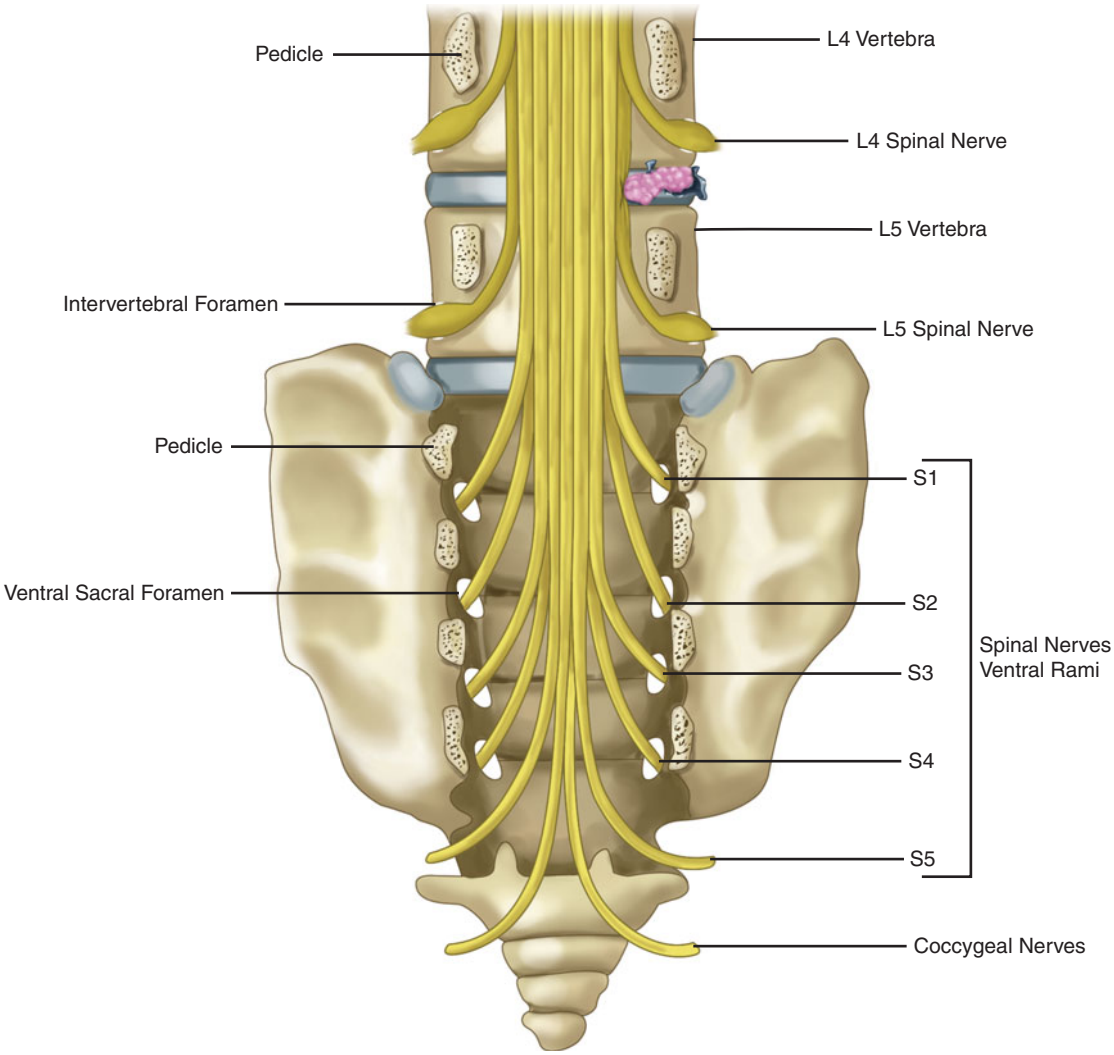

Figure 22–2. Anatomic correlations between disk herniation and affected nerve root in the lumbosacral spine.

of L4 and some of L5 are now confined within the lumbar rather than sacral plexuses.

The lumbar plexus is formed in the retroperitoneum, just inferior to the kidney and just behind the psoas muscle. Its blood supply originates from the internal iliac artery. Ischemic injury may occur from distal aortic or internal iliac arterial occlusion. The major branches of the upper lumbar plexus are the ilioinguinal, genitofemoral, and lateral cutaneous nerves of the thigh. The femoral, obturator, and lumbosacral trunks are the major components of the lower aspect of the lumbar plexus. The sacral plexus is formed within the concavity of the ventral surface of the sacrum, behind and lateral to the rectum. The L4 and L5 contributions to the sacral plexus and to the sciatic nerve are provided by the lumbosacral trunk, the conduit between the lumbar and the sacral plexuses. The lumbosacral trunk traverses the pelvic brim in the posterior aspect of the pelvis, over the sacral alae, just lateral to the sacroiliac joints. In this location, it is vulnerable to compressive injury during partuition. The major branches of the sacral plexus are the superior and inferior gluteal nerves, the posterior cutaneous nerve of the thigh, the peroneal and tibial divisions of the sciatic nerve, and the pudendal nerve.

Embryologically, the lower limb bud is initially oriented in a manner identical to the upper extremity so that the primordial flexor muscles of the foot are on the ventral surface and the great toe is the most laterally situated digit. As the lower limb develops, it rotates 180° medially. This is the basis of the spiral orientation of the dermatomes and hip ligaments. Muscles that were originally located on the posterior surface are innervated by the posterior branches of the lumbosacral plexus, e.g., femoral, peroneal, superior and inferior gluteal nerves as

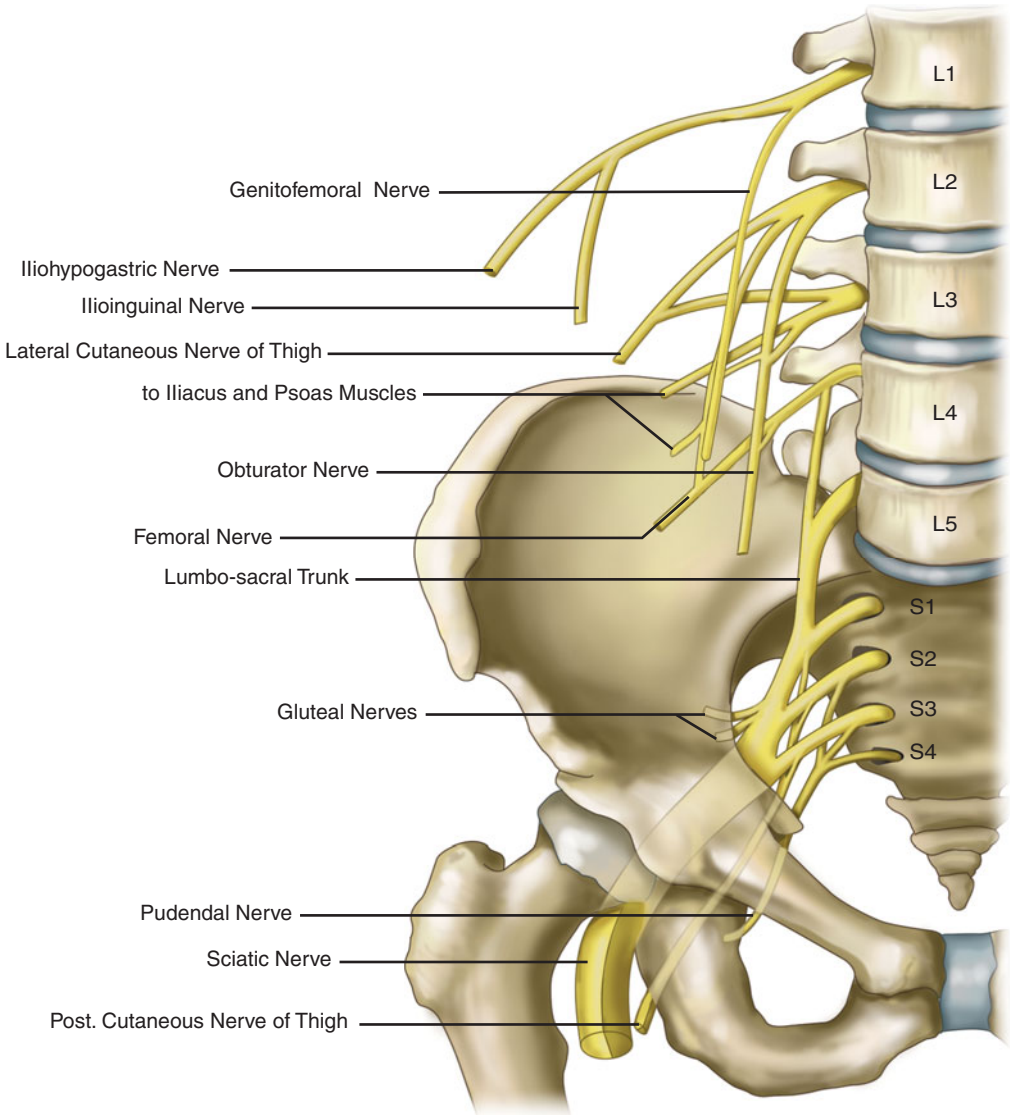

Figure 22–3. Lumbosacral plexus.

well as the lateral cutaneous nerve of the thigh. Muscles that were originally in an anterior location are innervated by anterior branches, e.g., genitofemoral, obturator, and tibial nerves.

Recognition of the existence and potential causes of mononeuropathies of the lower extremity are enhanced by an understanding of their anatomic associations as well as their functions. As the pattern of muscle weakness arguably provides the most objective localizing information, knowledge of the muscles that promote the major movements of the thigh, leg, foot, and toes and the nerves that innervate them is invaluable (Tables 22–1 and 22–2). The following paragraphs summarize the relevant anatomy of individual peripheral nerve anatomy.

The iliohypogastric nerve is primarily an extension of the L1 nerve root with some contribution from T12. It exits on the lateral border of the psoas muscle in proximity to the lower pole of the kidney and traverses the ventral surface of the quadratus lumborum muscle. It exits the abdominal wall superior to the iliac crest. It provides partial innervation to the transverse abdominus and internal oblique muscles of the abdominal wall. There are two cutaneous branches, one overlying the iliac crest in the posterior axillary line and a second innervating a small transverse patch above the pubic symphysis (Fig. 22–4).

The ilioinguinal nerve has similar L1 segmental origin and anatomic course. Its course is parallel but caudal to the iliohypogastric nerve along the upper border of the iliac crest. Its course is retrocolonic along the posterior abdominal wall. The nerve passes through the superficial inguinal ring to supply sensory branches to the

▶ TABLE 22–1. LUMBOSACRAL PLEXUS ANATOMY

Muscles Innervated	Cutaneous Distribution	Segmental Contribution	Plexus	Nerve
Transverse abdominus and internal oblique	Superior iliac crest at the posterior axillary line and small patch above the symphysis pubis	T12, L1	Lumbar	Iliohypogastric
Transverse abdominus and internal oblique	Skin overlying the inguinal ligament extending to the base of penis	L1	Lumbar	Ilioinguinal
Cremaster	Anterior proximal thigh in midline just caudal to the inguinal ligament and the serotum, labia majora, and adjacent thigh	L1, L2	Lumbar—anterior	Genitofemoral
None	Anterolateral thigh	L2–3	Lumbar—posterior	Lateral cutaneous nerve of the thigh
Psoas minor	None	L1–2–3	Lumbar	Branches of lumbar plexus and femoral
Iliacus and psoas major	None	L2–3–4	Lumbar	Branches of lumbar plexus and femoral
Sartorius	Anterior thigh	L2–3–4	Lumbar—posterior	Femoral
Rectus femoris, vastus lateralis–medialis–intermedius, and pectineus	Anterior thigh	L2–3–4	Lumbar	Femoral
None	Medial leg	L4	Lumbar	Saphenous
Gracilis, adductor magnus–longus–brevis, and obturator internus	Small patch of medial thigh	L2–3–4	Lumbar—anterior	Obturator
None	Posterior thigh, inferior buttock, lateral perineum, proximal medial thigh	S1–2–3	Sacral	Posterior cutaneous nerve of the thigh
Gluteus medius–minimus and tensor fascia lata	None	L4–5, S1	Lumbosacral trunk Sacral—posterior	Superior gluteal
Gluteus maximus	None	L5, S1–2	Lumbosacral trunk Sacral—posterior	Inferior gluteal
External anal sphincter	Distal anal canal and perianal skin	S2–3–4	Sacral	Pudendal—inferior rectal
Muscles of the pelvic floor, external urethral sphincter, and the erectile tissue of the penis	Perineum ventral to the rectum as well as the scrotum and labia	S2–3–4	Sacral	Pudendal—perineal
None	Penis or labia	S2–3–4	Sacral	Pudendal—dorsal nerve of the penis/labia
Semimembranosis/ semitendinosis	NA	L5, S1–2	Lumbosacral trunk Sacral—anterior	Sciatic—tibial
Long head of biceps	NA	L5, S1–2	Lumbosacral trunk Sacral—anterior	Sciatic—tibial
Short head of biceps	NA	L5, S1–2	Lumbosacral trunk Sacral—posterior	Sciatic—common peroneal
Tibialis anterior, extensor digitorum longus and brevis, and extensor hallucis longis	Interspace between first and second digits	L4–5, S1	Lumbosacral trunk Sacral—posterior	Common peroneal—deep peroneal

(*continued*)

▶ **TABLE 22–1. (CONTINUED)**

Muscles Innervated	Cutaneous Distribution	Segmental Contribution	Plexus	Nerve
Peroneus longus and brevis	Distal lateral leg and dorsum of foot	L4–5, S1	Lumbosacral trunk Sacral—posterior	Common peroneal—superficial peroneal
Flexor hallucis longus, flexor digitorum longus, and tibialis posterior	NA	L5, S1	Lumbosacral trunk Sacral—anterior	Tibial
Medial and lateral gastrocnemius, soleus, plantaris, and popliteus	NA	S1–2	Sacral—anterior	Tibial
None	Lateral surface of foot	S1	Sacral	Sural
Intrinsic foot muscles (toe flexors–adductors–abductors)	Sole of the foot	S1–2	Sacral—anterior	Tibial—medial and lateral plantar nerves, calcaneal nerve

skin overlying the inguinal ligament, extending medially and caudally to the regions just above and lateral to the base of the penis and scrotum (or labia). In other words, the area just above the genitals and just below the pubic symphysis is supplied by this nerve (Fig. 22–4). As with the iliohypogastric nerve, the ilioinguinal nerve provides motor branches to the transverse abdominus and internal oblique muscles.

The genitofemoral nerve receives near equal innervation from the L1 and L2 segments. It penetrates the psoas muscle in the retroperitoneum and descends vertically along its ventral surface. It lies in close proximity to the external iliac artery, ureters, terminal ileum on the right, and sigmoid colon on the left. As in the iliohypogastric nerve, it has two separate sensory branches. The larger of the two, the femoral branch, innervates the anterior, proximal thigh in the midline, just distal to the inguinal ligament. The second, smaller genital branch, supplies a small cutaneous zone on the lateral aspect of the root of the penis and scrotum or corresponding area of the labia. It overlaps with portions of the ilioinguinal and iliohypogastric territories (Fig. 22–4). The only muscular branch is to the cremaster muscle, which controls the ascent/descent of the testes in order to aid in temperature homeostasis within the testes.

The obturator nerve is formed by the second through fourth lumbar nerve roots (Fig. 22–5). It emerges from the medial border of the psoas muscle just cephalad to the pelvic brim and descends through the pelvis vertically, medial to the course of the femoral nerve, to exit the pelvis through the obturator foramen. It innervates the adductor longus, brevis, and a portion of the adductor magnus muscle, as well as the gracilis, and obturator externus muscles. The major function of these muscles is to adduct the thigh with contributions to thigh flexion and external rotation. Cutaneous sensation is supplied to a small patch on the inner thigh.

The femoral nerve is also an extension of the L2–4 segments (Fig. 22–6). It arises in a retroperitoneal location and passes between the psoas and the iliacus muscles before traveling under the iliacus fascia in the lateral pelvis, where it is potentially vulnerable to an iliacus compartment syndrome. It exits the pelvis below the inguinal ligament and lateral to the femoral artery. It provides motor branches to both the psoas and the iliacus muscles in the pelvis and to six muscles in the thigh, including the four components of the quadriceps, the sartorious, and the pectineus muscles. The primary function of the majority of these muscles is to extend the leg at the knee joint. The iliopsoas, sartorious, pectineus, and the rectus femoris, the latter being the only portion of the quadriceps that originates on the pelvis, flex the thigh at the hip joint. The sartorius is an unusual muscle that not only flexes but also externally rotates the thigh. Along with the hamstrings, it contributes to leg flexion at the knee as well. The pectineus is an external rotator and adductor of the thigh. The femoral nerve provides cutaneous innervation to the anterior surface of the thigh and, through its terminal sensory branch, the saphenous nerve, the medial aspect of the leg in a manner analogous to the musculocutaneous nerve in the upper extremity.

The lateral cutaneous nerve of the thigh (Fig. 22–6) is an extension of the second and third lumbar nerve roots, which also emerge from the lateral border of the psoas to traverse the lateral pelvis deep to the iliacus fascia. It exits the pelvis at the anterior superior iliac spine often by penetrating the lateral margin of the inguinal ligament. It is a purely sensory nerve that supplies sensation to the anterolateral thigh and the underlying fascia.

▶ TABLE 22–2. MUSCLES CONTRIBUTING TO SPECIFIC LOWER EXTREMITY MOVEMENTS

Thigh						Leg		Foot			
Flexion	Extension	Abduction	Adduction	External Rotation	Internal Rotation	Extension	Flexion	Dorsiflexion	Plantar flexion	Inversion	Eversion
• Iliopsoas • Rectus femoris • Sartorius • Pectineus • Adductor longus • Adductor brevis • Adductor magnus • Gluteus minimus • Tensor fascia lata	• Gluteus maximus • Adductor magnus • Long head of biceps femoris • Semitendinosis • Semimembranosis	• Gluteus medius • Gluteus minimus • Tensor fascia lata • Piriformis • Obturator internus • Gemelli	• Adductor magnus • Adductor longus • Adductor brevis • Gracilis • Iliopsoas • Pectineus	• Sartorius • Iliopsoas • Pectineus • Adductor longus • Adductor magnus • Gluteus maximus • Gluteus medius • Piriformis • Obturator internus • Gemelli • Obturator externus • Quadratus femoris	• Tensor fascia lata • Gluteus medius • Gluteus minimus	• Vastus medialis • Vastus lateralis • Vastus intermedius • Rectus femoris • Tensor fascia lata	• Semimembranosis • Semitendinosis • Short head of biceps femoris • Long head of biceps femoris • Sartorius • Gracilis • Popliteus • Gastrocnemius • Plantaris	• Tibialis anterior • Extensor digitorum longus	• Medial gastrocnemius • Lateral gastrocnemius • Soleus • Peroneus longus • Peroneus brevis • Plantaris • Flexor hallucis longus • Flexor digitorum longus • Tibialis posterior	• Tibialis posterior • Tibialis anterior • Flexor digitorum longus • Flexor hallucis longus	• Peroneus longus • Peroneus brevis • Extensor digitorum longus • Extensor hallicus longus

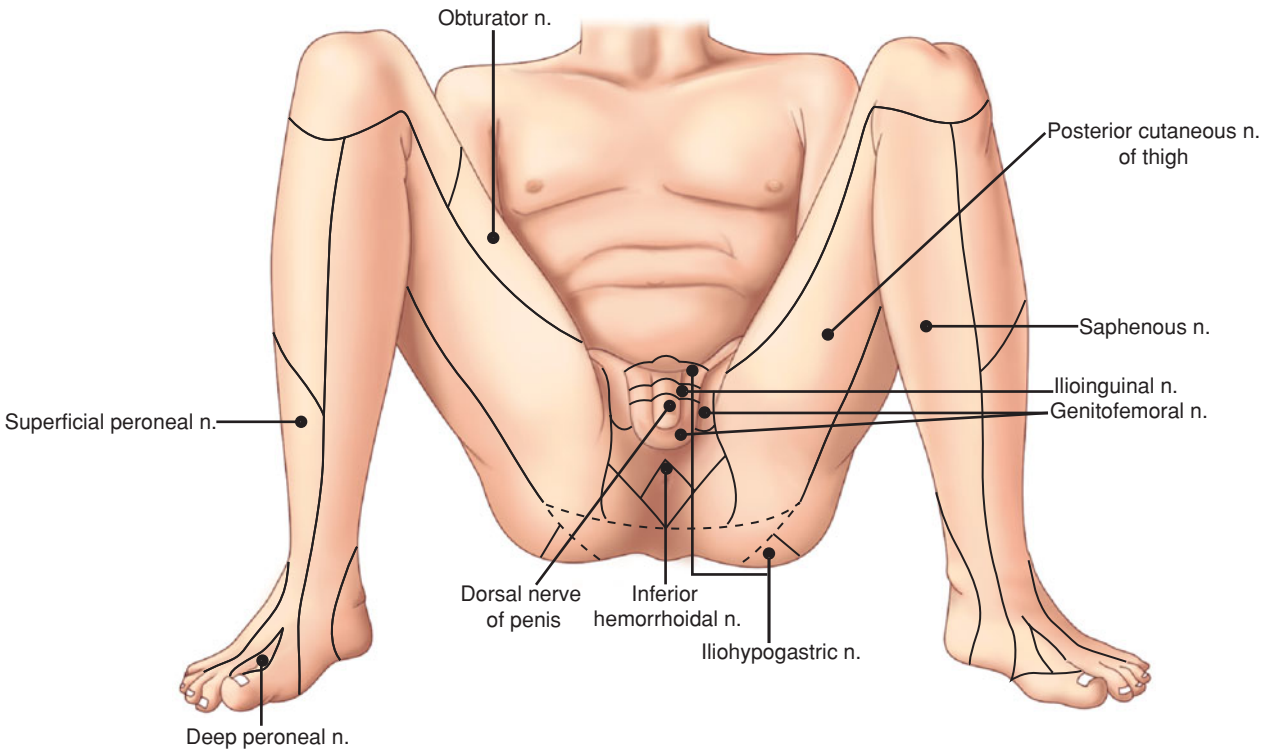

Figure 22–4. Cutaneous innervation of the groin, perineum, and genitals.

The sciatic nerve receives contributions from the L4–5 segments of the lumbar plexus, via the lumbosacral trunk as well as the first three sacral segments (Fig. 22–7). From its most proximal origins, it is really an amalgamation of two distinct nerves: the tibial and the peroneal. It should probably be clinically conceptualized in this manner for reasons that will be mentioned subsequently. The segmental contribution to these two nerves is somewhat different. The peroneal nerve contains few, if any, S3 fibers, whereas there is no meaningful L4 contribution to the tibial nerve in the majority of individuals. Prior to the actual formation of the sciatic nerve, there are two major nerve structures that are formed by branches originating from the upper sacral spinal nerves. The pudendal nerve is the more proximate of these, originating from branches of the S2–4 spinal nerves. Slightly more distal, the posterior cutaneous nerve of the thigh is formed by branches from two or more of the S1–3 segments, prior to their juncture with the lumbosacral trunk. This merge of the S1–3 segments and the lumbosacral trunk identifies the beginning of the sciatic nerve proper, just lateral and anterior to the sacrum. There are two major branches of the sciatic nerve in the pelvis: the superior and inferior gluteal nerves described in the next paragraph.

The superior and inferior gluteal nerves branch from the sacral plexus and originate from the L4–S1 and L5–S1 roots, respectively. The superior gluteal nerve is the only nerve to exit the sciatic notch above the piriformis muscle. The former innervates the gluteus medius and minimus as well as the tensor fascia lata. Their major action is to abduct the thigh at the hip. All three contribute to internal rotation of the thigh. The gluteus minimus provides a minor contribution to thigh flexion, and the posterior aspect of the gluteus medius contributes partially to external rotation of the thigh. The inferior gluteal nerve innervates the gluteus maximus, which is the primary thigh extensor muscle, but also contributes partially to external rotation. Neither nerve has a cutaneous sensory function. The pudendal nerve exits the pelvis in the caudal aspect of the sciatic notch near the sacral–coccygeal junction. It has three major branches: the inferior rectal or hemorrhoidal, the perineal, and the dorsal nerve of the penis/clitoris (Fig. 22–4). The former branch innervates the external anal sphincter and supplies sensation to the distal anal canal and perianal skin. The perineal nerve innervates the muscles of the pelvic floor, the external urethral sphincter, and the erectile tissue of the penis. Its cutaneous innervation includes the perineum ventral to the rectum as well as the scrotum and labia. The dorsal nerve of the penis is a purely sensory branch that innervates the skin of the penis and labia. The posterior cutaneous nerve of the thigh exits the pelvis through the lower sciatic notch, medial to the sciatic nerve and lateral to the pudendal nerve. As in the sciatic nerve, it may travel through the piriformis muscle in some individuals. It travels underneath and is protected by the gluteus maximus. At the level of the

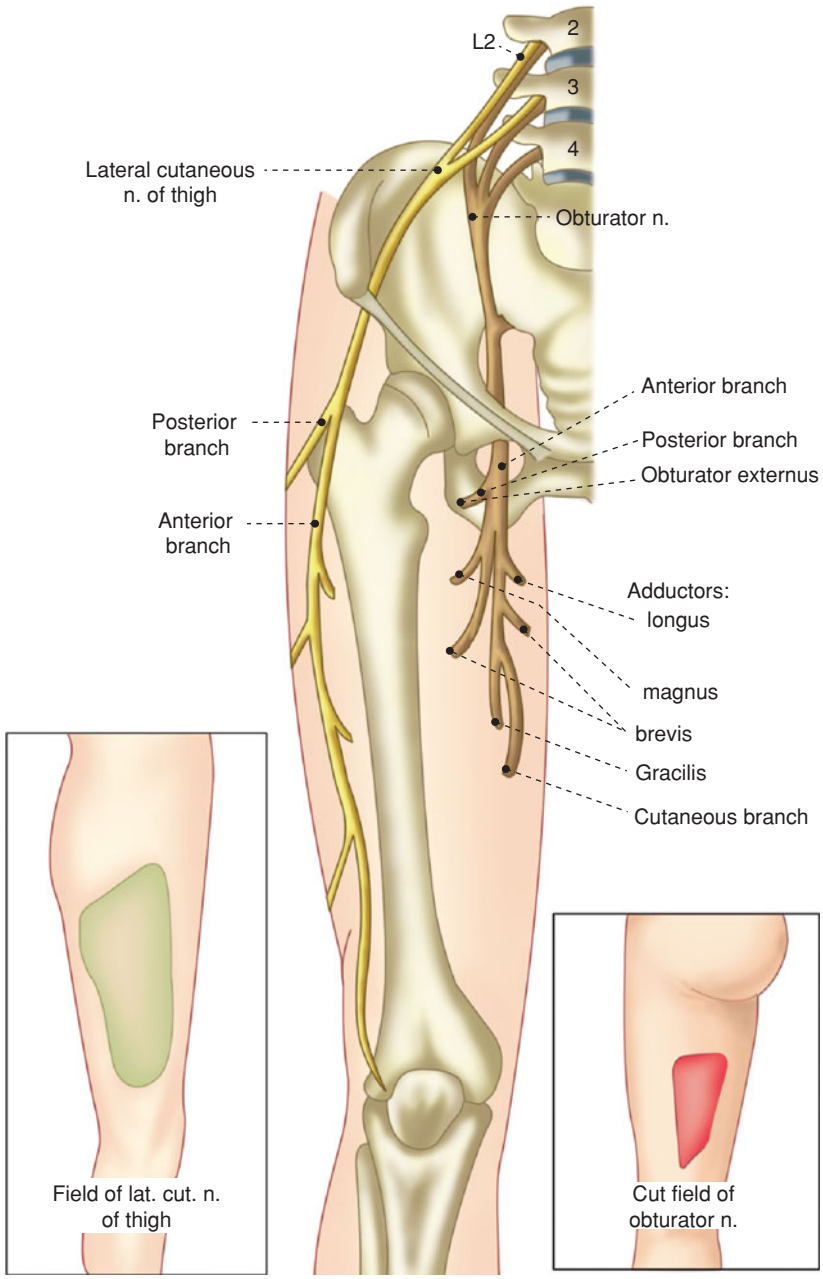

Figure 22–5. Obturator and lateral femoral cutaneous nerves.

gluteal crease, cluneal branches exit to supply the skin of the inferior buttock. There are perineal branches as well, which supply the skin and fascia of the lateral perineum, the proximal medial thigh, and the posterolateral aspect of the scrotum/labia as well as root of penis/clitoris. The terminal branch descends vertically to provide sensibility to the posterior thigh and often the proximal aspect of the posterior calf. It has no motor component.

The sciatic nerve leaves the pelvis posteriorly through the sciatic notch, typically below, but occasionally above or through the piriformis muscle, an alleged site of entrapment. It descends lateral to the ischial tuberosity of the pelvis and medial to the greater trochanter of the proximal femur, where it is potentially vulnerable to a misplaced intramuscular injection. In the thigh, the sciatic nerve innervates the hamstrings, the short head of the biceps innervated by the lateral trunk or peroneal portion of the nerve. The remaining three muscles, the semitendinosis, semimembranosis, and long head of the biceps, are innervated by the medial trunk or tibial division. In addition, the adductor magnus may receive partial innervation by the sciatic nerve, providing a potential source of electrodiagnostic confusion for the unwary. A lesion of the sciatic nerve proximal to the knee will produce a pattern of sensory

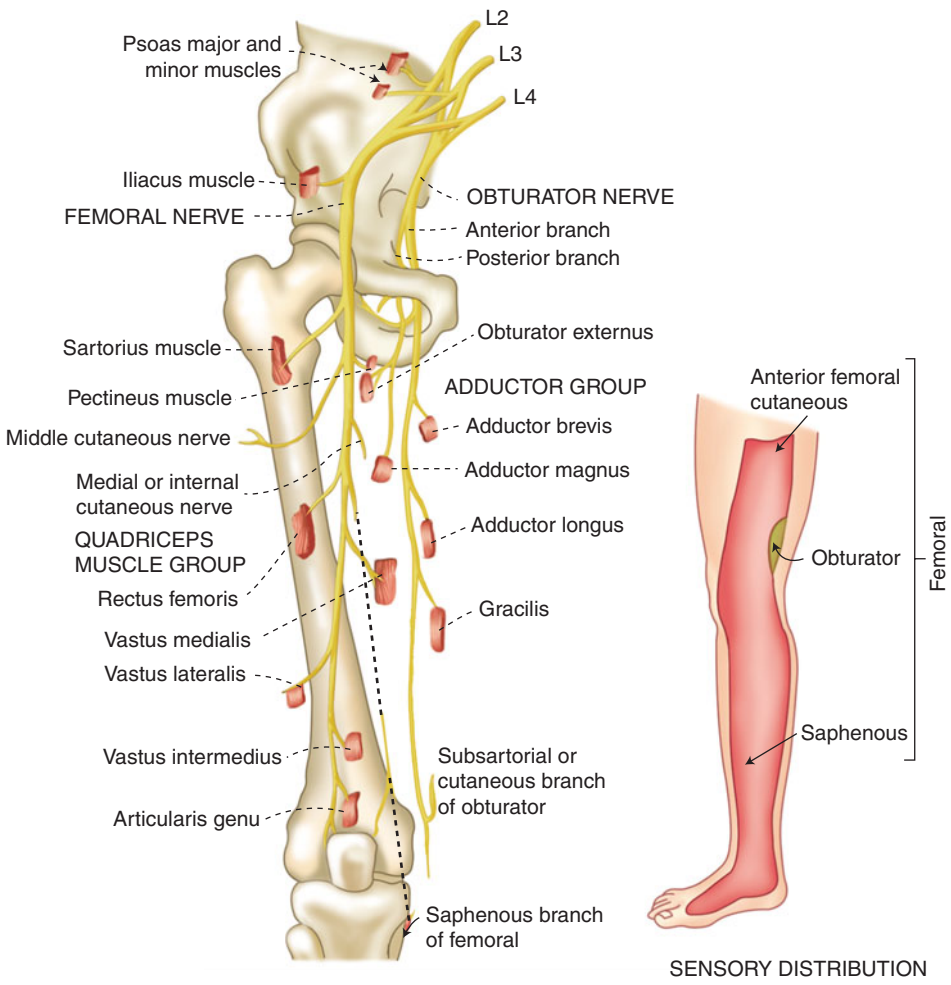

Figure 22–6. Femoral and obturator nerves.

symptoms or sensory loss that includes the entire foot and the distal half of the lateral surface of the leg, sparing the L4/saphenous innervated medial leg. The blood supply to the sciatic nerve originates predominantly from branches of the inferior gluteal artery and popliteal arteries. This creates a watershed at mid-thigh level, which has been proposed as the mechanism/location for sciatic neuropathies that may occur in the context of vasculitic illnesses.

In the leg, the common peroneal nerve bifurcates below the level of the fibular head into deep peroneal and superficial peroneal divisions (Fig. 22–8). The deep peroneal nerve innervates the muscles of the anterior compartment: the tibialis anterior, the extensor hallucis, and digitorum longus muscle. In the foot, it innervates a solitary muscle: the extensor digitorum brevis (EDB). Collectively, the major function of these muscles is to dorsiflex the foot at the ankle and the toes at the metatarsal–phalangeal joints. The superficial peroneal nerve innervates the lateral compartment of the leg, including the peroneus longus and brevis muscles. The major function of these muscles is to evert the foot at the ankle. The deep peroneal nerve has a predominantly motor function with a very small cutaneous contribution to the interdigital space between the first and second digits. The superficial peroneal innervates the skin of the dorsal surface of the foot and the distal lateral surface of the leg.

The tibial nerve receives contributions from the L5–S3 nerve roots and is the continuation of the medial cord of the sciatic nerve (Fig. 22–9). It separates itself from its peroneal counterpart in the distal thigh and passes through the popliteal fossa and then in front of the two heads of the gastrocnemius muscle. It innervates three of the four hamstring muscles in the thigh, ignoring only the short head of the biceps femoris. In the leg, it supplies the muscles of the posterior compartment including the two heads of the gastrocnemius muscle, the soleus, tibialis posterior, flexor digitorum longus, and flexor hallucis longus. In the foot, it supplies all intrinsic foot muscles except the EDB on the dorsal surface. Its primary functions are to flex the leg at the knee, to plantar flex and invert the foot at the ankle, and to flex, abduct, and adduct the toes. The three cutaneous branches of the

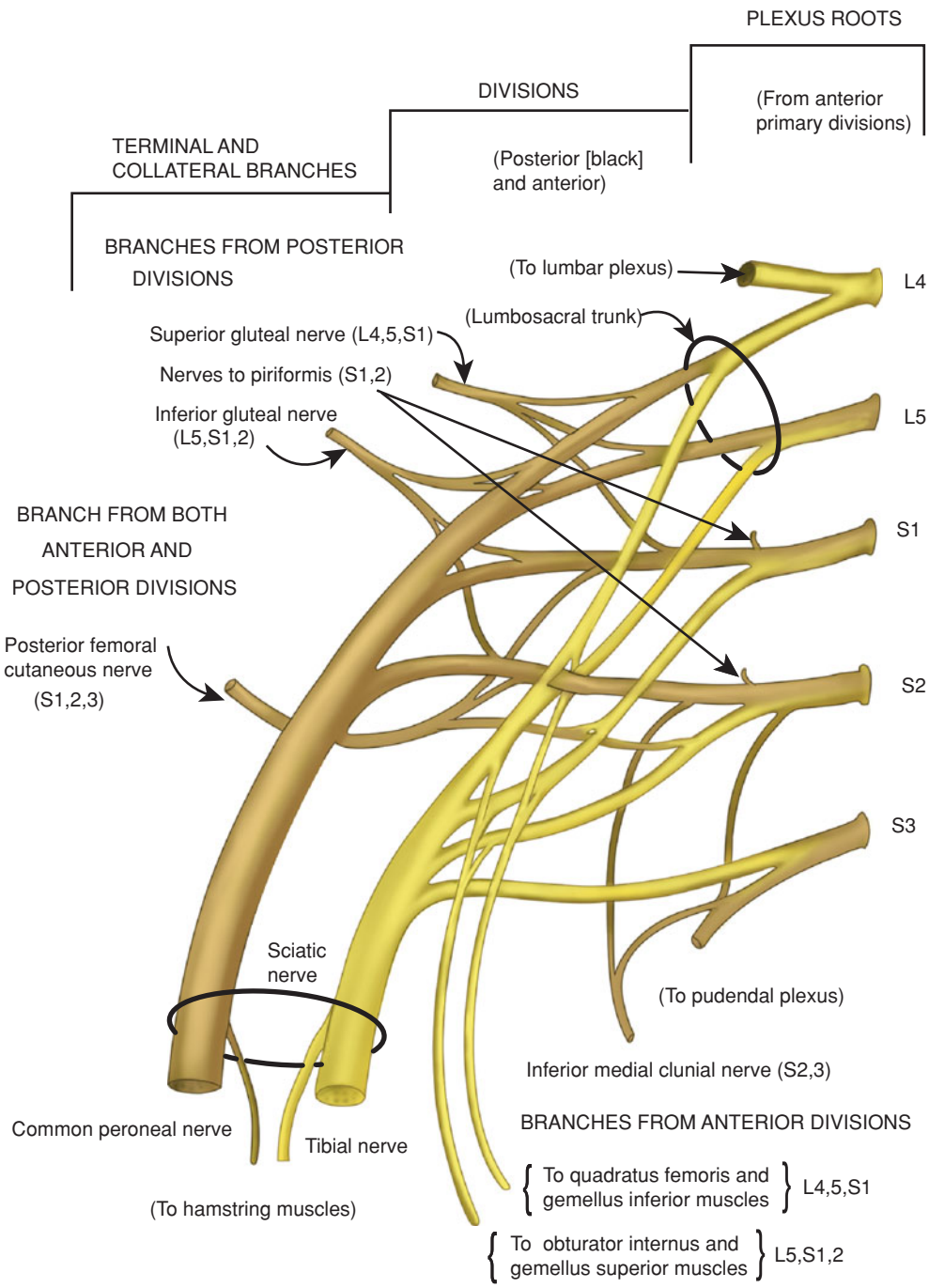

Figure 22–7. Lumbosacral trunk, sacral plexus and sciatic nerve.

tibial nerve all branch at the level of the medial malleolus and include the medial and lateral plantar and calcaneal nerves supplying the medial and lateral plantar surfaces of the anterior two-thirds of the sole and the heel, respectively.

The sural nerve is formed in the popliteal fossa by anastomotic contributions from the common peroneal and tibial nerves. It is derived primarily from the S1 nerve root. It descends in a fairly superficial position posteriorly in the calf, moving somewhat anteriorly as it passes behind the lateral malleolus.

▶ PATHOPHYSIOLOGY

The pathophysiology of peripheral nerve injury has been described in detail in Chapters 2 and 21. Disorders that infiltrate, infarct, inflame nerves, or compress them with sufficient intensity or for sufficient periods of time are dominated by Wallerian degeneration and axon loss. Pain is common, particularly if the pathology occurs acute or subacutely. Muscle weakness and atrophy, sensory loss that affects all modalities, loss of deep tendon reflexes if relevant to the nerve injured, and even

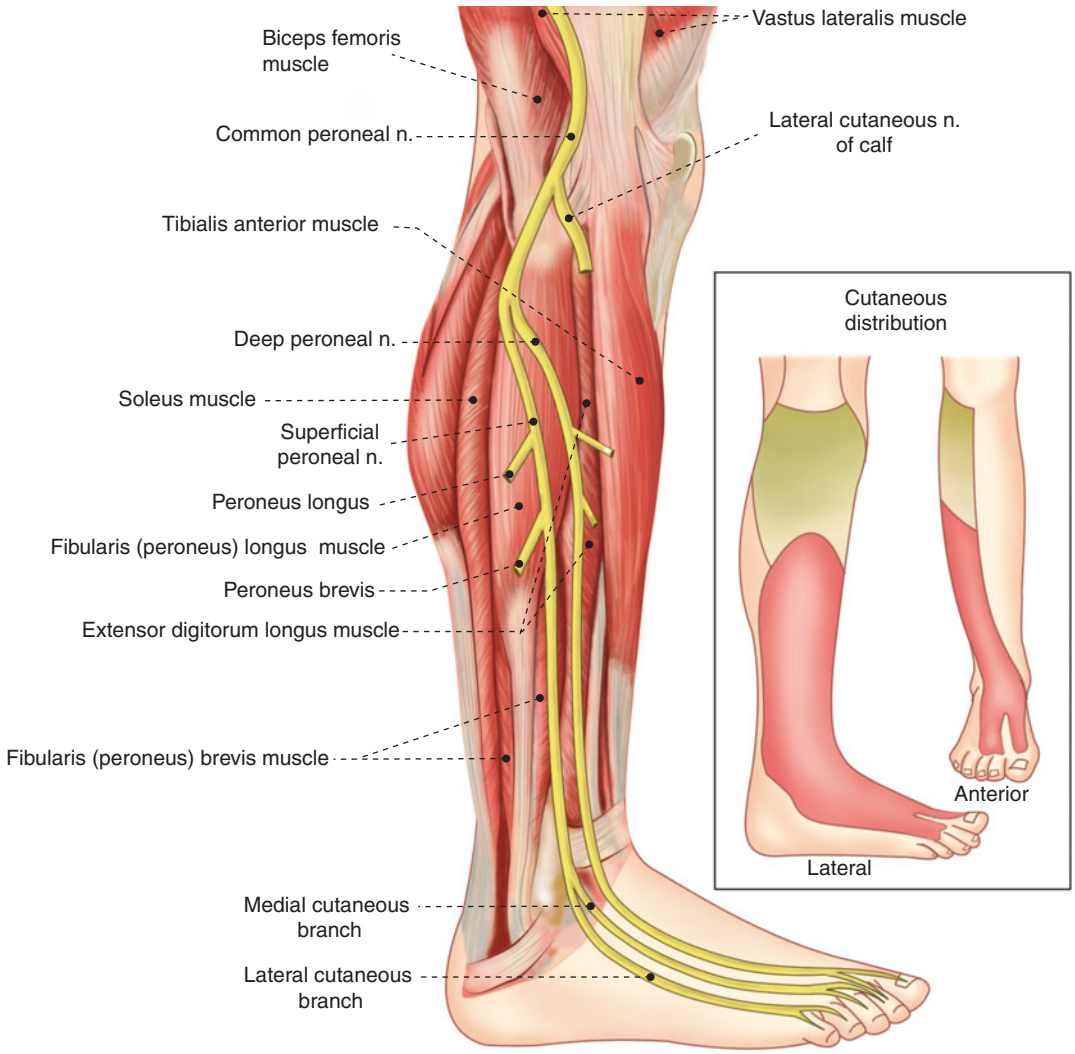

Figure 22–8. Peroneal (fibular) nerve.

dysautonomic manifestations including sweating and vasomotor abnormalities are anticipated. Electrodiagnostically, amplitudes of involved sensory and motor nerves diminish on nerve conductions and fibrillation potentials, and eventually enlarged, reconfigured motor unit action potentials develop.

Many experimental models of nerve compression support the belief that myelin is preferentially damaged in less severe entrapment or compression neuropathies. Electrodiagnostically, this may express itself by any combination of focal slowing, differential slowing (a.k.a. temporal dispersion), or conduction block. Demyelinating nerve injuries are, in general, less painful than their axonal counterparts. Clinically, focal slowing may produce paresthesias but no objective deficits. Differential slowing may impair modalities that are dependent on the synchrony of impulse transmission such as deep tendon reflexes and the perception of vibration. Conduction block causes weakness without atrophy (other than that attributable to disuse) and loss of sensory modalities dependent on large myelinated fibers including vibration and position sense. On the needle examination, there is reduced recruitment of motor unit potentials. Neither fibrillation potential nor motor unit remodeling occurs unless there is concomitant axon loss.

▶ APPROACH

As with all neuromuscular disorders, accurate localization is predicated upon determining what is involved, the pattern in which the involvement occurs, as well as what modalities are spared. The clinician needs to ascertain whether there is pain, muscle weakness, reflex loss, and sensory signs and symptoms. Equally important is the chronological course and pattern in which these signs and symptoms evolve. With focal neuropathies of the lower extremities including disorders of root, plexus,

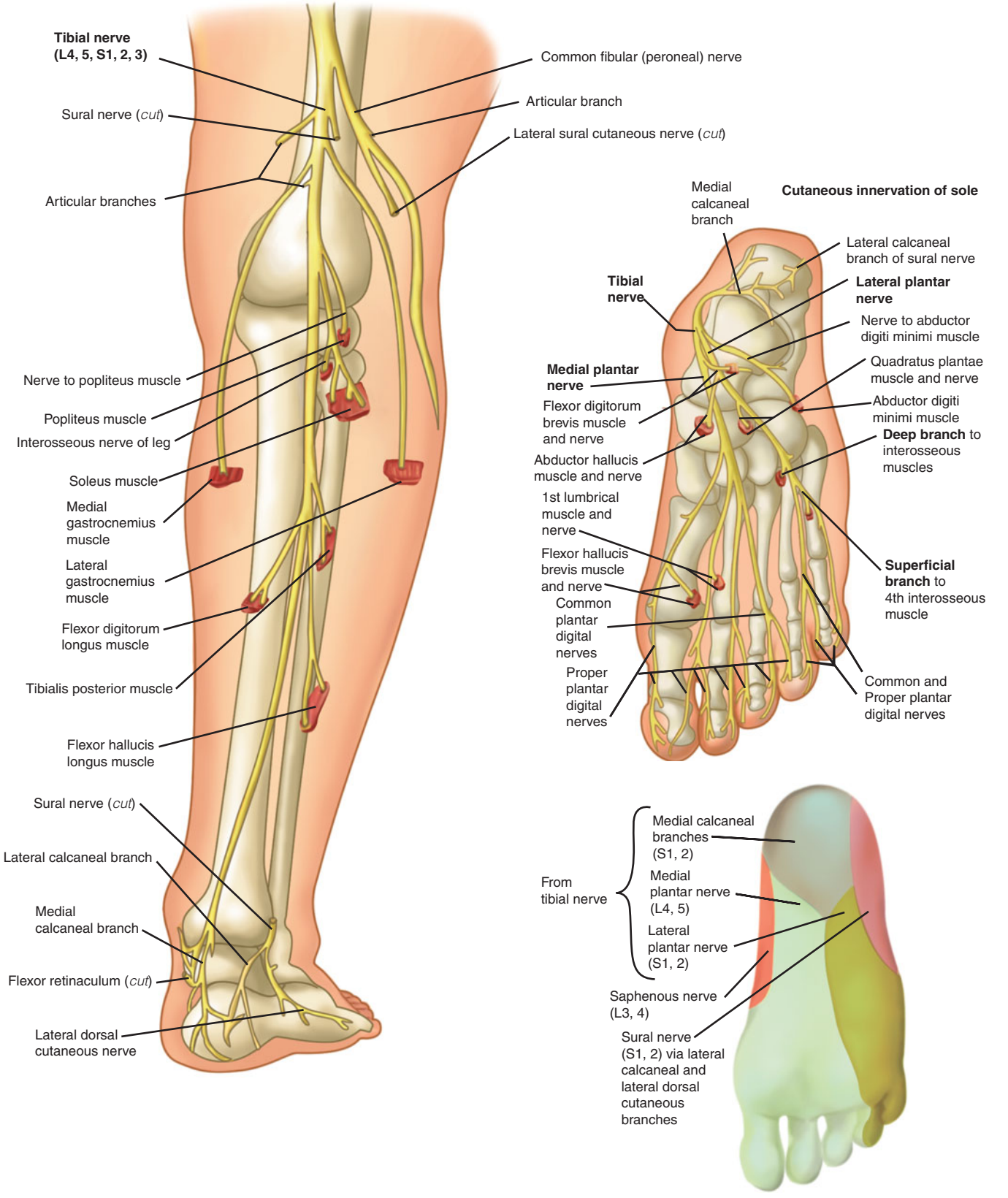

Figure 22–9. Tibial nerve.

and nerve, an attempt is made to identify whether the signs and symptoms are restricted to a single nerve or root. Identifying a plexopathy may be simple, particularly in the brachial plexus, if the pathology is localized to a discreet trunk or cord. More often than not, plexopathies may be patchy or multifocal and therefore difficult to distinguish from a disorder affecting multiple nerves or multiple roots affecting that same extremity. In this case, the clinician needs to rely on a detailed description of the evolution of symptoms, which may shed light on which of these localizations is most likely. The presence or absence of pain, its distribution, and the factors that exacerbate or suppress are integral components of the history as well.

One clinical corollary that follows from knowledge of nerve root anatomy is that pathology of a single nerve root rarely, if ever, produces complete paralysis of any given movement. There are two potential explanations for this. Virtually every muscle receives multiple myotomal innervation. Additionally, most movements receive contributions from multiple muscles, some of which may have differing segmental innervations.

With lower extremity neuropathies, particularly those affecting nerve roots or plexus, the history and examination should include a myriad of components, some of which may not be part of the traditional neurological history or examination. Traditional risk factors including family history of similar disorders, recent illness, surgery, exposures or vaccinations, bleeding diathesis, injury, and immunodeficiency should be explored. Inquiries should be made regarding the presence of constitutional symptoms as a potential indicator of an underlying systemic disease. Prolonged or unusual positioning, particularly in the setting of impaired responsiveness from drug effect or other reasons is of particular note. The history should include enquiries regarding other organ systems in anatomic proximity, including the aorta and great vessels and the gastrointestinal and genitourinary systems. Clinicians should be aware of specific risks associated with obstetrical and surgical procedures. Sciatic neuropathies are a recognized risk of hip surgery, prolonged lithotomy positioning, and misplaced gluteal injections. Prolonged lithotomy positioning appears to be a risk factor for femoral neuropathy and to a lesser extent obturator neuropathy as well. Focal neuropathies occurring in the aftermath of surgery or delivery are commonly assumed to be iatrogenic. In that vein, it is important to consider that an acute lumbosacral plexopathy, analogous to its more frequent upper extremity counterpart, may also occur as postoperative phenomenon unrelated to any iatrogenic influence.

The abdomen should be palpated and ausculted for mass lesions and bruits, respectively. Femoral, popliteal, and pedal pulses should be palpated as well. The back should be observed for midline cutaneous abnormalities that may raise suspicion of underlying myelodysplasia. The spine should be percussed in an attempt to localize bony pathology if back pain is present. A rectal and/or pelvic examination may disclose pelvic pathology responsible for compression or infiltration of plexus elements. A number of positional maneuvers may be used in an attempt to reproduce or exacerbate the pain. Straight leg raising may exacerbate disease of the L5 and S1 roots, the sacral plexus, or the sciatic nerve. Pain is typically experienced between 30° and 70° of elevation in the supine position.[9] Over 70°, the discomfort is more likely to be created by hamstring stretching. Once the patient reacts, flexing the knee without lowering the thigh should relieve the discomfort if it is neurogenic in nature. Another variation of the test is to lower the entire leg a few degrees once the painful angle is identified. At that point, passive dorsiflexion of the foot may recreate the pain without having to raise the leg a second time. Pain in the symptomatic limb may also be reproduced in some individuals by raising the opposite leg. This is thought to be a less sensitive but more specific maneuver. Reverse straight leg raising is used in an attempt to provoke pain originating from the upper lumbar roots. The patient is placed in the prone or lateral recumbent position, and the thigh is extended rather than flexed at the hip. Externally rotating the hip joint while maintaining the knee in a flexed position frequently reproduces pain originating from the hip joint. Radicular pain in some individuals may be reproduced by side bending either toward or away from the symptomatic leg, depending on the vector of disk herniation. In patients with spinal stenosis, it may be possible to obtain a history of improved standing or walking tolerance when the normal lordosis of the lumbar spine is reversed during activities such as walking behind a shopping cart. Unusual reflexes including the cremasteric, anal wink, and internal hamstring may be tested. Surveillance for neurocutaneous stigmata, particularly café-au-lait spots, is important if a nerve sheath tumor is suspected.

▶ SPECIFIC DISORDERS

MONORADICULOPATHIES

Clinical Features

Lumbosacral radiculopathies constitute 62–90% of nerve root disease.[10] As described in Chapter 1, monoradiculopathies are recognized when motor and sensory signs and symptoms, and if relevant reflex loss, develop in the distribution of a single nerve root. Pain is the rule rather than the exception regardless of mechanism, although residual weakness, sensory symptoms, and reflex loss are common after the painful component has resolved. Although back pain often accompanies the pain of nerve root compression, it does not occur in all patients and

may arise from a different pain generator than compression of the nerve root itself, such as the facet joints or other structures innervated by the sinuvertebral nerves. Arguably, lower extremity radicular pain more typically begins in the buttock, not at the back, and follows the course of the afflicted dermatome. It does not necessarily involve the entire length of the dermatome, i.e., it may be localized to buttock and leg without an interval thigh component. It is often aching or lancinating in character. Burning pain is distinctly uncommon. Patients often describe the sense that they may be able to relieve the pain by changing position, usually without complete success. The pain is frequently exacerbated by position as well, with attempted shoe tying being a particularly painful task in many individuals. Tenderness in limb muscles innervated by the involved nerve root may occur.[11] Not all pain radiating into the buttock and thigh originates from nerve root pathology, nor is the location of the pain reliable in defining which nerve root is compromised. The clinician will be most confident that leg pain has a radicular origin when it extends beyond the knee and is associated with paresthesias and objective abnormalities on neurological examination.

The pattern of weakness resulting from a monoradiculopathy is segmental in distribution (Table 22–3). It is a misconception, however, to assume that detectable weakness occurs in all cases of nerve root compression or, for that matter, that every muscle innervated by the affected root will be detectably weak. There are a number of potential explanations for this. Selective involvement of the dorsal root may occur. There may be considerable anatomical variation between individuals, and the majority of muscles are innervated by multiple segments. A muscle that may be weak in the majority of patients with root disease at a specific level may be spared in certain individuals in whom that muscle has limited innervation by the diseased segment. Monoradiculopathies are commonly incomplete lesions. Fibers destined to innervate a specific muscle may be relatively spared. In addition, it is well recognized that a sizeable number of motor units must fail before weakness is clinically detectable. Finally, reinnervation may restore strength in muscles that were previously weak. This is particularly true in the more proximally located muscles innervated by the involved segment.

The evaluation of muscle weakness in the lower extremity differs in comparison to the upper limb. The lower extremity has fewer testable muscles and actions than the upper extremity. For example, there is no pronation or supination at the knee, and the intrinsic foot muscles cannot be tested with the same bedside precision as the intrinsic hand muscles. There is also significant overlap that may occur between nerve and segmental innervation. For example, it may be clinically difficult to distinguish between a femoral neuropathy and an L3–4 radiculopathy, as the primary function of both is to flex the hip and extend the knee. What is advantageous, however, particularly from an electrodiagnostic perspective, is that many myotomes are represented both proximally and distally in the lower extremity. For example, both foot dorsiflexion and hip abduction have strong L5 innervation in most individuals. In contrast, in the upper extremity, all muscles belonging to the same segment tend to cluster at different levels of the upper extremity, e.g., C5 around the shoulder and C8–T1 in the hand.

Paresthesias (i.e., positive sensory symptoms) and, to a lesser extent, numbness (i.e., negative sensory symptoms or sensory loss) are commonplace in monoradiculopathies. As emphasized in Chapter 1, it is important to recognize that the occurrence of paresthesias without demonstrable sensory loss is a common clinical event. It is equally important to realize the clinical significance of dermatomal overlap. The topographical distribution of paresthesias described by the patient and sensory loss that may be demonstrated is far smaller than predicted, based on commonly published dermatomal maps (Fig. 22–10). Paresthesias and sensory loss resulting from a monoradiculopathy commonly persist long after radicular pain and weakness have resolved.

▶ TABLE 22–3. MONORADICULOPATHIES: PATTERNS OF CLINICAL INVOLVEMENT

Nerve Root	Muscle Action Most Commonly Weak	Other Muscle Actions That May Be Weak	Characteristic Areas of Sensory Symptoms/Sensory Loss	Reflex Loss
L2	Hip flexion	NA	Anterior thigh	Cremasteric
L3	Knee extension (one leg partial squat)	Hip flexion and adduction	Medial knee	Quadriceps reflex
L4	Knee extension (one leg partial squat)	Hip flexion and adduction	Medial leg	Quadriceps reflex
L5	Great toe dorsiflexion	Dorsiflexion of digits II–V and foot, ankle inversion and eversion, knee flexion, and hip abduction	Great toe, dorsum of foot, and distal-lateral leg	+/− Internal hamstring
S1	Ankle plantar flexion (one leg rise on ball of foot)	Toe and knee flexion and hip extension	Digits IV and V, lateral foot, and heel and plantar surface	Achilles reflex

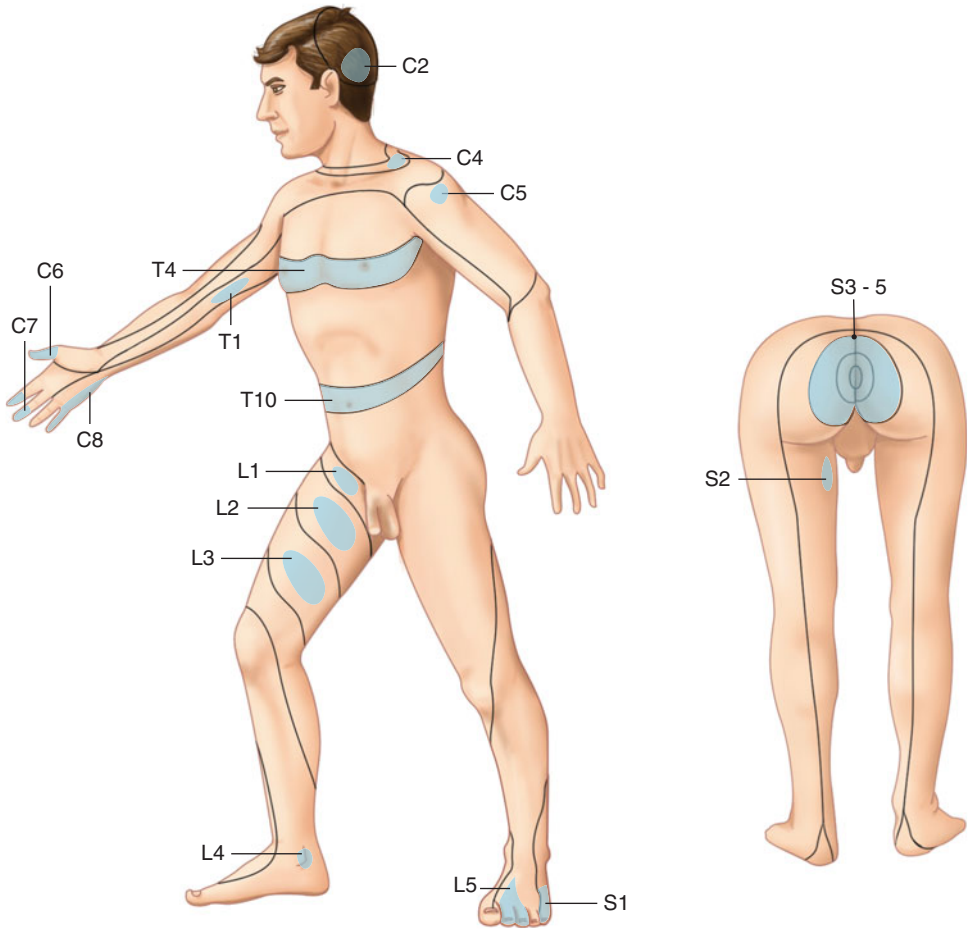

Figure 22–10. Clinical dermatome map.

Suppression of muscle stretch reflexes is a common although not invariable component of a monoradiculopathies. In most instances, only the C6, C7, L3–4, and S1 segments are available for reflex testing. If internal hamstring reflexes are present, asymmetry may aid in the detection of an L5 radiculopathy. This occurs infrequently enough to be of limited benefit. Straight leg raising is a time-honored means by which to reproduce radicular pain in compressive monoradiculopathies due to disk herniations. It is of little or no value in spondylytic disease. A positive sign is nonlocalizing and may occur in disorders affecting the more distal nerve elements of the sacral plexus or sciatic nerve. It is important to distinguish the reproduction of radicular pain from the discomfort of hamstring stretching. Pain occurring at $<70^{\circ}$ is felt to be abnormal and to occur in 90% of patients with disk herniation.[12] Straight leg raising of the contralateral, nonsymptomatic limb that reproduces radicular pain in the symptomatic limb is felt to be a less sensitive and more specific test. In upper lumbar disk disease, pain may be reproduced by reverse straight raising, i.e., by passively extending rather than flexing the thigh at the hip joint.[13] A history of radicular pain (not back pain) produced by increased intrathoracic pressure, e.g., the Valsalva maneuver or cough, is a very specific but insensitive indicator of lumbosacral root compression.

Although classic presentations include "sciatica or radicular pain" accompanied by segmental motor, sensory, and reflex findings, it is important to recognize that variations on this theme do occur. Patients may have either dermatomal sensory symptoms or myotomal motor signs in the absence or relative absence of pain. On occasion, patients will have radicular pain with paresthesia that will abruptly resolve, only to be replaced by weakness in a segmental pattern. It has been hypothesized that this may occur as a result of disk sequestration and migration.[14] The authors' personal observations of this syndrome occurring in the immediate aftermath of spinal manipulation would support this contention.

L1–2

Monoradiculopathies affecting these roots are uncommon and typically present with pain referred into the inguinal region and perhaps the proximal, anterior thigh. Nonetheless, pain in this region is uncommonly

neurogenic in nature. Other than L1–2 radiculopathies, neurogenic pain with this topographic distribution may result from mononeuropathies of the ilioinguinal or genitofemoral nerves. Suspicion of L1 or L2 root disease should prompt an increasing level of suspicion for an etiology different from the customary discogenic/spondylytic causes. Paresthesias occur in the trochanteric and/or upper groin regions in L1 lesions and the anterior thigh in L2. Weakness is uncommon but may be detectable in hip flexion with L2 root disease. The ipsilateral cremasteric reflex may be lost.

L3–4

These lesions have the potential for substantial morbidity if quadriceps weakness occurs. Pain and sensory symptoms (paresthesia and numbness) typically involve the anterior thigh and medial knee. Paresthesias or sensory loss of the medial leg implies that L4 is the affected root. Either lesion may lead to diminished amplitude of the knee jerk and weakness of hip flexion and adduction, and most importantly of knee extension. As the quadriceps is a particularly strong muscle, mild weakness may only be detectable by asking the patient to get up from a chair on one leg at a time without using the arms. Experience would suggest that most nonobese middle-aged or younger individuals are capable of doing this. Many texts suggest that the tibialis anterior receives partial innervation through the L4 segment. In the authors' experience and in the published experience of others, weakness of foot dorsiflexion and denervation of the tibialis anterior rarely occur in documented L4 monoradiculopathies.[15] The differential diagnosis of L3–4 radiculopathy includes femoral mononeuropathies and lumbar plexopathies. Distinction in the former case is usually not difficult due to the clinical weakness and electrodiagnostic denervation in the hip adductors innervated by the L3–4 roots but not by the femoral nerve. The more difficult distinction is from lumbar plexopathies due to diabetes, retroperitoneal pathology, or idiopathic causes, all of which may share a similar pattern of pain, sensory involvement, weakness, and denervation. A combination of imaging of the back and retroperitoneum, EDX, and the clinical contextual features may be required to resolve this differential diagnostic dilemma.

L5

L5 monoradiculopathies are the most common monoradiculopathy of the lower extremity. The pain of an L5 radiculopathy typically extends from buttock to posterolateral thigh to anterolateral leg. Sensory symptoms are felt in the lateral leg, instep, and particularly the big toe. In most people, weakness will be most commonly and readily detected in great toe extension. Weakness of foot dorsiflexion, eversion, and inversion commonly occur as well. Weakness of knee flexion and hip abduction are less frequent and/or more difficult to detect. The differential diagnosis of L5 radiculopathies is essentially the differential diagnosis of foot drop. As many causes of neuropathy, motor neuron disease, and even myopathy have a predilection to affect foot dorsiflexion, this differential diagnosis is expansive. As the most common of these is the common peroneal neuropathy, it is extremely important to assess the strength of ankle inversion. In L5 monoradiculopathies with foot drop, ankle invertors are typically weak, commonly more so than ankle evertors. In contrast, ankle invertors are spared in common peroneal neuropathies, as these muscles are tibial innervated. A diagnosis of L5 monoradiculopathy should be made cautiously in the absence of pain and/or sensory symptoms or when the ipsilateral ankle jerk is depressed. The former raises the possibility of motor neuron disease, rarely myasthenia or distal myopathy if bilateral. The latter may occur in a large disk herniation affecting the S1 root concomitantly but should raise at least the consideration of sciatic neuropathy or sacral plexopathy.

In patients who are very strong or who have potential "giveway" weakness, or with examiners who are weak, potential weakness of foot dorsiflexion should be assessed by watching the patients walk on their heels. Weakness of hip abduction, which receives strong L5 innervation, may occur in severe cases. If reflexes can be elicited from the internal hamstring tendons, ipsilateral loss or depression would provide supportive evidence of an L5 radiculopathy as well.

S1

This is the second most common lower extremity monoradiculopathy. The radicular or "sciatic" pain of S1 root disease typically extends from buttock down the posterior surface of thigh and leg into the heel and at times into the lateral toes. Sensory symptoms are most pronounced in the posterior lateral leg and particularly in the lateral and plantar surfaces of the foot and little toe. Detectable muscle weakness, if present, most commonly occurs in foot plantar flexion. Detection may be once again hampered by the considerable baseline strength of the muscles that contribute to this and other S1 functions including knee flexion and hip extension. Subtle weakness of foot plantar flexion is detected by asking the patients to rise up on their toes while weight bearing on one foot. As this is a test of strength, not balance, the patients should be supported by either their examiner or a nearby wall. Weakness in knee flexion may occur in some cases but may be obscured by the contribution of the semitendinosis and semimembranosis, which receive considerable L5 innervation. Detectable weakness in S1-innervated hip extension is uncommon and is most rigorously tested by having the patient extend the thigh at the hip while in the prone position. A suppressed or absent ankle jerk is expected. The differential diagnosis of an S1 radiculopathy is not as extensive as its L5 counterpart.

TABLE 22–4. MONORADICULOPATHY: ETIOLOGIES

Herniated nucleus pulposis
Spondylitis—osteophytes and hypertrophied ligaments
Nerve sheath tumors
Diabetes (rare)
Herpes zoster

Tibial, sural, and plantar neuropathies are uncommon. Sciatic neuropathies are more common than the previously mentioned mononeuropathies, but the phenotype is typically dominated by deficits arising from its peroneal division. Sacral plexopathies are usually readily distinguished from S1 root disease because of the more widespread pattern of weakness and sensory loss.

Etiologies

Table 22–4 lists the more common causes of monoradiculopathies. Herniation of intervertebral disks causes the vast majority of monoradiculopathies in those <50 years of age. Spondylosis is a far more common cause of root disease in older adults. Typically, the clinical deficits are more evident in a monoradiculopathy caused by disk herniation than in spondylosis, probably due to its relative acuity. Spondylytic disease is typically more insidious in its development and commonly affects multiple levels bilaterally in an older population, a feature that may be evident only through electrodiagnostic evaluation. Contrary to common belief, disk herniations are rarely the result of significant traumas such as motor vehicle accidents. These are more apt to occur from lifting in an awkward position or even more trivial movements.

Alternative causes deserve a higher index of suspicion if a monoradiculopathy evolves rapidly into a polyradiculopathy, or with symptoms suggesting an associated systemic disease. Atypical etiologies of monoradiculopathy are usually disorders that frequently evolve to affect other roots but may begin with preferential involvement of a single root. These disorders will be discussed in the differential diagnosis of polyradiculopathy.

Nerve sheath tumors are perhaps the most common nondiscogenic/spondylytic cause of a persistent monoradiculopathy. Any slowly progressive monoradiculopathy should prompt a careful discussion of family history and search for neurocutaneous stigmata, including subcutaneous and Lisch nodules, café-au-lait spots, and axillary freckles. Diabetes is not commonly considered as a cause of monoradiculopathy, but rare cases probably occur. Herpes zoster, a.k.a. shingles, is a fairly common cause of a dorsal root ganglionopathy, presenting with a vesicular rash in a dermatomal distribution associated with a combination of segmental hypo/hyperesthesia. Less frequently recognized is the syndrome of zoster motor paresis, which is estimated to occur in approximately 5% of patients who are afflicted. In this disorder, the reactivated virus is presumed to migrate in a retrograde fashion to incite an inflammatory, necrotizing lesion of the ventral horn. If this occurs in the lumbosacral region, weakness in muscles innervated by the affected or contiguous myotomes may occur.[15–19]

Evaluation

Imaging and EDX play complementary roles in the evaluation of any focal neuropathy of the lower extremity. There is no universal algorithm for their use. Application depends on a number of variables, including the potential location and etiology of the neuropathy, the bias and experience of the ordering physician, and individual patient characteristics. Imaging provides the potential benefit of identifying disease etiology, something that EDX may imply but rarely accomplishes. Imaging is hampered by the identification of irrelevant anatomic abnormalities that accumulate with age, particularly in the spine; potential focus on the wrong area of involvement; and the inability to identify nonstructural pathologies. EDX, on the other hand, is a physiological test, capable of detecting disordered nerve function in the absence of imaging abnormalities. As in imaging, it frequently detects abnormalities irrelevant to the problem at hand, which may result from a preexisting neuromuscular problem or again be a consequence of the vagaries of aging.

The EDX examination serves to localize the lesion, and characterize the pathophysiology of mononeuropathies, plexopathies, and radiculopathies affecting the lower extremity, has been described in detail in Chapter 2. In general, although demyelinating lesions can be inferred by findings on the needle examination, these can be confidentially documented only if the stimulation and recording sites are on opposite sides of the nerve lesion. Practically speaking, this pertains only to motor nerve conduction studies. For that reason, demyelinating lesions are most readily identified when the pathology is distal to the knee in the lower extremity and then usually only in the peroneal nerve due to technical issues germane to stimulation of the tibial nerve in the popliteal fossa. Demyelinating lesions can also be inferred to exist in a proximal location if either F-wave or H-reflex latencies are significantly prolonged and at the same time distal conduction speed is normal. As prolongation of F and H latencies usually occurs in addition to, rather than instead of, distal conduction slowing, this pattern is uncommonly detected, usually in the setting of early-acquired demyelinating neuropathies such as Guillain–Barré syndrome. Focal nerve lesions restricted to discreet segments of nerve constitute the majority of disorders discussed in this chapter. Even though demyelinating lesions probably occur on a fairly

frequent basis, these are commonly difficult to detect in proximal locations, as any conduction slowing in a discreet segment of nerve will be diluted by the normal conduction over the much longer expanses of nerve studied by either F or H studies. H reflexes have three distinct advantages over F waves. Unlike F waves, particularly with attempted recording from the common peroneal nerve, H reflexes are reliably present in normal, nonsenescent adults. Additionally, H-reflex amplitude as well as latency can be used as a reliable parameter in assessing axon loss within the S1 reflex arc innervating the soleus muscle. Lastly, H reflexes reflect conduction not only in motor fibers also but in sensory fibers, both proximal and distal to the dorsal root ganglion of the S1 root but to some extent within the spinal cord as well.

Sensory nerve conductions are integral to the localization process. These are abnormal in an axon loss process that occurs at or distal to the dorsal root ganglion (e.g., plexus and nerve trunk injury). These are normal in disorders affecting the dorsal root or central nervous system. In normal individuals, SNAPs can be obtained from the superficial peroneal and sural nerves. Although these may be lost in seemingly normal individuals based on age alone, it is the author's experience that they can be reliably obtained in most normal patients <80 years of age. Reduction in the superficial peroneal SNAP indicates for all intents and purposes of axon loss within the superficial or common peroneal nerves, the sciatic nerve, the lumbosacral trunk or lumbar or sacral plexus, or the L5 spinal nerve distal to the dorsal root ganglion. By the same token, reduced sural amplitudes imply axon loss in that nerve, the tibial portion of the sciatic nerve, the sacral plexus, or the S1 spinal nerve. The saphenous nerve is terminal branch of the femoral nerve and is largely composed of L4 fibers in most individuals. Unfortunately, it may be difficult to elicit for technical reasons. If bilaterally absent, no reliable conclusions can be reached. Otherwise unexplained unilateral loss suggests axon loss within the saphenous or femoral nerves, the lumbosacral trunk, or the lumbar plexus. The medial and lateral plantar nerves are mixed nerves, which are terminal branches of the tibial nerve. Their characteristics are similar to the saphenous nerve. These are diagnostically helpful if absent unilaterally.

Amplitudes of compound muscle action potentials (CMAPs) are typically normal in monoradiculopathies but are commonly reduced in polyradiculopathies and plexopathies in the peroneal, tibial, and femoral nerves if studied, femoral nerves in polyradiculopathies and plexopathies. Tibial nerve recordings are typically obtained from the abductor hallucis muscle but are readily obtainable from the abductor digiti quinti and from the soleus during H reflex recordings. Peroneal motor recordings are typically from the EDB and frequently from the tibialis anterior as well. Femoral nerve recordings are not done routinely in most laboratories but may be helpful in certain clinical contexts. Reduced CMAP amplitudes occur, with axon loss occurring anywhere between the appropriate anterior horn cell and the muscle recorded from. In other words, a reduced CMAP amplitude recording from the EDB may occur with motor neuron disease, a lesion of the L5 ventral root, the lumbosacral trunk either the lumbar or sacral plexuses, the sciatic nerve, the common or deep peroneal nerve, a neuromuscular transmission defect, or a loss of muscle in the EDB.

As repeatedly emphasized, denervation in focal lower extremity neuropathies should ideally occur in a pattern consistent with both the nerve structure involved and the affected location within that structure. For example, an axon loss lesion of the common peroneal neuropathy at the fibular head would be expected to produce fibrillation potentials in all peroneal innervated muscles below the knee but spare the short head of the biceps. Denervation of this muscle would be anticipated, however, if the peroneal branch of the sciatic nerve were affected more proximally at the hip. Unfortunately, not all muscles innervated by a given segment are necessarily affected. There may be selective involvement of certain nerve fascicles with denervation of the muscles that affected fascicles innervate with sparing of others. Preferential involvement of the peroneal division in sciatic nerve injuries is the most notable example of this in the lower extremities. In addition, both denervation and reinnervation may affect proximal muscles before distal muscles. Thus, depending on timing of the study, the pattern of denervation may take on a pseudo-length dependency and not correspond to the pattern anticipated by location of the lesion.

Denervation in the paraspinal muscles is anticipated in axon loss lesions affecting anterior horn cells, ventral roots, or primary posterior rami, but not in lesions of the lumbosacral plexus or specific peripheral nerves. Having said that, denervation in the paraspinals is not always demonstrable in root disease. Conversely, it is not specific for root disease, as it may occur in motor neuron disorders, in certain myopathies, following back surgeries, in diabetics, and even in seemingly normal individuals.[6] Denervation occurring in paraspinal muscles without concordant denervation occurring in a myotomal pattern in the affected limb should be interpreted cautiously.

In a patient with a straightforward presentation of an uncomplicated monoradiculopathy, it is reasonable to follow that patient clinically without application of ancillary testing. If patients fail to improve, worsen, or develop symptoms suggesting that their problem may not be diskogenic/spondylytic, imaging should be obtained and is mandatory before any surgical procedure. Magnetic resonance imaging (MRI) is the imaging modality of choice. Typically MR is performed without gadolinium due to little additional diagnostic benefit and the increasing awareness of gadolinium risk. There may be more of a role for gadolinium in patients with persistent or recurrent symptoms following back surgery, in order

to distinguish between fibrosis and recurrent/persistent disk material. Due to the presence of epidural fat in the lumbosacral spine, a natural contrast agent, computerized tomography (CT) has had historical utility in the evaluation of lumbosacral monoradiculopathies. As its resolution is less than either MR or postmyelographic CT, it has a limited contemporary role. There are advocates for CT done following the intrathecal injection of water-soluble contrast agents. Although image resolution is frequently excellent and the opportunity for concomitant cerebrospinal fluid (CSF) analysis is provided, it remains a second-line imaging procedure in large part due to its invasive nature. It is typically performed when MR is not available, is contraindicated, or provides equivocal results in a patient in whom there is a high clinical index of suspicion of root pathology. Although EDX may provide complimentary or confirmatory information, it is often used when imaging results are equivocal or when surgical results are unsatisfactory. One unfortunate limitation of EDX in the assessment of monoradiculopathy has been alluded to previously. A precise correlation between the affected disk space and the involved nerve root does not always occur. As an example, a disk herniation occurring at the L4–5 interspace typically affects the L5 root. If the vector of herniation is far lateral, the L4 root may be preferentially affected. Conversely, a median or paramedian disk herniation may hit the still descending S1–5 roots, producing a mono- or polyradiculopathy. There is a limited role for CSF analysis in patients with single root lesions.

Arguably, imaging plays a greater role than EDX in the evaluation of root disease. Unlike EDX, imaging provides the potential benefit of confirming the existence of a lesion as well as insight into its probable etiology. In general, as the localization of focal neuropathies of the lower extremity become more distal, the role for EDX expands. Part of this is due to the increased EDX accessibility to nerve structures in distal locations. Part of the explanation undoubtedly arises from the increased probability that focal nerve injuries are more likely to result from microscopic as opposed to macroscopic pathologies in distal limb locations. The major danger of imaging is the significant risk of a false-positive result, with the identification of an abnormality unrelated to the patient's symptoms. Clinically silent disk herniations in particular occur with relative frequency.[20,21]

As both imaging and EDX have their limitations, other testing modalities have been applied to patients with focal neuropathies of the lower extremities, particularly those with suspected nerve root disease. Somatosensory-evoked potentials (SEPs) have the theoretical advantage of detecting preganglionic pathology of sensory pathways that routine sensory nerve conduction studies cannot. There are many potential pitfalls. If the pathophysiology is demyelinating, the same problem inherent in H reflexes and F-wave determination occurs. Conduction slowing occurring in a short segment of nerve will be diluted by the necessary inclusion of long segments of normally conducting nerve in the test response. Additionally, unlike nerve conductions where normative data relate to latency measurements over precisely measured segments of nerve, latency measurements in SEPs are very much influenced by the variability of leg length. Although the opposite side can be used as comparison, the potential for bilateral involvement diminishes the utility of this strategy.

Even if axon loss occurs, interpretation may remain difficult. Axon loss determination in sensory nerve fibers is implied by loss of waveform amplitude; SEPs share another shortcoming with F-wave determinations, i.e., amplitude measurements are not reliable. Additionally, SEPs are commonly elicited by stimulating peripheral nerve trunks. As the majority of nerves, e.g., the common peroneal, contain fibers from multiple dermatomes, axon loss of a single root is usually accompanied by normal SEP results.[6,22,23] This is presumably the result of an incomplete lesion or the contributions from other unaffected roots. In an attempt to overcome problems inherent in stimulating nerve trunks to detect monoradiculopathies, SEPs obtained by cutaneous nerve or dermatomal stimulation has been attempted. Reports regarding these techniques have provided disparate conclusions. In general, it is probably accurate to suggest that SEPs done by any technique have a limited role to play in the evaluation of a patient with suspected radiculopathy.

Motor-evoked potentials may be recorded from muscles in response to electrical stimulation of nerve roots, or magnetic stimulation of nerve root or motor cortex. The problems associated with the performance and interpretation of electrical stimulation nerve roots are elaborated upon in Chapter 2. In general, none of these techniques appear to be easy enough to perform or adequately accurate or reproducible enough to warrant their routine use in clinical practice.[6]

The current gold standard for the evaluation of patients with suspected monoradiculopathies of the lower extremities remains anchored to the clinical evaluation supplemented by imaging and/or conventional EDX. The primary goal in developing new testing methodologies is to improve upon the imperfection of current methodologies. Unfortunately, without sensitivities and specificities that reproducibly approach the existing gold standard, confidence in the significance of an isolated test result in any newer testing method must be viewed with suspicion.

Management

Rational management of lumbosacral monoradiculopathies requires an understanding of the natural history of the disease. As mentioned in the previous section, the patient with an unambiguous presentation of a monoradiculopathy can be followed clinically without

additional diagnostic testing. Ancillary testing can be reserved for atypical cases or those who fail to respond to conservative treatment. Long-term follow-up studies suggest that eventual outcome is independent of whether surgical or conservative treatment is applied.[24–26] It is generally suspected that pain relief may be expedited in the short run by surgical intervention. The incidence of chronic pain and neurologic deficit are probably similar in an operated and a nonoperated group. As it is estimated that 60% of patients with symptomatic radiculopathy associated with imaging confirmed disk herniations will respond favorably to bed rest and other conservative measures, the commonly recommended approach is to proceed to laminectomy only in patients with documented, anatomically relevant nerve root compression who are experiencing refractory pain after a reasonable trial of conservative therapy.[27] Each case needs to be considered individually, based on the severity of pain and neurological deficit. At minimum, 2 weeks and preferably 1 month should elapse prior to surgical intervention. The one potential exception to this would be the large midline disk herniation that produces genitourinary dysfunction and bilateral leg weakness. Although there is no evidence basis to support early surgical intervention in this rare situation, it undoubtedly remains the standard of care.

The efficacy of the time-honored treatment of bed rest for acute monoradiculopathies has been called into question.[28] If used, prolonged bed rest may actually have a deleterious effect on functional recovery in comparison to short periods of immobilization.[29] Although physical therapy is frequently used in chronic back and leg pain, its prescription would seem counterintuitive in the acute setting. As inflammation is believed to be at least partly responsible for pain production in nerve root compression, short courses of corticosteroids are used in patients in whom their use is not contraindicated. Although there is evidence suggesting lack of benefit,[30] it provides both a rational and an anecdotally efficacious means of promoting rapid pain relief. A dose of 1 mg/kg of prednisone for 5–7 days followed by a rapid taper over the next week to 10 days is one of the many regimens. Nonsteroidal anti-inflammatory agents are frequently prescribed for this purpose as well. The short-term use of narcotic analgesia is reasonable when required. If this need persists for more than 2 weeks, then alternative etiologies, confounding psychosocial factors, or, in the absence of either, surgical intervention should be considered. Muscle relaxants are of limited utility. Although predominantly of historical interest, chymopapain injections and lumbar traction are mentioned as treatments whose time has come and gone. Epidural steroids have enjoyed recent popularity as a treatment option. Evidence would suggest that short-term pain amelioration may occur as a result of epidural steroid use. There is no evidence that would indicate a benefit in reducing the duration of functional impairment, reduce the need for surgery, or impact pain beyond 3 months.[31,32] Fluoroscopically guided blockade of selective nerve roots with a combination of local anesthetic and steroidal agents has been used, both as a diagnostic and a therapeutic intervention. Its use has been most frequently promoted when clinical, imaging, and electrodiagnostic information are discordant. It is a technique that does not appear to have been universally adopted, in part due to a high incidence of placebo effect.[33]

POLYRADICULOPATHIES

Clinical Features

Polyradiculopathy refers to the signs and symptoms resulting from the simultaneous or sequential injury of multiple nerve roots. The most common cause is spinal stenosis resulting from spondylitic disease or congenital narrowing of the central spinal canal and/or the neural foramina resulting in compression of the cauda equina.[34] The signs and symptoms of spinal stenosis are limited to the back and lower extremities and occasionally to bowel, bladder, and sexual function. Onset is typically insidious and protean in nature with nonspecific low back discomfort and morning stiffness, relieved by activity. The most recognizable symptomatic expression of spinal stenosis is neurogenic claudication. With this syndrome, patients experience pain in their back, buttocks, or legs, often bilateral, provoked by standing and walking. Symptoms are typically diminished by sitting, lying down, or assuming a flexed lumbar posture, which may be accomplished by walking behind a shopping cart or walker. The same mechanism underlying improved stamina may be noted by the relative ease of ascending rather than descending stairs and by endurance while riding an exercise bicycle as opposed to walking. The examination of a patient with symptomatic spinal stenosis is often normal except in severe cases. Straight leg raising does not reproduce symptoms. Although it may be possible to elicit abnormal findings on the neurologic examination after the patient is rendered symptomatic by walking, the yield of this strategy is seemingly low. Although less well recognized and somewhat controversial, it has been suggested that sensory symptoms[35] or even weakness[36] occurring without significant pain may be the dominant initial symptoms of this disorder. The former may mimic a length-dependent polyneuropathy, presumably due to the more successful reinnervation process in proximal limb locations. Paradoxically, unilateral calf hypertrophy has also been reported to occur in lumbosacral spinal stenosis.[37,38] The author's personal experiences would support the validity of all of these seemingly uncommon presentations.

Alternatively, harm to nerve roots may result from meningeal-based pathology, which may not only affect lumbosacral roots, but cervical and thoracic roots and

cranial nerves as well. The majority of these disorders are painful and are commonly associated with systemic disorders that produce constitutional or other symptoms indicative of non-neurological end-organ involvement. These are most readily recognized by the sequential development of motor, sensory, and reflex deficits, which are segmental in their pattern and asymmetric and haphazard in their distribution. Eventually, these deficits may become confluent and with their localization less recognizable unless the history can be recalled in a precise and chronological fashion.

The differential diagnosis of polyradiculopathy includes multifocal neuropathy (a.k.a. multiple mononeuropathies or mononeuritis multiplex), the other neurological localization that may produce a similar pattern of motor, sensory and reflex deficits affecting the lower extremities. Multifocal neuropathies are discussed in Chapters 1, 9, and 13. These are typically caused by disorders that infarct or infiltrate nerves or, alternatively, predispose them to compressive injury. Cranial nerve deficits and pain and sensory symptoms affecting the trunk would favor the diagnosis of polyradiculopathy over multifocal neuropathy, although the clinical distinction is often difficult. Electrodiagnostic or CSF examinations are often required to resolve this diagnostic dilemma. Disorders of the lower spinal cord parenchyma, i.e., the conus medullaris syndrome, may produce motor and sensory deficits in the lower extremities, which appear segmental in nature, in addition to the common and often initial symptoms of bowel, bladder, and sexual dysfunction. For the most part, unlike polyradiculopathy and multifocal neuropathy, signs and symptoms would be expected to remain confined to the lower extremities and genitourinary function. Etiologies of the conus medullaris syndrome usually differ from cauda equina syndrome. Dural vascular malformations,[39–42] and other causes of spinal cord infarction,[43] primary spinal cord tumors such as ependymomas, syringomyelia,[44] inflammatory spinal cord diseases such as multiple sclerosis,[45] and infectious causes such as schistosomiasis[46] may present in this fashion.

Polyradiculoneuropathies are disorders that appear to affect both nerve root and nerve trunk. The acute (Guillain–Barré syndrome) and chronic inflammatory demyelinating polyradiculoneuropathies are the most common cause of this syndrome. As the phenotype typically affects both upper and lower extremities in a symmetric fashion, the phenotype of polyradiculoneuropathy is more in keeping with that of a polyneuropathy than a polyradiculopathy and is therefore considered in more appropriate detail in Chapters 11 and 12.

Etiologies

The potential etiologies of lumbosacral polyradiculopathy are more extensive than monoradiculopathy (Table 22–5).[47] The more notable etiologies will be elaborated on here. Spondylosis producing the syndrome of spinal stenosis is the most common cause of lumbosacral polyradiculopathy, estimated to occur with a prevalence of 5 in every 1000 Americans over the age of 50 years.[28,34,48,49] This same syndrome may be produced by alternative mechanisms including central canal stenosis, which is congenital rather than acquired in nature. Conversely, the syndrome may be created by a normal canal size with enlarged nerve elements. This has been reported to occur with hypertrophic nerve roots in chronic inflammatory demyelinating polyneuropathy and Charcot–Marie–Tooth disease.[50–54] Large, midline disk herniations may produce an acute or subacute cauda equina syndrome but are relatively uncommon due to the protective nature of the posterior longitudinal ligament.

▶ TABLE 22–5. POLYRADICULOPATHY: ETIOLOGIES

Arachnoiditis
Degenerative
Spondylosis (spinal stenosis)
Central disk herniation
Epidural lipomatosis
Diabetes (polyradiculoplexus neuropathy)
Iatrogenic (epidural and caudal anesthesia)
Ischemic
Dural vascular malformations
Spinal cord infarction
Nonsystemic vasculitic neuropathy
Infectious
CMV
HIV (CMV, herpes simplex, syphilis, *Cryptococcus*, and atypical mycobacteria)
Lyme disease
Schistosomiasis
Spinal epidural abscess
Inflammatory
Sarcoidosis
Neoplastic
Meningitis
Primary spinal cord tumors—ependymomas, lipomas, dermoid, epidermoid, hemangioblastoma, paraganglioma, and ganglioneuroma
Primary nerve sheath tumors—neurofibromas and schwannomas
Primary vertebral tumors—cordomas, multiple myeloma, and osteoma
Primary paravertebral tumors—lymphomas
Metastatic vertebral tumors—breast, lung, and prostate
Intravascular tumor—lymphoma
Osseous
Paget disease
Inflammatory spondyloarthropathies, e.g., ankylosing spondylitis
Radiation

CMV, cytomegalovirus.

Spinal epidural abscess may present as a monoradiculopathy evolving into polyradiculopathy.[55–60] Suspicion should be heightened in context of fever or other constitutional symptoms, intravenous drug abuse or indwelling catheters, percussion tenderness of the spine, or recent bacteremia. Either primary or metastatic tumors with an affinity for the lumbosacral spine, the paravertebral lymph nodes, or meninges should be considered with prominent back pain, which dramatically worsens at night or persists unabated in the supine position.

Chordomas and myeloma are examples of primary tumors of the vertebral spine, which may produce a cauda equina syndrome through a compression mechanism. Prostate, breast, and lung cancer are the more common causes of tumors with an affinity to metastasize to bone. Metastatic disease to the lumbosacral spine is estimated to account for <1% of patients with low back pain. Back pain as a presenting feature of an occult malignancy is even rarer. Vertebral metastases occur in the lumbosacral region in approximately 30% of the time.[61] Primary tumors with an affinity for cauda equina include schwannomas,[62] ependymomas, neurofibromas, meningiomas, lipomas, hemangioblastomas, or dermoid tumors. Polyradiculopathy can also occur as a manifestation of occult myelodysplasia. It has been reported to occur in association with epidural lipomatosis.[63]

A number of malignancies have a predilection for meninges and are capable of producing a polyradiculopathy via invasion and/or encasement of nerve roots (and/or cranial nerves). Leukemia, non-Hodgkin lymphoma, breast, lung, melanoma, and gastroesophageal malignancies are the most common underlying tumors. Usually painful, sequential nerve root lesions affecting arms, trunk, and cranial nerves in addition to lumbosacral roots are the characteristic signature of this disorder. A coexisting encephalopathy due to obstructive hydrocephalus or direct cerebral infiltration may coexist.[64–67]

Arachnoiditis is a nonspecific syndrome in which the arachnoid becomes thickened, scarred, and adherent. The cauda equina may be adversely affected due to the direct effects of "strangulation" or indirectly by obliteration of its blood supply. Historically, the syndrome was most closely linked to use of myelographic contrast agents. With the development of water-soluble contrast agents, and the declining use of myelographic examinations, the incidence of arachnoiditis not caused by more specific disease processes discussed in this section is undoubtedly diminished. Arachnoiditis may also be caused as an unintended consequence of intended intrathecal injection of therapeutic agents, e.g., chemotherapy, or the unintended intrathecal injection of agents that are potentially toxic.

Diabetes is a common cause of lower extremity pain and weakness. It is currently considered to be a radiculoplexus neuropathy, based on pathological and electrodiagnostic data. It will be discussed in detail as a plexopathy as well as in Chapter 19.

Dural malformations commonly present with the stepwise progression of lower extremity sensory and motor signs and symptoms, with or without signs and symptoms of genitourinary tract involvement.[39–42,68] Technically, it should be classified as a myeloradiculopathy, as both spinal cord parenchyma and nerve root are vulnerable to the ischemic changes, which is probably the major pathophysiology of this disorder. Symptoms may initiate with some traumatic event and may be noted to intensify with either the upright position or the Valsalva maneuver. Approximately half of patients who are afflicted will have a significant painful component. Although anatomically a myelopathy in which both lower and upper motor neuron features are clinically apparent, approximately 30% of patients with dural malformations are estimated to have motor features that are predominantly or exclusively lower motor neuron in characteristic. As a result, if imaging focuses on the lower lumbar spine and excludes the spinal cord, the unwary physician may overemphasize the significance of asymptomatic spondylytic change, leading potentially to unnecessary lumbar laminectomy. At times, the sensory signs and symptoms created by dural malformations are minor and may be overlooked. In this situation, both the clinical and the electrodiagnostic patterns may suggest motor neuron disease. Abnormalities in the H reflex, which may occur in dural malformations, are a potentially helpful means to distinguish these disorders.[39,40,47,69] Spinal cord infarction from whatever cause, technically a conus rather than cauda disorder, may mimic a lumbosacral polyradiculopathy, particularly from an electrodiagnostic perspective.[70,71]

Radiation may result in a neuropathy affecting the lower extremities.[72–80] Its onset is typically delayed. It most commonly occurs in the context of treatment of testicular cancer or lymphoma. Radiation doses typically exceed 4000 cGY. The latency between radiation and onset of symptoms averages 6 years. The range, however, is exceedingly broad, with onset latency varying between 4 months and 25 years. As postirradiation neuropathy is frequently a pure motor syndrome, the actual localization of nerve injury has been in dispute. Less than a third of patients have notable sensory symptoms or signs. Whether the pathology preferentially occurs in the anterior horn cells of the conus medullaris, the ventral roots, the lumbosacral plexus, or a combination of any of the aforementioned elements is uncertain.[73] Current evidence, including reports of root enhancement on MR imaging in some patients, favors a polyradiculopathic localization.[72,73,81,82] Typically the deficits are bilateral and asymmetric, although monomelic presentations do occur.[76] Any segment may be affected, with L5 and S1 deficits being the most frequent. Pain may occur but typically follows the development of weakness

and is usually not a major issue. Nodular enhancement of nerve roots and the conus medullaris with MR imaging resulting from radiation effect have been reported.[83] Understandable confusion with polyradiculopathy secondary to neoplastic meningitis will occur under this circumstance.

Polyradiculopathy is one of numerous HIV-related neurological syndromes.[84] It is estimated to affect approximately 2% of patients who are infected, typically patients with established acquired immunodeficiency syndrome (AIDS) and CD4 counts <100 cell/μL. It may present as a pure motor syndrome.[85] Polyradiculopathy may also result from infections with cytomegalovirus, herpes simplex, atypical mycobacteria, *Cryptococcus*, and treponemal agents in this patient population as well as with lymphoma.[86–89]

Polyradiculopathy is one of the more common neurological manifestations of Lyme disease, affecting approximately half of the patients with peripheral nerve involvement.[90] Dermatomal sensory loss and pain are the most common symptoms. Segmental weakness occurs commonly but is less prevalent. It typically occurs within days to weeks of the characteristic rash, seemingly linked to the hematogenous dissemination of the organism. In addition to the meninges and nerve roots, joints, peripheral nerves, and the cardiac conduction system seem to be the end organs at particular risk. Potential or known exposure risk to the transmitting *Ixodes* tick species, seasonal predilection, prior rash, arthralgias, trunkal pain secondary to thoracic and upper abdominal root involvement, and facial palsy are helpful diagnostic clues.[91,92]

Sarcoidosis has a diverse phenotypic spectrum that includes peripheral and central nervous system manifestations. It is estimated that 5% of individuals with sarcoidosis will have symptomatic nervous system involvement. The majority of texts and review articles imply that neurosarcoidosis is a rare presenting manifestation of the disease. This may be true from the perspective of a generalist but differs from the authors' perspective. In one series of sarcoidosis associated with a focal neuropathy, polyradiculopathy was the most common pattern affecting 22 of 57 reported patients.[93] Other neuropathic patterns that may result from sarcoidosis include a radiculoplexus neuropathy, a multifocal neuropathy, or a length-dependent polyneuropathy. The cauda equina, in particular, seems to be at risk.[94,95] Pain and sensory symptoms occur more frequently than motor signs in most cases, being typically multifocal and non-length dependent in distribution and monophasic in their chronological course. Constitutional symptoms as well as symptoms referable to other end organs frequently affected by this disease are commonplace.

Polyradiculopathy has also been reported as an iatrogenic complication of epidural injections for both analgesic and anesthetic purposes.[96,97] Patients with preexisting spinal stenosis would appear to be at greater risk of this apparently rare and unintended consequence of a common procedure. Although systemic and nonsystemic vasculitic neuropathies are most closely aligned with a multifocal neuropathy phenotype, the latter has been reported to present with a polyradiculopathy phenotype.[98]

Evaluation

In patients with suspected polyradiculopathy, the evaluation proceeds based on the weighting of the differential diagnosis. When polyradiculopathy occurs in the setting of neurogenic claudication, MR imaging and postmyelographic CT are both excellent tests. EMG may be useful in suspected polyradiculopathy in determining that back and leg pain are neurogenic in nature, to identify its polyradicular nature, and to aid in the assessment of both disease acuity and severity. With spinal stenosis, EDX may be normal or may display a common pattern of predominantly chronic denervation occurring in a bilateral, polysegmental distribution, with changes of active denervation confined to distal muscles. This pattern has been estimated to occur in approximately half of patients with anatomically documented spinal stenosis associated with the clinical syndrome of neurogenic claudication.[6] As the EDX pattern of early motor neuron disease restricted to the legs may be similar to that described above, a diagnosis of polyradiculopathy should be offered cautiously in a patient without pain or sensory symptoms. If chronic meningitis is suspected, CSF analysis is indicated. Testing for causes of chronic meningitis due to neoplasm, sarcoidosis, Lyme disease, viral agents such as cytomegalovirus, and fungal and acid-fast microorganisms should be considered. HIV testing should be considered with suggestion or evidence of unusual central nervous system infections. Although lesions intrinsic to the conus medullaris are uncommon, these have considerable clinical overlap with polyradiculopathy. If a conus lesion is suspected, MRI should be performed as it is the best way to detect neoplastic, inflammatory, ischemic, or structural changes within the spinal cord. The diagnosis of spinal dural arteriovenous fistulas requires a high index of suspicion. The most common, although nonspecific, abnormality is a spinal cord that is swollen, with increased signal characteristics over multiple segments on T2-weighted MR images. A more specific, although less commonly seen, feature is the presence of serpiginous flow voids representing engorged venous structures typically located dorsal to the spinal cord.

Management

Optimal management of spinal stenosis in a given patient is hampered by the lack of knowledge of the natural history of the disorder. The current weight of evidence favors but does not mandate an operative approach. In the

majority of cases, there is no urgency to intervene and an initial conservative course is reasonable, particularly in patients with minimal clinical deficits.[34] Spinal dural arteriovenous fistulas are typically managed by a combination of selective catheterization and embolization of feeding arterial structures and surgical decompression, assuming that the diagnosis is made prior to complete and permanent ischemic injury to the spinal cord. As it is associated with abnormal CSF findings, current recommendations for the treatment of Lyme polyradiculopathy are to treat with parenteral antibiotics, typically a cephalosporin.[91,92] Symptomatic sarcoidosis is typically treated with corticosteroids or other immunomodulating agents. Neoplastic meningitis may be treated with local radiation of intrathecal chemotherapy, depending on patient attitude, disease burden, and current quality of life. Specific treatment regimens for the differing infectious causes of polyradiculopathy are beyond the scope of this text.

PLEXOPATHIES

Clinical Features

Plexopathies are typically recognized when motor, sensory, and, if applicable, reflex deficits occur in multiple nerve and segmental distributions confined to one extremity. This is particularly true if deficits can be localized to a single plexus segment, although discrete plexus lesions are not particularly common and are more difficult to sort out in the lumbosacral plexus than in its brachial counterpart. If localization within the lumbosacral plexus can be accomplished, designation as a lumbar plexopathy, a sacral plexopathy, a lumbosacral trunk lesion, or a pan-plexopathy is the best localization that can be expected. Although lumbar plexopathies may be bilateral, usually occurring in a stepwise and chronologically dissociated manner, sacral plexopathies are more likely to behave in this manner due to their closer anatomic proximity.

The differential diagnosis of plexopathy includes disorders of the conus medullaris and cauda equina (polyradiculopathy). If there is a paucity of pain and sensory involvement, motor neuron disease needs to be considered as well. In general, intraspinal causes of lower extremity neuropathy are more likely to be bilateral than causes of lumbosacral plexopathy. Exceptions are frequent enough, however, to diminish the value of this rule in the evaluation of the individual patient. When the differential diagnosis of plexopathy includes a direct neoplastic effect vs. the adverse effects of radiation, pain as an initial symptom and unilaterality favor a direct neoplastic effect whereas an insidious onset of painless weakness suggest radiation injury.[79]

▶ TABLE 22–6. PLEXOPATHIES: ETIOLOGIES

Retroperitoneal hematoma
Psoas abscess
Malignant neoplasm
Benign neoplasm
Radiation
Amyloid
Diabetic radiculoplexus neuropathy
Idiopathic radiculoplexus neuropathy
Sarcoidosis
Aortic occlusion/surgery
Lithotomy positioning
Hip arthroplasty
Pelvic fracture
Obstetric injury

Etiologies

The numerous causes of lumbosacral plexopathies are listed in Table 22–6. Diabetic radiculoplexus neuropathy is a fairly common cause of painful leg weakness. It has been historically referred to by a considerable number of names, including diabetic amyotrophy, diabetic femoral neuropathy, and the Bruns–Garland syndrome.[99–102] Although there may be considerable variation in the phenotype, almost all individuals who are affected experience severe hip and/or thigh pain as their initial symptom, followed within days by awareness of unilateral leg weakness. Adjectives such as aching, stabbing, lancinating, and burning have all been used. The exact onset of weakness may be obscured by the severity of pain. It typically is recognized and evolves over days to weeks and becomes bilateral in a substantial proportion of individuals who are affected within a matter of months. This weakness dominates in the distribution of the lumbar plexus affecting hip flexion, adduction, and particularly knee extension. The latter can be exceedingly debilitating, and the need for durable equipment to prevent falls is quite prevalent. Two-thirds of individuals will have weakness in the L5 myotome and half in the S1 dermatome in addition to the muscles innervated by the L2–4 roots.[103] Rarely, L5 and S1 myotomal weakness may occur without concomitant involvement of proximal myotomes. The reference to diabetic monoradiculopathies earlier in this chapter probably represents a limited expression of this disorder. Paresthesias and sensory loss may occur but are typically overshadowed by the pain and weakness. A small percentage will have a concurrent or chronologically proximate trunkal neuropathy, which is a helpful clue in support of a diabetic etiology. Weight loss, so-called diabetic cachexia, is a common comorbidity. Approximately a half of individuals who are afflicted will have signs and symptoms attributable to dysautonomia if sought after, including orthostatic intolerance, urinary dysfunction, constipation and diarrhea,

tachycardia, and impotence.[101] Concurrent, sensory predominant, length-dependent, and symmetric polyneuropathy occurs in the majority of patients based on clinical and EDX assessments but may be absent in approximately a quarter of patients.[103]

As in other focal diabetic neuropathy phenotypes, diabetic radiculoplexus neuropathy, in comparison to the symmetric neuropathy phenotypes, is not as clearly related to disease duration or control and appears to have a more favorable natural history.[102,104] Pain typically relents within weeks to months. Eventual improvement in strength and significant functional recovery occur in many patients over the course of 1–3 years. As in most neuropathies in which proximal and distal muscle weakness occurs, successful recovery is more likely in proximal muscles.

The mechanisms of diabetic neuropathy are hypothesized to evolve from the consequences of deranged glucose metabolism and/or the hypoxic/ischemic effects of disordered nerve microvasculature. In this disorder, current thinking favors an ischemic mechanism. Evidence of microvasculitis including epineurial and perivascular inflammation and multifocal fiber loss on nerve biopsy are common pathological features.[101,105]

A similar, perhaps identical, phenotype has been described as an idiopathic condition.[69,102,106–110] Again, the lumbar plexus appears to be predominantly affected in most cases, although both sacral plexopathies and pan-plexopathies may occur as well. As in its diabetic counterpart, delayed involvement of the opposite side may occur. The disorder is also monophasic in most individuals but can be relapsing or progressive in some.[108,111] As in its brachial plexus analog, an antecedent immunization or symptoms of infection may occur. This phenomenon appears to be more common in children than in adults.[110] In the past decade, a number of authors have suggested that the incidence of impaired glucose tolerance without overt diabetes is significantly greater in patients with burning feet and suspected length-dependent small fiber polyneuropathy in comparison to aged-matched controls.[112] Along those same lines, one recent report found impaired glucose tolerance in approximately two-thirds of individuals with apparent idiopathic lumbosacral plexopathy.[104] In addition, nerve pathology in diabetic and nondiabetic radiculoplexus neuropathy appears to be similar if not identical, lending further support to the hypothesis that these represent a singular disorder.[107]

Acute lower extremity monoplegia has been reported as a rare presenting manifestation of acute aortic occlusion.[113] The localization of nerve injury in this condition may be at the level of the conus medullaris, cauda equina, lumbosacral plexus, proximal nerve trunks, or combination thereof. It is classified here as a plexopathy as the phenotype that it most closely approximates.[43]

Lumbosacral plexopathies are a well-recognized complication of retroperitoneal hemorrhage.[114,115] Various primary and metastatic malignancies can affect the lumbosacral plexus as well as treatment with radiation and interarterial chemotherapy.[78] Reported tumor types include carcinoma of the cervix, endometrium and ovary, osteosarcoma, testicular cancer, multiple myeloma, lymphoma, acute myelogenous leukemia, colon cancer, multiple myeloma, squamous cell carcinoma of the rectum, adenocarcinoma of unknown origin,[79,116,117] and intraneural spread of prostate cancer.[118] Radiation, particularly for cervical and endometrial malignancies, may produce a plexopathy with a predilection for the lumbar plexus.[74,79,116,119] Other reported etiologies include psoas abscess, intraneural spread of amyloid,[120] pelvic fracture,[121] benign tumors such uterine leiomyoma,[122] sarcoidosis,[123] lithotomy positioning,[124] and hip arthroplasty.[125] Obstetrical injury often associates with a phenotype that approximates a lumbosacral trunk injury, both clinically and electrically.[126,127] Woman of short stature seem to be at increased risk.

Evaluation

Arguably, most patients with plexopathies will undergo both imaging and EDX evaluations. Again, MR imaging has become the modality of choice. Its resolution is in general superior to CT, and it provides the added benefit of viewing the area of interest in three planes. The value of gadolinium is dependent on the nature of the pathology. Gadolinium may be required to detect focal nerve inflammation in immune-mediated neuropathies or nerve sheath tumors. Enhancement of the lumbosacral plexus in idiopathic lumbosacral radiculoplexus neuropathy has been reported to occur with gadolinium-enhanced MR imaging.[128]

The EDX signature of sacral plexopathies may be strikingly similar to that of a sciatic neuropathy.[129] Similar abnormalities of sensory and motor nerve conductions may be seen as well as the pattern of denervation. Needle examination of muscles innervated by the superior and inferior gluteal nerves is critical in this discrimination. Abnormalities of these muscles would be expected in a sacral plexopathy but unexpected in an otherwise uncomplicated sciatic neuropathy.

Diabetic radiculoplexus neuropathy is thought to affect nerve root, plexus, and peripheral nerve trunk in view of reported pathological, EDX, and CSF findings. Paraspinal denervation is commonplace in both the diabetic and the idiopathic forms of radiculoplexus neuropathy, suggesting denervation occurring at the level of the primary posterior ramus, anterior horn, or presumably ventral root level.[100,110] Elevation in CSF protein levels are also commonplace in diabetic radiculoplexus neuropathy and occur in the idiopathic form as

well, further supporting nerve root involvement.[102,109] By the same token, asymmetric reduction of lower extremity SNAP amplitudes is typical, thereby implicating axon loss distal to the dorsal root ganglion either in the plexus or in the distal nerve trunks. Additionally, nerve biopsy changes in sensory nerve specimens obtained below the knee provide support for more distal nerve trunk involvement.[102] Although EDX is routinely performed in patients with a radiculoplexus neuropathy phenotype, nerve biopsy is not. Nerve biopsy is typically undertaken when clinical or imaging features suggest an increased probability of nerve infiltration by lymphoma, sarcoid or amyloid, infarction from vasculitis, or other pathology in which nerve biopsy might be diagnostic. CSF examination on the other hand is commonly performed to exclude causes of the infectious, inflammatory and neoplastic causes of chronic meningitis, and associated polyradiculopathy.

Both the EDX and, if performed, nerve biopsy results are essentially identical in idiopathic lumbosacral plexopathy, in comparison to those identified in a diabetic cohort.[102] For these reasons, if an idiopathic plexopathy is to remain as a distinct nosologic entity, it would be appropriate to refer to it as an idiopathic lumbosacral radiculoplexus neuropathy.

Management

There are no known effective treatments for either the idiopathic or the diabetic forms of lumbosacral radiculoplexus neuropathy. Various immunomodulating agents such as corticosteroids, intravenous immunoglobulin (IVIG), plasma exchange, and cyclophosphamide have been used both in diabetic and in idiopathic forms of radiculoplexus neuropathy.[102,110,130] A suggested benefit has been achieved with a number of these small case series. The effects of both intravenous methylprednisolone and intravenous immunoglobulin are being studied in prospective trials in patients with diabetic radiculoplexus neuropathy. Case reports suggest a benefit of IVIG in idiopathic lumbosacral radiculoplexus neuropathy.[131] If any treatment is to be used prior to proof of efficacy, it is suggested that it be used early in the clinical course.

There is no adequate evidence basis by which to decide whether plexopathies associated with retroperitoneal hemorrhage fare better with surgical evacuation as opposed to conservative management consisting of reversal of anticoagulation. If surgery is to be done, it is rational to do it expeditiously rather than on a delayed basis after axon loss is more likely to have occurred.

The goals of symptomatic treatment in this and other paralyzing disorders are to assuage pain and to promote independent ambulation and mobility without compromising safety. There is no universally effective or single recommended analgesic agent. Tricyclic and selective noradrenergic and serotonergic antidepressant agents such as venlafaxine and duloxetine, gabapentin and pregabalin, and, if necessary, narcotics have all enjoyed anecdotal success in some patients. Their prescription is usually necessary for 3 months or less. Durable medical equipment is frequently required. Single or multiple point canes, crutches, walkers, or wheelchairs are recommended depending on the severity of weakness and other variables such as arm strength and premorbid balance. Patients are often reluctant to accept these. Portraying these devices as opportunities rather than setbacks, analogous to the benefits of eye glasses, may be a helpful strategy in improving acceptance and compliance rates.

Knee braces, i.e., knee–ankle–foot orthoses were historically prescribed on a limited basis. The benefit provided is that the drop lock hinge at the knee joint prevented unexpected knee "buckling" and resultant falls every time the patients inadvertently placed their weight on a knee joint that was not fully locked and extended. Drawbacks include the weight of the orthosis, the difficulty involved in getting the brace on and off, and the not so aesthetic appeal of an appliance that extends from upper thigh to ankle. In addition, sitting requires the cumbersome act of manually unlocking the hinge. Even more troublesome is the risk of more severe injury that could occur if the patient did fall with the drop lock in place resulting in a patient "falling over" rather than "falling down" in a more controlled and less injurious fashion. Recently, a more technologically advanced hinge with a mercury switch has been developed, which prevents unwanted knee buckling while at the same time allowing the knee to flex while sitting without the delay or nuisance of manual intervention.

MONONEUROPATHIES

Clinical Features

Mononeuropathies are usually the result of compression (an unnaturally occurring force originating outside the body), entrapment (a force occurring inside the body generated by the altered anatomy of a normal structure), or direct trauma from stretch, laceration, or percussion. Rarely, these are caused by systemic disorders, which provide the opportunity for the nerve to be infiltrated or infracted. Hereditary conditions such as the hereditary liability to pressure palsy, diabetes, and perhaps previous radiation therapy make peripheral nerves more vulnerable to compressive nerve injury. Compression and entrapment syndromes are far less common in the lower extremity than in the upper, with only the peroneal nerve at the fibular head and the lateral femoral cutaneous nerve at the anterior superior iliac spine occurring with any frequency.

The sensory symptoms/deficits of a mononeuropathy conform to the topographical distribution of that

nerve assuming that nerve is not purely motor in its constituency. When present, motor deficits theoretically involve all muscles innervated by that nerve, beyond the point where that nerve is damaged. As previously mentioned, nerve injuries are frequently partial. That, and the principle of selective fascicular involvement, may result in a pattern of weakness that is not as fully developed as would be anticipated based on the location of nerve injury. This is particularly the case with bedside examinations, providing yet another potential benefit of EDX. This test may identify denervation in muscles in which clinical weakness may not be evident. In any given mononeuropathy syndrome, motor or sensory deficits may dominate. This is understandable when the affected nerve is purely sensory (lateral femoral cutaneous nerve) or predominantly motor (deep peroneal). At times, mononeuropathies affecting nerves that contain ample populations of motor and sensory fibers may have a phenotype dominated by dysfunction by one or the other. For example, it is not uncommon for common peroneal neuropathies to present as a painless foot drop with minimal sensory signs and symptoms. The pathophysiology of the nerve lesion, i.e., whether it is predominantly axonal or demyelinating, may have some influence on this.

It has been hypothesized that otherwise unexplained mononeuropathies in the upper extremity, of acute to subacute onset, may represent a forme fruste of acute brachial plexus neuritis. It has also been suggested that a similar relationship may exist in the lower extremities where an acute, idiopathic mononeuropathy may be what, in essence, a limited form of idiopathic lumbosacral neuritis.[110]

Etiologies and Clinical Recognition of Individual Mononeuropathies

Table 22–7 provides a list of many of the reported causes of the more common mononeuropathies of the lower extremity. Iliohypogastric neuropathies typically result from surgery in the lower quadrants including appendectomy and nephrectomy or from pathology in the retroperitoneum. Recognition is based on sensory complaints in the appropriate topographic areas, along the superior iliac crest at the posterior axillary line and a second small patch above the symphysis pubis. At times, injury is accompanied by "neuralgic" pain in the groin. Paresis in the ipsilateral lower abdominal musculature may be demonstrable.

Ilioinguinal neuropathies occur more frequently than their iliohypogastric counterparts and usually have a far greater clinical consequence. Their prevalence probably relates to the frequency of potentially causative surgical procedures. Herniorraphies are the most notorious. Suprapubic (Pfannenstiel), nephrectomy, and appendectomy incisions may cause this injury as well. Ilioinguinal neuropathies have also been rarely described as a complication of partuition, bone harvesting from the iliac crest, and an abdominal wall entrapment syndrome. The ilioinguinal nerve provides cutaneous innervation to the skin overlying the inguinal ligament extending to the base of penis. As in the iliohypogastric nerve, it also provides motor branches to the transverse abdominus and internal oblique muscles of the lower abdominal wall. The clinical consequences include both sensory loss and hyperesthesia in the aforementioned territories and, potentially, weakness of lower abdominal wall musculature. In addition, ilioinguinal neuropathies are frequently painful, with the discomfort being relieved by hip flexion and aggravated by walking and hip extension. As a result, patients often maintain a flexed posture while walking.

Genitofemoral neuropathies typically result from surgical procedures such as herniorraphies or appendectomies. These have been reported to occur with psoas abscess. The phenotype usually consists of sensory complaints in medial groin, exacerbated by standing or hip extension. The loss of the cremasteric reflex on the symptomatic side provides diagnostic support but inexplicably is not invariably lost with injuries to this nerve.

The superior and inferior gluteal nerves are virtually never affected in isolation. There have been reports of superior gluteal nerve injuries in response to injection injuries and inferior gluteal nerve injuries with pelvic malignancy. The latter usually occurs with concurrent injury to the sciatic nerve, pudendal nerve, and/or posterior cutaneous nerve of the thigh. Posterior cutaneous nerve of the thigh injuries has been reported to occur with injection injuries, lacerations, and prolonged bike riding. Recognition is based on sensory complaints/loss of the posterior thigh and inferior buttock. An intermittent neuralgia of this nerve has been reported.[132]

Meralgia paresthetica refers to a mononeuropathy of lateral cutaneous nerve of the thigh.[133] Of historical note, Sigmund Freud is one of the first known patients, credited with the description of this syndrome in himself.[134] This disorder has been most commonly attributed to entrapment of or injury to the nerve as it passes through the lateral portion of the inguinal ligament, just medial to the anterior superior iliac spine. The disorder seems to be most commonly idiopathic. Identifiable causes that have been reported include retrocecal appendectomy, hip surgery, cesarean section, pelvic fracture, and aortobifemoral bypass grafting. As in other compression or entrapment mononeuropathies, patients with diabetes may be overrepresented, although only four patients with diabetes were represented in one series of 120 patients.[133] Obesity is commonly listed as a risk factor, but only 25% of patients in this same series were considered to have an endomorphic body habitus. In addition, the disorder is frequently unilateral, which is seemingly discordant with a theory that involves obesity.

▶ TABLE 22–7. MONONEUROPATHIES: ETIOLOGIES

- Iliohypogastric
  - Lower quadrant surgery—appendectomy and nephrectomy
  - Retroperitoneal tumor
- Ilioinguinal
  - Surgery—herniorraphies, suprapubic (Pfannenstiel), nephrectomy, and appendectomy incisions
  - Partuition
  - Bone harvesting from the iliac crest
  - ? Abdominal wall entrapment syndrome
- Genitofemoral
  - Surgery—herniorraphy and appendectomy
  - Psoas abscess
- Obturator
  - Tumor—transitional cell carcinoma of the bladder, cervical carcinoma, lymphoma, prostatic carcinoma and sarcoma, histologically undefinable
  - Partuition
  - Prolonged lithotomy position
  - Hip arthroplasty
  - Surgical tourniquets
  - Myositis ossifications
  - Obturator hernias
  - Pelvic surgery including those done laparoscopically
  - Pelvic fracture
- Femoral
  - Retroperitoneal or iliacus hematoma
  - Lithotomy positioning
  - Hip arthroplasty or dislocation
  - Iliac artery occlusion
  - Femoral arterial procedures—diagnostic or therapeutic
  - Femoral artery aneurysms or pseudoaneuryms
  - Infiltration by hematogenous malignancies
  - Penetrating groin trauma
  - Pelvic surgery
  - Idiopathic
  - Mechanical pressure clamp on the femoral artery
- Lateral cutaneous nerve of the thigh
  - Meralgia paresthetica
  - Bone graft harvesting
  - Retrocecal appendectomy
  - Hip arthroplasty
  - Cesarean section
  - Pelvic fracture
  - Aortobifemoral bypass surgery
- Sciatic
  - Gluteal compartment syndrome from hematoma and "toilet seat" neuropathy
  - Hip arthroplasty and fracture–dislocation
  - Femoral fracture
  - Groin injury including gunshot wound
  - Infarction due to vasculitis or vascular surgical procedures of the lower extremity
  - Lithotomy positioning
  - Gluteal injection injury
  - Immobilization with impaired consciousness
  - Intraoperative thigh tourniquet
  - Infiltration by lymphoma
  - Endometriosis
  - Gluteal artery aneurysms
  - Gluteal varicosities
  - Compression from lipoma or nerve sheath tumor
  - Umbilical artery injections in neonates
  - Persistent sciatic artery
  - Cardiac surgery
  - Compression from prominent lesser trochanter
  - ???? Piriformis syndrome
- Peroneal
  - External compression—stockings, casts, and leg crossing
  - Weight loss
  - Stretch—bungie jumping, acute plantar flexion/inversion, and prolonged knee flexion during childbirth
  - Prolonged squatting
  - Cysts and tumors of the tibiofibular joint
  - Postoperative
  - Closed or open trauma
  - Fibular fractures
  - Dislocated knees
  - Surgery in the popliteal fossa
  - Vasculitis
  - Baker cyst
  - Acute occlusion of femoral or popliteal arteries
- Tibial
  - Trauma—compression from casts or tourniquets, hip arthroplasty, gunshot and other penetrating wounds, tibial plateau fracture/dislocations, and gluteal injections
  - Ischemia—acute large artery occlusive disease or posterior compartment syndrome
  - Tumor—neurofibroma, neurosarcoma, osteochondroma, and lymphoma
  - Miscellaneous—ruptured Baker cyst, popliteal hemorrhage, sclerosing treatment of varicose veins, and repetitive foot plantar flexion occupations
  - Tarsal tunnel syndrome
- Sural
  - Ankle injury
  - Vein stripping procedures
  - Schwannomas
  - Ganglionic cysts
  - Baker's cyst or surgery
  - Fracture of the base of the fifth metatarsal
  - Compression from the hard upper edges of ski boots
  - Vasculitis
  - Calf muscle biopsy
  - Arthroscopic surgery
  - Idiopathic

Pain, paresthesia, and sensory loss occur almost universally. Burning pain and hypersensitive skin in the appropriate "pants pocket" distribution of the anterolateral thigh are commonplace. In the eloquence of Freud, there is a "furry sensation, a feeling of alien skin almost imperceptible at rest but exacerbated by walking, frequently accompanied by painful short, pricking at right angles to the skin as well as a disagreeable sensitivity to the rubbing of underclothes."[134] As a pure sensory nerve, the absence of motor or reflex abnormalities is important

in order to exclude a plexopathy or polyradiculopathy resulting from a more ominous cause.

The reported causes of femoral mononeuropathies are varied and include retroperitoneal or iliacus hematoma,[87,135] lithotomy positioning, hip arthroplasty or dislocation,[33] iliac artery occlusion, femoral arterial procedures that are either diagnostic or therapeutic, mechanical clamping following those procedures,[136] infiltration by hematogenous malignancy, penetrating groin trauma, pelvic surgery including hysterectomy and renal transplantation, or idiopathic. In the vast majority of cases, the phenotype of femoral mononeuropathies is dominated by quadriceps weakness. Sensory symptoms occurring on either the anterior thigh and/or the medial leg occur in only half of reported cases. A prominent painful component is the exception rather than the rule, may be delayed, and is often self-limited in nature. The quadriceps (patellar) reflex is diminished or lost in virtually every case.[137]

Obturator neuropathy is an infrequently occurring lower extremity mononeuropathy. Causes include pelvic instrumentation, or either occult or previously recognized malignancy.[138,139] Associated malignancies that have been reported include transitional cell carcinoma of the bladder, cervical carcinoma, lymphoma, prostatic carcinoma and sarcoma, or tumors that are histologically undefinable. Other reported causes include childbirth, the prolonged lithotomy position, total hip arthroplasty, surgical tourniquets, myositis ossifications, obturator hernias, pelvic surgery including those done laparoscopically, and pelvic fracture.

Pain in the groin, anterior, and/or medial thigh is the initial symptom in the majority of patients. Paresthesias in the medial thigh occur but are often obscured by pain. Weakness may not be evident clinically, and denervation confined to obturator-innervated muscles may be required to identify the cause of groin and thigh pain. Weakness occurs predominantly in hip adduction, although weakness in hip flexion may coexist.[138] Ipsilateral leg edema may occur. In the authors' as well as others' experience, diabetic radiculoplexus neuropathy may rarely present with preferential weakness of hip adduction that may clinically mimic an isolated obturator mononeuropathy.[139] Prognosis is in large part determined by etiology, although, in general, acute-onset neuropathies fare far better than their chronic analogs.

Sciatic neuropathies have been associated with a number of different pathological conditions.[140,141] These most commonly occur as the result of trauma, which may be iatrogenic in nature, most notably hip arthroplasty[142] and fracture/dislocations.[33] Sciatic neuropathies can occur from penetrating trauma, including injections; hemorrhage into the piriformis region; aneurysm of the inferior gluteal artery; prolonged lithotomy positioning; vasculitis lesions; endometrial implants leading to "catamenial sciatica[143]; prolonged immobility including a posterior thigh and gluteal compartment syndromes, the latter occurring from hematoma resulting in "toilet seat" neuropathy[144,145]; infiltration by lymphoma[146]; intraoperative thigh tourniquet; persistent sciatic arteries[147]; gluteal varicosities[148]; nerve sheath tumors; and inadvertent injection into the umbilical artery of the newborn. Sciatic neuropathy has been reported to occur in association with cardiac surgery, presumably due to an ischemic mechanism related to intra-arterial balloon placement or concomitant peripheral vascular disease.[149] Sciatic neuropathies are often painful and may be associated with a causalgic syndrome. Sensory complaints and sensory loss occur in the entire foot and the distal lateral leg. The ankle jerk and, on occasion, the internal hamstring reflex are diminished or more typically absent on the affected side. Weakness involves all motions of the ankles and toes as well as flexion of the leg at the knee. The latter is quite debilitating in terms of attempted ambulation. Abduction and extension of the thigh at the hip should be spared. As previously mentioned, the peroneal functions of the sciatic nerve are typically involved disproportionately to their tibial counterpart. Misdiagnosis of a common peroneal neuropathy can be readily made by those unaware of this phenomenon.

The piriformis syndrome is one of a number of controversial nerve entrapment/compression syndromes.[150,151] Theoretically, it is caused by sciatic nerve compression by either an abnormal relationship with the piriformis muscle or an abnormal piriformis muscle at the level of the sciatic notch. Symptoms consist of buttock and posterior thigh pain, tenderness in the region of the sciatic notch and buttock, and pain reproduction by maneuvers that stretch the sciatic nerve. Objective clinical, EDX, and imaging evidence of nerve injury are notable for their absence.

Causes of common peroneal neuropathy include structural pathology of the fibular head including cysts of the tibiofibular joint,[152] external compression particularly following weight loss or habitual leg crossing,[153] casts or compression stockings,[154] surgery, closed or open trauma,[62] prolonged squatting,[155] fibular fractures, dislocated knees, surgery in the popliteal fossa, vasculitis, fibular tumors, Baker cysts, stretch injuries from acute plantar flexion/inversion or prolonged knee flexion during childbirth,[156] trochanteric anomalies,[157] and acute occlusion of femoral or popliteal arteries.[10] Thirteen of 103 patients in one series were diabetic, representing a possible predisposition to compressive injury.[62] Peroneal neuropathies occur in childhood as well.[158] Recognition is commonly prompted by the development of foot drop and the audible sound it creates during walking. As foot drop is a common result of a number of different neuromuscular disorders, it is important to document that the pattern of weakness conforms to that of the common peroneal nerve distribution. There is at least some degree of sensory involvement on the distal lateral

leg and dorsum of the foot. Deep tendon reflexes are spared in the absence of a second confounding problem. Sensory complaints tend to be less dominant in common peroneal neuropathies, in part because these are more likely to be related to manifest as a sign, i.e., a negative phenomena, and the loss of sensation to a stimulus, rather than a symptom, i.e., a positive phenomenon, i.e., paresthesia. The distal, lateral leg may be affected or may be spared. Weakness should be limited to the muscles that dorsiflex and evert the ankle and extend the toes. Any other pattern of involvement should raise at least the consideration of an L5 monoradiculopathy, a sciatic neuropathy, a lumbosacral trunk lesion or other plexopathy, or even motor neuron disease. Pain is notable in less than a fifth of patients.[62] The onset is more often than not acute but may be insidious as well. Bilateral peroneal neuropathies are not rare.

Tibial neuropathies proximal to the ankle are uncommon and occur most frequently resulting from trauma, tumor, or ischemia. These are most commonly confused with S1 monoradiculopathies. Traumatic causes account for approximately half of all cases. The nature of the trauma is variable and may include compression from casts or tourniquets, hip arthroplasty, gunshot and other penetrating wounds, tibial fractures, and gluteal injections. Acute limb ischemia was the most common nontraumatic cause in one series affecting approximately 20% of patients (see length-dependent monomelic neuropathy below).[159] Coexistent peroneal neuropathies may occur in both traumatic and ischemic etiologies. Rare causes include idiopathic hypertrophic nerve lesions, ruptured Baker cysts, and hematoma formation in the popliteal fossa.

The pattern of weakness of a tibial mononeuropathy in isolation varies by location. Knee flexion is weak with a lesion near or proximal to the hip joint but is spared with lesions located distal to the proximal thigh. Lesions in the distal thigh or proximal leg are typically associated with weakness of foot plantar flexion and inversion, toe flexion, and, if detectable, toe abduction. Sensory symptoms and sensory loss are confined to the sole of the foot and the very distal aspect of the dorsal surface of the toes. Depression or loss of the ankle jerk is invariable.

Tarsal tunnel syndrome is a controversial entity most closely associated with external compression from tight-fitting foot wear or prior ankle injury.[160–162] Arguably, it is associated with symptoms more than signs. In a manner analogous to carpal tunnel syndrome, patients may be typically plagued by pain in the ankle and foot and paresthesias of the sole that are intermittent and worse nocturnally. As weakness of intrinsic foot muscles may be difficult to clinically detect, objective motor deficits are uncommon. Due to the frequent calloused condition of the sole of the foot, detection of credible sensory loss may be challenging. The validity of Tinel sign at the flexor retinaculum is uncertain. As mentioned below, the prevalence of tarsal tunnel syndrome is controversial, its objective documentation frustrating, and its optimal management uncertain.

Sural mononeuropathies are uncommon other than as a consequence of nerve biopsy. Sural neuropathies present with some combination of numbness, pain, or paresthesias on the lateral foot in the cutaneous distribution of the nerve. Sural neuropathies are most commonly traumatic in etiology associated with ankle injury, surgery, or vein stripping procedures. Schwannomas, ganglionic cysts, Baker cysts or their surgery, fracture of the base of the fifth metatarsal, arthroscopic knee surgery, muscle biopsy of the calf, compression from the hard upper edges of ski boots, vasculitis, and idiopathic are other recognized causes.[163,164] Electrodiagnostic confirmation is readily obtained.

Pudendal neuropathy may result from pelvic and hip fractures, injection injuries, hemorrhage into piriformis, neoplastic invasion, surgical procedures, childbirth, or prolonged or inordinate pressure on perineum from ill-fitting bicycle seats or pressure devices that may be used to reduce hip dislocations. Recognition of pudendal neuropathy follows from sensory symptoms of the penis, scrotum, labia majora, and perineum, impotence, and fecal and urinary incontinence if bilateral.

Evaluation

EDX is the primary adjunctive diagnostic modality in the evaluation of the patient with a suspected lower extremity mononeuropathy. The goals are to identify the existence of nerve injury if possible, localize the injury both to and within the course of an individual nerve, define the pathophysiology if possible, and, by doing so, estimate prognosis and aid in management decisions.

There are no reliable, routinely performed nerve conduction study techniques that assess the function of ilioinguinal, iliohypogastric, genitofemoral, pudendal, or posterior cutaneous nerve of the thigh. In the appropriate clinical context, needle electromyographic evidence of denervation confined to abdominal muscles supports but does not prove the existence of an ilioinguinal or iliohypogastric mononeuropathy. Although it is theoretically possible to do an electromyographic evaluation of the cremaster muscle to support the diagnosis of a genitofemoral mononeuropathy, this is rarely if ever performed. Needle electromyography of the external anal sphincter can be done but may be difficult to interpret. It fires tonically, thereby making electrical silence difficult to achieve and fibrillation potentials difficult to detect. The small motor unit action potentials that populate this muscle may also confound the detection of fibrillation potentials.

Sensory nerve conduction studies of the lateral cutaneous nerve of the thigh have been described and are

fairly reproducible. Although potentially technically difficult in overweight individuals, identification of a SNAP of lateral cutaneous nerve of the thigh on the asymptomatic side with an absent or reduced amplitude of the analogous response on the symptomatic side provides strong diagnostic support in the appropriate clinical context.

EDX support for a femoral mononeuropathy is based primarily on the findings of acute and or chronic changes of denervation confined to femoral innervated muscles. Femoral motor conduction studies can be performed but may be more uncomfortable than many other conduction studies if performed percutaneously in overweight individuals. Additionally, there may be considerable side-to-side variation in CMAP amplitudes within a normal population, rendering convincing side-to-side amplitude comparisons difficult. One potential benefit of femoral motor conductions is in the patient with severe quadriceps weakness secondary to a demyelinating conduction block in the proximal femoral nerve. If such a patient were studied more than 7–10 days after the onset of weakness, a CMAP amplitude from the symptomatic side, which approximated that of the asymptomatic side, associated with involuntary knee extension far greater than the patient can voluntarily generate, would generate one of two conclusions. These would be either a conduction block injury with its associated optimistic prognosis or, alternatively, malingering. Other features including the presence or absence of a patellar reflex or neurogenic recruitment pattern on needle examination would aid in distinguishing between the two possibilities.

The other EDX parameter of interest in a suspected femoral neuropathy would be the saphenous sensory response. Its value is also slightly diminished by its inability to be detected in a certain percentage of normal individuals, particularly those that are older and endomorphic. A unilateral abnormality in a symptomatic leg, however, would once again strongly support the existence of an axon loss femoral mononeuropathy, assuming that the clinical and needle electromyographic patterns were also compatible with this conclusion. A unilateral abnormality of the saphenous SNAP would also be compatible with a lumbar plexopathy or lumbosacral trunk lesion. Conversely, a normal saphenous SNAP would be consistent with a more proximally located, predominantly demyelinating neuropathy.

There are no motor or sensory conduction studies that are available for the assessment of obturator neuropathies. EDX findings are limited to denervation in obturator-innervated muscles with axon loss injury, or reduced motor unit recruitment in the unlikely possibility of a demyelinating pathophysiology with conduction block.

Sciatic neuropathies commonly occur at the level of the proximal thigh or buttock and are often incomplete. It has been repeatedly stressed that the fibers destined to become the peroneal nerve are anatomically separated even at this level and more vulnerable to most injuries than their tibial nerve counterparts.[140,141] Theoretically, with axon loss sciatic nerve lesions, both peroneal and tibial CMAPs and superficial peroneal and sural SNAPs should be reduced or absent on the affected side as well as the mixed nerve plantar responses if tested. In reality, not all components are always affected or equally affected. Along the same lines, all muscles below the knee as well as all four hamstrings should be affected with sparing of muscles innervated by the femoral, obturator, superior, and inferior gluteal nerves. Again, denervative changes may be more patchy than anticipated.

As previously mentioned, the most precise localization of focal nerve lesions occurs when these are demyelinating in nature. In the lower extremity, a common peroneal neuropathy occurring at the fibular head is the only demyelinating mononeuropathy that will be demonstrable with any frequency. Approximately 45% of common peroneal neuropathies will have at least a component of demyelinating conduction block.[62] It may be necessary to record from the tibialis anterior rather than the traditional EDB in order to demonstrate this. With an axon loss common peroneal neuropathy occurring at the fibular head, reduced CMAP amplitudes recording from both the EDB and the tibialis anterior muscles are anticipated. The superficial peroneal SNAP will be reduced or absent in axon loss lesions, whereas it will be relatively spared in predominantly demyelinating lesions. Changes of active and/or chronic partial denervation and reinnervation of muscles innervated by both the deep peroneal and the superficial peroneal nerves below the knee will be evident in axon loss lesions. It may be recalled that many partial injuries to the sciatic nerve preferentially injure the peroneal division. In this situation, both the clinical examination and the nerve conduction study results may appear similar to that expected in an axon loss common peroneal neuropathy. Denervation in the short head of the biceps, the only peroneal-innervated muscle above the knee, provides a major clue by which to distinguish between these two entities.

Predominantly demyelinating common peroneal neuropathies occur fairly commonly. CMAP amplitudes recording from either the EDB or the tibialis anterior are typically normal or mildly reduced if any component of axon loss is present. It should be emphasized that when conduction block occurs, it tends to do so slightly distal to the prominence of the fibular head. To adequately identify it, the electromyographer may have to make an effort to move the stimulator to a slightly more distal location than typically used, in order to demonstrate the abrupt increase in CMAP amplitude that can be elicited below the lesion. Superficial peroneal SNAPs are similarly spared in predominantly demyelinating

common peroneal neuropathies. Needle examination may demonstrate fibrillation potentials if some axon loss is present. This is commonly the case and does not by itself portend a poor prognosis for recovery. The most dramatic feature on the needle examination in predominantly demyelinating common peroneal mononeuropathies is the reduced recruitment pattern, proportionate to the degree of conduction block and clinical weakness. Isolated deep peroneal and superficial peroneal neuropathies are uncommon. Although the deep peroneal nerve has a small sensory branch, it is not readily accessible. Reduced CMAP amplitudes of the EDB and tibialis anterior occur, depending on the site of lesion and proportionate to the degree of axon loss. With the superficial peroneal nerve, motor conductions are not routinely performed, but the superficial peroneal SNAP would be anticipated to be reduced in amplitude or absent. In both cases, needle EMG findings would be restricted to those muscles innervated by the respective nerves.

Tibial neuropathies are also uncommon and typically occur at or distal to the knee. With axon loss lesions, the CMAP recording from the soleus muscle with H-reflex assessment or a tibial-innervated foot muscle, typically the abductor hallicus, in response to direct tibial nerve stimulation would be reduced in amplitude. The sural SNAP may be affected or spared, depending on how proximal the lesion is. The mixed plantar responses would be affected with any significant axon loss tibial mononeuropathy.

The electrodiagnostic assessment of a tibial neuropathy at the ankle, i.e., the tarsal tunnel syndrome, is a matter of considerable controversy. As a potential entrapment neuropathy related to compression by a flexor retinaculum, it is a theoretical analog to carpal tunnel syndrome of the upper extremity. It either occurs, or is proven to exist infrequently. Part of the problem may be technical. Even if slowing of tibial nerve conduction through the tarsal tunnel occurs, it is extremely difficult to demonstrate in the experience of the authors. There are a number of potential explanations. It is very possible that tarsal tunnel syndrome is a rare syndrome. It is equally possible that tarsal tunnel syndrome, unlike carpal tunnel syndrome, has predominantly an axonal pathophysiology in which conduction slowing across flexor retinaculum does not occur. Lastly, there are technical issues that may play a role. Normative data for distal latencies for both tibial motor fibers and mixed plantar responses are not as "tight" as their upper extremity counterparts, thus precluding the detection of mild degrees of focal slowing. Mixed plantar responses may be absent in normal individuals. Their absence neither proves the existence of nerve injury nor localizes the problem, if one exists, to the tarsal tunnel. Fibrillation potentials in tibial-innervated foot muscles may occur in normal individuals. Even if pathological, these may more likely represent an early peripheral neuropathy, a far more common clinical problem, and once again does not provide anatomic localization to the tarsal tunnel. In summary, confident electrodiagnostic support for the tarsal tunnel syndrome is a rare electrodiagnostic event.

Prognostication for recovery in mononeuropathies is imprecise. In general, mild deficits, younger age, fewer comorbidities, and less of a distance between the site of injury and the structure being innervated, increase the likelihood of a satisfactory outcome. Electrodiagnostically, the demonstration of a predominantly demyelinating lesion in the absence of persistent nerve insult usually predicts a complete or near-complete recovery occurring over a period of 3 months or less. In one study of femoral mononeuropathy, axon loss of >50% comparing the area of the femoral CMAP on the affected vs. unaffected side predicted an incomplete recovery of quadriceps function.[137]

The availability of MR imaging has greatly enhanced the value of imaging in the assessment of mononeuropathies. MRI with the addition of gadolinium is the test of choice to identify a suspected nerve sheath tumor (Fig. 22–11). MRI may also be used to identify an abnormal structure that is compressing and injuring a peripheral nerve such as an osteochondroma of the fibular head or a Baker's cyst within the popliteal fossa. Ultrasound can be useful in specific circumstances. Although usually addressed more readily by EDX, MRI can detect signal changes restricted to muscles that serve to define a pattern of denervation. As previously mentioned, MRI can demonstrate enlargement and signal changes within the muscles of a given anatomic compartment that help to define a compartment syndrome. Although immune-mediated, inflammatory neuropathies are typically

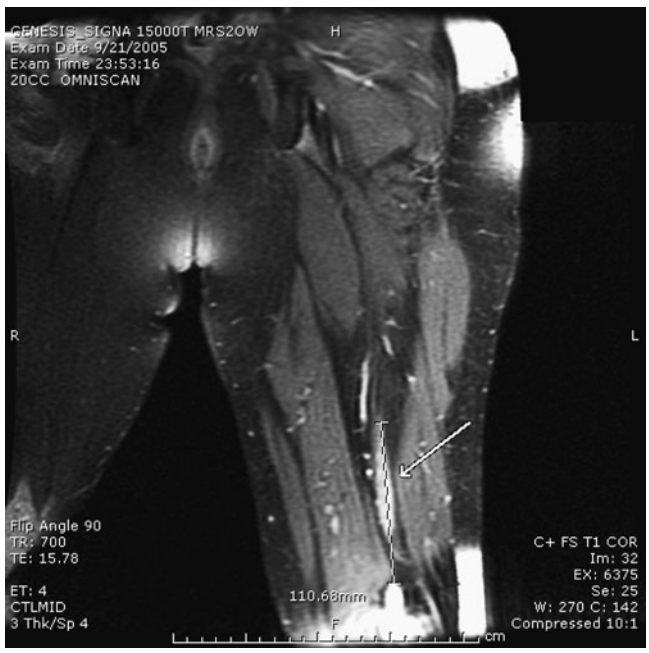

Figure 22–11. Enhancing, fusiform lesion of the distal sciatic nerve (schwannoma).

multifocal in nature and are rarely confused with the phenotypes of any of the disorders described in this chapter, these may initially present as a mononeuropathy. As the involved segment of nerve may enhance with gadolinium, imaging has the potential to aid in this diagnosis as well.

Management

The management of mononeuropathy is dependent on the etiology, location, severity, and duration of nerve injury. With rare exception, monophasic compressive nerve injuries are treated conservatively. If it can be determined that a nerve injury is progressive and due to a definable cause of external compression, the source of compression should be surgically altered or removed. Surgical intervention in diabetics with mononeuropathies should be undertaken cautiously, as the already potentially compromised microvasculature may be further injured with nerve manipulation or transposition.

In case of trauma from "clean" penetrating injuries such as knife or glass wounds in which complete loss of function implicates potential nerve transaction, immediate exploration with attempted primary reanastomosis is considered. If potential nerve transaction occurs from trauma associated with considerably surrounding tissue damage such as a gun shot wound, exploration is typically delayed for a month of more, assuming that there is no suggestion of recovery from either a clinical or an EDX perspective. If the nerve is transected, nerve grafting will be required if anastomosis is attempted, as the retraction of the severed ends will prevent primary reanastomosis on a delayed basis. If the nature of the injury makes nerve transaction unlikely, even in the setting of complete or near-complete nerve injury, surgical exploration is usually not attempted for at least 6 months. If there is partial but convincing improvement measured either clinically or electrically, it is unlikely that surgical intervention will improve outcome. If there is no evidence of improvement, exploration may be considered. The goals in this case would be to perform nerve grafting if the nerve is transected, to identify and remove any external source of nerve compression (external neurolysis), and potentially to perform internal neurolysis. The latter is considered if the epineurium is intact, but intraoperative nerve conductions indicate that there is no impulse transmission through the injured segment. The intent is to dissect out individual fasicles and to potentially free them from any scarring that has taken place within the confines of the epineurial sheath. Alternatively if upon dissection, all fasicles are anatomically discontinuous despite preservation of epineurial continuity, a predictably rare event, nerve grafting may be attempted as part of the previous.[165]

The outcome of surgical intervention for peripheral nerve injury is often disappointing. The age of the patient, comorbid illnesses, and the distance between injury and reinnervating target are key variables. In general, proximal muscles are far more likely to regain meaningful function than distal muscles with axon loss lesions occurring in proximal locations, regardless of whether surgical intervention takes place or not.

Meralgia paresthetica is frequently a self-limited disorder, although recovery may take months. Weight loss is often recommended, although the historical role assigned to obesity is probably overstated. Drugs that may be effective for "neuropathic" pain, as discussed above, may be used. Injections of corticosteroids and local anesthetics in the vicinity of the anterior iliac spine may have both diagnostic and therapeutic benefit. Surgical exploration and release is rarely required or performed but has been reported to have 78% efficacy in patients refractory to conservative management.[166]

As discussed in the plexopathy section, bracing and other forms of durable equipment may improve both mobility and safety. With common peroneal or sciatic neuropathies, custom-fitted ankle–foot orthoses (AFO) are recommended if the patients "catch their toes" and are at risk of falling. Some patients benefit from AFOs by improving their gait as well as by diminishing their risk of falling. Selected patients with femoral neuropathies may benefit from a knee–ankle–foot orthoses. In addition, a cane, walker, or even wheelchair may be necessary, depending on the severity of quadriceps weakness and the strength of unaffected muscles. Patients with quadriceps weakness may also benefit from lift chairs, which will aid them in getting to their feet, and stair lifts if access to second floors or basements in their homes or places of work is required and cannot be accomplished by some other means.

MONOMELIC POLYNEUROPATHIES

The monomelic polyneuropathies are relatively uncommon disorders that typically result from acute limb ischemia. Occlusion of major limb vessels such as the aortic bifurcation, external iliac, or superficial femoral artery resulting from embolus or instrumentation such as intra-aortic balloon pumping or arterial cannulation associated with coronary bypass grafting are the typical causes in the lower extremities.[10,70,167,168] Implicit in the description of this syndrome is the belief that nerve is either more readily injured or less readily recoverable with acute limb ischemia than are other limb tissues. Chronic limb ischemia has been reported to associate with electrodiagnostic findings, suggesting length-dependent axon loss.[169–172] Whether this ever translates into a clinically evident neuropathy in the absence of other tissue damage is a matter of controversy.

Most disorders that affect multiple nerves or multiple nerve roots are systemic disorders that typically affect more than one extremity. Monomelic polyneuropathies bear resemblance to plexopathies in that both

motor and sensory deficits occur, affecting more than one nerve distribution, but confined to a single extremity. The dominant feature is deep, persistent, burning pain in the foot associated with cutaneous hypersensitivity. The distribution of motor and sensory deficits is typically length dependent, affecting all nerves below the knee and typically below mid calf. Muscle innervated by those same nerves and segments more proximally located are spared.[10] Although motor deficits occur, like length-dependent axonal polyneuropathies, these are typically less evident from a clinical perspective. Part of this stems from the clinical difficultly in assessing intrinsic foot muscles, those that are most severely affected. From an EDX standpoint, this syndrome may resemble a sciatic neuropathy. Notable differences are that the hamstring muscles tend to be spared and the saphenous sensory response will be abnormal in monomelic polyneuropathy if it can be reliably contrasted to the uninvolved opposite limb. The EDX pattern of monomelic polyneuropathy is unique in that it is a multifocal neuropathy, but one that is both length dependent and confined to one limb.

COMPARTMENT SYNDROMES

Compartment syndromes refer to ischemic tissue damage within confined anatomic spaces typically bordered by taut fascial membranes. Peripheral nerves are at risk from the cycle of ischemia that is created by increased compartmental pressure. Typically, an initial injury promotes edema and increased compartment pressure. This impairs compartment perfusion and promotes further ischemic injury and, as a result, further swelling. A vicious positive feedback cycle is thus created. Pressure blisters, a swollen limb, and/or myoglobinuria are potential associated clinical features that may warn of impending nerve injury or aid to clarify the mechanism of nerve injury.[173] Many of the mononeuropathies previously mentioned in this chapter are at risk of injury from immobilization, either due to a direct pressure or in association with nerve injury occurring from more diffuse compartmental pressure. Recognized compartment syndromes in the lower extremity include sciatic neuropathy from the gluteal compartment or posterior compartment of the thigh syndromes,[174,175] femoral neuropathy from the iliacus compartment or within the anterior thigh, and a peroneal palsy resulting from an anterior compartment syndrome in the leg.

Evaluation

Imaging of the involved area will typically identify swelling and signal changes within the muscle of that compartment. Manometric measurements may confirm elevated pressure within that compartment, pressures as low as 30 mm Hg being potentially injurious to nerve.[173]

Management

A compartment syndrome is a surgical emergency that requires decompression and potentially debulking of the involved anatomic compartment(s).

▶ SUMMARY

Focal neuropathies of the lower extremities are common neurological problems that are frequently caused by compressive mechanisms. Clinically directed localization supplemented by electrodiagnostic testing (when required) provides the foundation for the evaluation of these disorders. When the neuropathy cannot be readily attributed to a common compressive mechanism, imaging rationally directed by the localization process is often the means by which disease etiology is identified. Focal neuropathies are potentially more amenable to surgical intervention than are the majority of disorders described elsewhere in this text. Imaging provides the opportunity for potential benefit, and potential risk. Many of these disorders will have natural histories that are self-limited, and false-positive imaging results unrelated to the clinical context are frequent. For this reason, the risk of unnecessary intervention looms large. Once again, the skilled and judicious neuromuscular clinician is in a unique position to provide both accurate disease identification and optimal management.

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CHAPTER 23

Disorders of Neuromuscular Transmission

▶ INTRODUCTION

Disorders of neuromuscular transmission (DNMT), particularly myasthenia gravis (MG), represent the "prize pupils" of neuromuscular clinicians (Table 23–1). Most of these disorders have either an autoimmune or a toxic etiology, the latter resulting from either infectious or other biological sources. MG is the prototypic autoimmune disease. Its study has provided insights into its biology as well as of other disorders of autoimmunity. The basic science underlying the pathology and pathophysiology of MG is conceptualized better than virtually any other neuromuscular disorder. As MG is an eminently manageable disorder in the majority of cases, both patient and physician are gratified by its identification and treatment. In many cases, treatment of MG and other DNMT represent the effective translation of basic science to the bedside.

The historical highlights of DNMT can be summarized as follows. The initial insights were physiological. The concept that neuromuscular function is mediated electrically was initially promoted in the late eighteenth century and championed by Galvania and Matteucci. That transduction of an electrical to a chemical signal served as a mediator of neuromuscular transmission (NMT) was most notably promoted by Bernard, Vulpian, and Langley through the eighteenth and early nineteenth century. Their deductions arose from observations made by the actions of the neuromuscular blocking agent curare and the stimulant nicotine. Descriptions of the anatomy of the neuromuscular junction (NMJ) began with the advent of light microscopy in the mid-nineteenth century and have been further expanded by electron and confocal laser scanning microscopy. Doyere, Ranvier, Tello, Cajal, and Couteaux are notable contributors to our knowledge, the latter credited with insights into junctional architecture.[1] Thomas Willis, a seventeenth-century physiologist, is frequently credited for initially describing the clinical syndrome of MG. Erb, Oppenheim, and Goldflam are commonly credited with "putting it on the map" during the last two decades of the nineteenth century. The relevance of junctional anatomy to MG came into focus in the 1930s, when Mary Walker discovered and described the benefits of cholinesterase inhibitors in these patients. In 1960, Simpson first proposed that MG was an autoimmune disease resulting from an antibody-mediated blockade of NMT. Daniel Drachman and colleagues took advantage of radiolabeled α-bungarotoxin in the early 1970s to demonstrate that antiacetylcholine receptor (AChR) numbers were reduced in patients with MG. Within a few years, Lindstrom and colleagues were instrumental in identifying the AChR antibodies proposed by Simpson.

This chapter will review the clinical, pathophysiological, and pathological characteristics of, as well as the diagnostic and management issues pertaining to, the more common or notable pre- and postsynaptic DNMT.

▶ CLINICAL FEATURES

MYASTHENIA GRAVIS

The incidence of MG ranges between 1 and 9 per million, while prevalence is estimated to be between 25 and 142 per million.[2–11] The incidence of MG is slightly greater in women than in men. The age of onset is bimodal for both men and women. Women demonstrate annual peak incidences at ages 20–24 and 70–75 years, while men have peak rates between 30–34 and 70–74 years. In the early disease presentation group, a female-to-male ratio is roughly 7:3, while in the late-onset group, the gender ratio is 1:1. The mean mortality rate per million population approximates 1.7 (0.9–3.1) for all patients with a diagnosis of MG, while the mortality rate directly attributable to the disease itself is 0.8 $\times$ 10^6 (0.0–2.2). These figures differ significantly from a previous era where knowledge of the disease and therapeutic options were limited, and the adjective gravis was more apt than is currently the case.

DNMT, particularly autoimmune MG, have clinical features that distinguish them from most other neuromuscular diseases.[12] Many of these distinctive features, particularly the fluctuating nature of a patient's strength or stamina, are derived from the unique pathophysiology of impaired NMT. This pathophysiology produces, in many cases, a dynamic rather than fixed disorder. This behavior is in part due to the biology of NMT, which

▶ TABLE 23–1. DISORDERS OF NEUROMUSCULAR TRANSMISSION

Presynaptic
Lambert–Eaton myasthenic syndrome
Botulism and botulinum toxin
Tick paralysis (Australian)
Congenital myasthenia gravis
Choline acetyltransferase deficiency
Paucity of synaptic vesicles and reduced quantal release
Drugs and toxins
Hypermagnesemia
Envenomation—black and green mamba, Australian tiger snake, *Pandinus* scorpion, conus marine snails, multibanded krait, Brazilian rattlesnake, and black and brown widow spider
Aminoglycosides and other antibiotics
Calcium channel blocking agents (minor)
Aminopyridines
Corticosteroids
Hemicholinium-3
Synaptic
Congenital myasthenic syndromes—end plate acetylcholinesterase deficiency
Drugs and toxins
Cholinesterase inhibitors—edrophonium, pyridostigmine, and neostigmine
Organophosphates
Postsynaptic
Myasthenia gravis
Transient neonatal myasthenia
Drug-induced myasthenia gravis
Penicillamine
Alpha-interferon
Congenital myasthenic syndromes
Primary kinetic defects—slow and fast channel syndromes
Primary AChR deficiency
Rapsyn deficiency
Sodium channel myasthenia
Plectin deficiency
MuSK mutations
Dok-7
Drugs and toxins
D-Tubocurarine, vecuronium, and other nondepolarizing blocking agents
Succinylcholine, decamethonium, and other depolarizing blocking agents
Tetracyclines, lincomycin, and other antibiotics
Envenomation by banded kraits, Siamese cobra, Conus marine snail

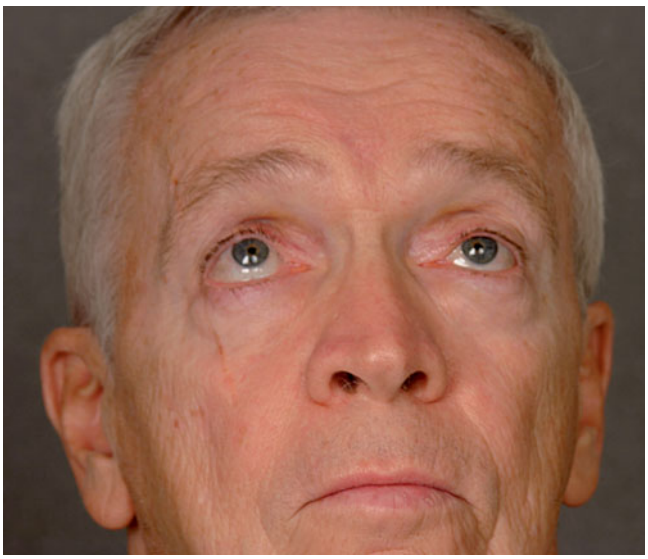
AChR, antiacetylcholine receptor; MuSK, muscle-specific tyrosine kinase.

includes the relative ease by which NMJs are repaired, particularly in comparison to other components of the neuromuscular system. Many diseases that affect the cell bodies of either sensory or motor neurons, peripheral nerve axons or their myelin sheaths, or even muscle are more likely to have persistent if not permanent effects once established. The biology of the NMJ allows the symptoms of MG, and to a lesser extent Lambert–Eaton myasthenic syndrome (LEMS), to fluctuate on a minute-to-minute, diurnal, or week-to-week basis. This fluctuation is a key diagnostic feature of the DNMT.

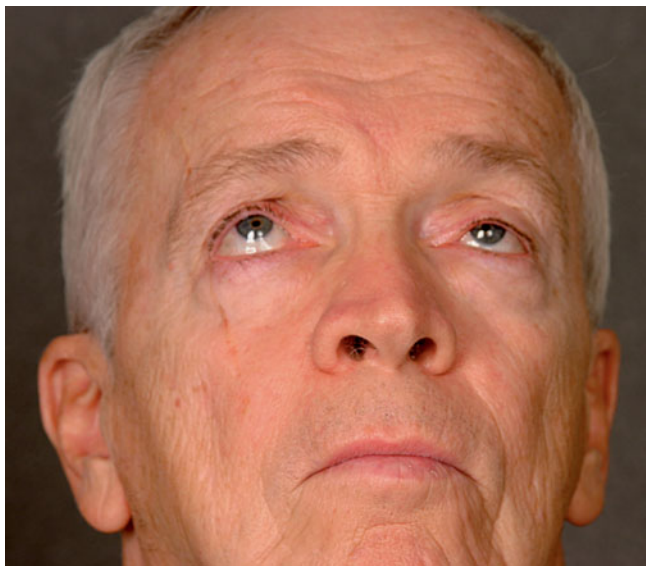
DNMT may also provide a fairly distinctive pattern(s) of weakness. Many have a predilection for muscles innervated by cranial nerves. The basis of this is not completely understood but, in the case of MG, may be related to the differences in the type and distribution of NMJs in at least some of the muscles that myasthenia tends to affect.[1]

The diurnal fatiguing nature of the painless weakness of MG is a quality that may be a dominant feature of the patient's history or may be overlooked.[13–18] Patients may complain of various factors that exacerbate their feeling of weakness or fatigue in addition to exercise such as warm weather, systemic infections, menses, anxiety, emotional stress, and pregnancy.[7,19–30,30–32] Enquiries referable to specific muscles, brought on or worsened by physical activities or simply by the rigors of the evolving day, should be made. Occasionally, variation in disease severity over weeks to months unrelated to interventions or other variables may be notable in patients with MG as well.

The pattern as well as intensity of weakness in MG can be extremely variable. It may be focal, multifocal, or diffuse. Any voluntary muscle may be affected, although those controlled by cranial nerve motor fibers are typically the most susceptible. Visual obscuration related to ptosis, diplopia, dysarthria, dysphagia, and difficulty chewing are among the most common symptoms. Approximately half of patients with MG will initially have isolated ocular symptoms.[17,33–35] Ptosis is the presenting symptoms in 50–90% of patients, while 15% complain of blurred vision or frank diplopia.[36,37] If not a presenting symptom, external ocular muscle involvement is present at some point in about 90–95% of patients. Different speech patterns may be noted. The voice may be hypophonic due to vocal cord or expiratory muscle weakness, either of which may be the presenting complaint.[38–40] The patient may be dysarthric as a result of weakness of the lips, tongue, or cheeks. It may have a nasal quality due to palatal insufficiency and air leak. Palatal and pharyngeal muscle weakness eventually manifests in roughly 40% of all patients. Nasal regurgitation of food and liquid, difficulty removing food from between the cheek and teeth due to tongue weakness, as well as ineffective sniffing, coughing, nose-blowing, or throat-clearing may be noted. Presentations dominated



A



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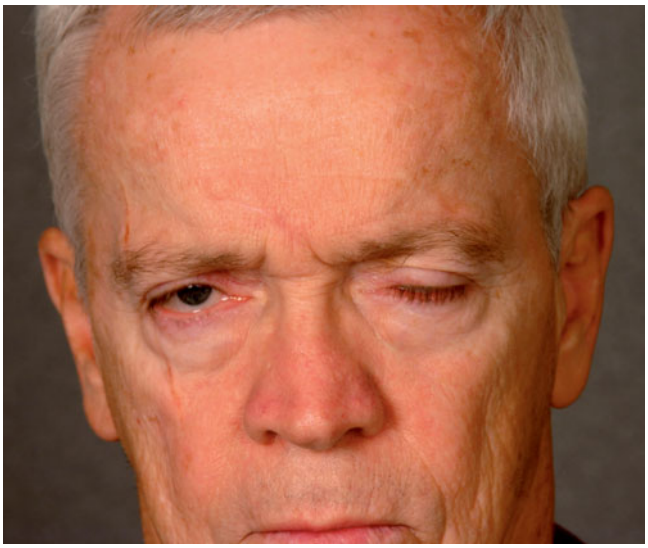


C

Figure 23–1. Ocular myasthenia with fatigable L ptosis. (A) immediately upon sustained upgaze, (B) 30 seconds into sustained upgaze, (C) and after completion of 1 minute of upgaze demonstrating left > right ptosis. In (C) note subtle elevation of left eyebrow as indicator of frontalis use in attempt to compensate for ptosis.

by the "bulbar" symptoms of dysphagia and dysarthria without ptosis or ophthalmoparesis are not rare. Facial weakness is common and can be detected by having the patients close their eyelids tightly. Patients who are affected may be unable to bury their eyelashes or maintain eye closure against resistance. An inability to whistle, making a kissing noise, or puffing the cheeks out against resistance can be noted. From time to time the "myasthenic snarl" may be noted. Failure of the corners of the mouth to be withdrawn in association with lip retraction causes this appearance as the incisors and canine but not the premolars are revealed.

As NMT may actually be improved by cooler temperatures, cold food and liquids may be easier to manage than their warmer counterparts. Weakness may be made more evident by muscle exercise. Looking for ptosis or ocular malalignment after sustained upgaze or eccentric gaze is a common provocative maneuver (Fig. 23–1A–C). The latter may result in pseudonystagmus as the jerking movements of the eyeballs may be observed, as fatiguing extraocular muscles fail in their attempt to sustain eccentric gaze.[41,42] An additional maneuver of some benefit is Cogan sign. This is fairly specific for MG and refers to a saccadic maneuver that brings the eye back to the primary position after sustained downgaze. A positive Cogan sign refers to a brief overshoot of the upper lid, resulting in scleral exposure between the upper limbus and the upper lid followed by rapid return of ptosis. Weakness of eye closure or eye opening (ptosis), extraocular movement, jaw opening and closing, tongue protrusion, palate elevation, and neck flexion and extension are commonly found in isolation or combination. As these functions are subserved by multiple, anatomically dispersed cranial nerves, a combination of these

findings occurring in absence of pain or cranial sensory symptoms is virtually strongly suggestive of DNMT. Concomitant weakness of eye opening (ptosis—third cranial nerve) and eye closure (seventh cranial nerve) is one such notable and fairly frequent combination. Limitation of eye movements that is not readily explained by a mononeuropathy of the third, fourth, or sixth nerves should also place MG high on the differential diagnostic list. By the same token, MG may mimic any of these neuropathies or even intranuclear ophthalmoplegia.[41] Migratory weakness may also occur in MG, e.g., ptosis of the right eye on one examination and of the left eye on the next. A diagnosis of MG can also be solidified at the bedside by the demonstration of fatigue. This is perhaps most commonly done by having the patients sustain upgaze for a minute while observing their eyelids for evidence of involuntary descent by comparing upper lid position in relationship to the pupil.

MG may affect the strength and stamina of limb muscles as well. Limb muscle weakness is the basis for the presenting symptoms in approximately 20–30% of affected individuals. Limb weakness preferentially affects proximal muscles, producing a limb-girdle pattern in most patients.[43] One potential but undoubtedly partial explanation is the warmer temperatures in the proximal limbs.[44,45] Typically, limb weakness occurs in concert with the signs and symptoms mentioned in the previous paragraph. In approximately 10% of patients, MG may be initially restricted to distal limb muscles, with foot or finger drop being notable initial manifestations.[46–53] Again, the pattern may be focal, multifocal, or diffuse.[17,52] In view of its pure motor characteristics, MG presenting with unilateral foot, finger, or wrist drop may lead to initial consideration of a mononeuropathy or radiculopathy, motor neuron disease, or a motor neuropathy. Head drop secondary to neck extensor weakness is not uncommon and can be the presenting feature. Ventilatory insufficiency is a rare presenting symptom of MG but occurs in a significant percentage of patients with untreated or refractory generalized disease.[40,54] Along with dysphagia, it is undoubtedly the predominant basis for mortality in MG and for the historical designation of "gravis." Having the patients count out loud for as long as they can after taking as deep a breath as possible is a bedside means to estimate vital capacity. Multiplying the number the patient can achieve with one breath by 100, e.g., $35 \times 100 = 3500$ ccs will provide a reasonable estimate of the vital capacity.

As in all clinical diagnoses, it is important to consider not only what is affected but also what is not. Signs and symptoms of bowel and bladder dysfunction unrelated to medication effect are uncommon in MG in the absence of severe generalized disease. As MG is exclusively a disorder of nicotinic cholinergic receptors, dysautonomia does not occur. The Osserman scale has been used to classify disease severity and behavior.[7,29] Adult MG is subdivided into Group 1 (ocular: 15–20%), Group 2A (mild generalized: 30%), Group 2B (moderately severe generalized: 20%), Group 3 (acute fulminating: 11%), and Group 4 (late severe: 9%). Those patients in Group 1 primarily have complaints related to external ocular movements, at least at onset. Group 2A patients have both oculobulbar and limb muscle involvement. Ventilatory muscle weakness is not a prominent aspect of this disease group who frequently respond to anticholinesterase medications. Group 2B patients have similar but more severe complaints than those in Group 2A. These individuals have marked ptosis, diplopia, dysarthria, dysphagia, and difficulty with activities requiring physical exertion. Group 3 patients are defined by severe generalized weakness progressing relatively quickly over the course of 6–8 months, often with the development of ventilatory compromise. In Group 4, patients usually begin with a relatively mild form of the disease and maintain somewhat of a plateau for 2 or more years but then progress into the severe disease category.

Our understanding of the natural history of myasthenia is suboptimal and is derived, in large part, from historical data accumulated prior to the availability of treatment options. It is recognized that approximately 15–40% of patients who begin with isolated oculomotor symptoms will not develop generalized disease. Those who do will typically generalize within the first 2 years of symptoms.[55–57] Patients with MG are known to achieve spontaneous remissions. The frequency, intensity, and duration of these are impossible to predict in any individual patient.[58]

The welfare of both child and mother are of concern when a myasthenic female becomes pregnant.[59,60] In an extensive review of the literature involving 322 pregnancies in 225 myasthenic mothers, 31% of mothers had no change in their myasthenic symptoms, 28% improved, and 41% deteriorated during the pregnancy.[61] In addition, 30% had exacerbation of their myasthenia in the postpartum period. In general, pyridostigmine and, if necessary, prednisone are used preferentially, and other immunomodulating agents are avoided if possible because of teratogenic concerns. Pregnant patients with myasthenia should be considered at high risk and followed closely by a neuromuscular clinician, an obstetrician, and a neonatologist. Magnesium sulfate should be avoided if possible if preeclampsia develops secondary to its neuromuscular blocking properties. Regional anesthesia is preferred for delivery and cesarian section. There is a theoretical risk of transmitting IgG AChR antibodies in breast milk, although most infants have no problem with breast-feeding. Of major concern is the potential for transient neonatal myasthenia, which is discussed in detail below.

Attempts have been made to correlate phenotype with serological profile.[62] There appears to be an essentially identical phenotype in patients with and without acetylcholine receptor (AChR)-binding

antibodies.[63–68] High titers of AChR receptor modulating antibodies seem to convey an increased risk of thymoma.[69–71] Individual patients who are muscle-specific tyrosine kinase (MuSK) antibody positive may be phenotypically indistinct from patients who are AChR antibody positive or seronegative. A number of authors have suggested that these patients have phenotypic, electrodiagnostic (EDX), and therapeutic tendencies that differ, in general, from the other two categories of patients with MG.[72–90]

Patients who are MuSK antibody positive have a higher female to male ratio, with a tendency for disease onset in the third or fourth decades. They may have prominent oculobulbar weakness with dysarthria, an almost universal symptom.[72,73] Face and tongue atrophies have been reported in cases with long-standing disease and could conceivably make the clinical distinction from bulbar amyotrophic lateral sclerosis (ALS) more difficult. Another somewhat distinctive pattern is neck (including dropped head syndrome), shoulder, and ventilatory muscle weakness. Initial reports suggested that MuSK antibodies were never found in purely ocular presentations of MG.[90] Recent reports have refuted this notion.[91,92] Myasthenic crises appear to be more frequent in patients with MuSK antibodies.[72,73]

Recently, 11 patients with a particularly severe phenotype characterized by bulbar involvement, myasthenic crises, thymoma, myocarditis, and prolonged QT electrocardiographic interval have been described.[93] These individuals were seropositive for antibodies directed against the Kv1.4 voltage-gated potassium channel in addition to AChR-binding antibodies.

Juvenile MG

Juvenile MG represents a "subclassification" of autoimmune MG.[94–100] It is estimated that approximately 10% of acquired (non-neonatal) autoimmune MG cases will occur before 18 years of age, the majority subsequent to puberty. [94] This statistic may be inflated, as some reported seronegative cases could easily represent congenital myasthenic syndromes (CMS). Few studies have been specifically directed toward this patient population. As a result, only modest data are available.

The mean age of onset for juvenile MG ranges from 7 to 14 years.[96,99] The distinction from adult MG may be artificial, as all features seem identical except age. The clinical features are similar to adult-onset MG, with the majority of patients initially presenting with primarily ocular symptoms.[99] Serum AChR antibodies are present in the majority of affected children. The electrophysiologic findings are also identical to the adult form of the disease.[100]

Neonatal MG

Transient neonatal autoimmune MG develops in approximately 10% of infants born to mothers with MG.[101–124] Onset is usually within the first 3 days of life. The most notable features include a weak cry, difficulty feeding due to a poor suck, hypotonia, respiratory difficulty, ptosis, and diminished facial expression (facial muscle weakness). The disorder is temporary, with a mean duration of about 18–20 days. The most important aspect of this disorder is that it is only temporary and there appears to be no increased risk of the child developing MG in later life.

Associated Conditions

Effective management of MG requires knowledge of neoplastic and other autoimmune disorders that occur with an increased incidence in patients with MG. It is tempting to speculate that many of these historically described cases were examples of Dok-7 myasthenia described previously. Pathology of the thymus gland is the most notorious disease association.[132] As many as 70% of patients with MG have thymic hyperplasia, while approximately 10% have a thymoma.[133,134] Conversely, 55% of patients with thymoma will have MG.[71] Thymomas are much more common in patients between the ages of 50 and 70 years. Thymomas have been reported to be associated with other neurological and neuromuscular disorders as well, including granulomatous myositis, Issac's syndrome, rippling muscle disease limbic and cerebellar encephalitis, and autonomic neuropathy including the syndrome of intestinal pseudo-obstruction.[70,71,135,136]

Seventy-four percent of patients with thymomas and myasthenia have circulating serum striational antibodies in addition to anti-AChR antibodies.[71] Less than half that number with thymoma will have striational antibodies without MG. Other autoantibodies can be found in patients with thymoma, with or without MG, including ganglionic (as opposed to the nicotinic found on muscle) AChR antibodies, anti-voltage-gated potassium channel antibodies, and CRMP-5-IgG.[70,71] Thymic abnormalities in patients with anti-MuSK antibodies are uncommon and typically minimal when they occur.[88] This point is emphasized in a study of 167 patients with thymoma.[71] Of the 92 who had MG, only one of them was seropositive for MuSK antibodies, which rarely, if ever, coexist with their AChR-binding.

Other autoimmune diseases that occur with increased frequency in a myasthenic population (and vice versa) include rheumatoid arthritis, systemic lupus erythematosus, Sjögren syndrome, red blood cell aplasia, ulcerative colitis, sarcoid, Addison disease, and hyper- and hypothyroidism.[31,137–140]

Other neuromuscular disorders can be seen concurrently in patients with MG as well, particularly if thymoma is coexistent.[141] Both acute and chronic inflammatory demyelinating polyneuropathies have been reported in patients with concurrent MG.[142–144] There have been reports of patients who develop a severe

autonomic neuropathy (e.g., intestinal pseudo-obstruction) with or without encephalopathy concomitant with the MG and thymoma.[142,145,146]

Various autoimmune channelopathies occur in patient with MG. Rare patients have a combination of MG and LEMS serologically and electrophysiologically.[147–151] Approximately 5% of patients with MG also have an inflammatory myopathy.[116,127–129,152,153,154] Most of these patients also have a thymoma with or without myocarditis. The histopathology often reveals a giant cell or granulomatous myositis. Serum CK levels are usually elevated with concomitant inflammatory myopathy, which would not be expected in MG alone. A number of relatively rare conditions have been reported to coassociate with MG and thymoma. These include acquired neuromyotonia or Isaacs' syndrome,[77,136,153,155–158] rippling muscle disease,[69,70,153,155,159,160] stiff-persons' syndrome.[161,162]

CONGENITAL MYASTHENIC SYNDROMES

The congenital myasthenic syndromes (CMS) represent rare or at least uncommonly recognized genetic defects in specific proteins, which, under normal circumstances, facilitate efficient NMT at presynaptic, synaptic, or postsynaptic locations.[163] As in MG, their phenotype is typically dominated by fatiguing weakness. Unlike MG of LEMS, these are not disorders of autoimmunity. In general, the clinical manifestations of CMS may be somewhat heterogeneous, even within the limited phenotypic repertoire of the neonate and infant. Reduced uterine motility may be recognized by the mother of the affected child. Arthrogryposis multiplex congenita has been reported in at least three of the syndromes. Most affected individuals will suffer from neonatal hypotonia in combination with a poor suck, weak cry, variable but usually symmetric ptosis, stridor, choking spells, and/or ventilatory difficulties that may include apnea. Ophthalmoparesis may be observed. As in other DNMT, the intensity of the children's problems may worsen as the day progresses, as the child ages, or with physical activity. The natural history of these disorders varies both within and between the different syndromes. Delayed motor milestones are the norm in those affected in infancy. Some individuals have a seemingly static course, whereas slow disease progression is anticipated in two of the syndromes. Most affected individuals are affected at birth or soon thereafter, but milder forms presenting later in life with fatigable limb or oculobulbar weakness do occur.[163,164] Identification of other family members in keeping with a recessive inheritance pattern or consanguinity is supportive of the diagnosis, but the absence of other affected family members does not preclude CMS from consideration. Some forms of the slow channel syndrome are inherited in a dominant fashion.[165–168]

The following represents the current classification of these disorders based on the location of the NMT defect. Mutations affecting epsilon subunit of AChR (primd-eficiency), rapsyn, and Dok-7 result in the most common forms of CMS. Clinical features that are characteristic of individual disorders distinct from the general characteristics mentioned above are listed.[163]

Presynaptic Disorders

- Choline acetyltransferase deficiency—This recessively inherited syndrome was originally designated as a familial infantile myasthenia. Children affected by this tend to have an episodic rather than a static disorder characterized by feeding difficulties due to fatigue while sucking, a weak cry, intermittent ptosis, and spontaneous apnea episodes that may be provoked by fever, emesis, or excitement.[169–177] Children may expire due to these apneic periods, although these episodes tend to resolve if the child survives to adolescence or adult life.
- CMS with paucity of synaptic vesicles and reduced quantal release—The reported phenotype in this disorder included ptosis, ophthalmoparesis, facial weakness, and generalized fatigable extremity weakness beginning in infancy.[178,179]
- Other undefined.

Synaptic Disorders

- End-plate acetylcholinesterase (AChE) deficiency—Patients born with a congenital deficiency of AChE present soon after birth or in early childhood with the phenotype described above.[172,173,180–184] In addition, there is mild slowing of the pupillary light response. Patients do survive into adulthood but tend to have an overall reduced amount of muscle bulk and significant axial weakness leading to hyperlordosis and kyphoscoliosis and are often confined to wheelchairs.

Postsynaptic Disorders

- Primary kinetic defect +/− AChR deficiency—The slow channel syndrome is dominantly inherited in most cases. There is a tendency toward a progressive course, although the severity of the phenotype can be quite variable. Adult patients may have a pattern of weakness that frequently involves cervical, wrist, and finger extensor muscles accompanied by mild ophthalmoparesis, whereas infants may be wheelchair and ventilator dependent.

  The natural history and the extent of affliction of the fast channel syndromes are variable as well. Severe weakness may be present at birth

with poor suck and weak cry; relatively mild focal weakness may occur in adulthood.[163,178,185,186] Weakness of both bulbar and limb muscles occur. Temperature elevation and exertion may exacerbate the weakness.

- Primary AChR deficiency +/− kinetic defect—Arthrogryposis may occur in AChR delta and gamma subunit mutations. Mutations in the AChR epsilon subunit correlate with a mild phenotype due to surrogate function of the fetal gamma subunit. These tend to have a nonprogressive phenotype with limb and oculobulbar, but rarely ventilatory, muscle involvement. In contrast, non-epsilon AChR subunit mutations typically correlate with a severe phenotype with respiratory crises precipitated by choking and/or ventilatory weakness, with a resultant shortened life expectancy.
- Rapsyn deficiency—The phenotype is once again variable. There may be arthrogryposis. Increasing weakness, which may include ventilatory muscles, may be provoked by intercurrent illness or pregnancy and is characteristic of this disorder. Late-onset cases can readily be mistaken for seronegative MG.[164]
- Sodium channel myasthenia.
- Plectin deficiency.
- Dok-7 myasthenia—Disease severity is variable, ranging from the mildly to severely symptomatic. A progressive course is most common. The typical phenotype is a limb-girdle pattern of weakness, with ptosis presenting in childhood to the third decade of life. Extraocular movements are typically spared. Significant bulbar symptoms may occur. Severe disability including ventilatory failure may occur by the third decade but is not invariable.[187–189]

Familial Limb-Girdle Myasthenia

This is in many ways an overlap syndrome between autoimmune acquired MG and the congenital (heritable) myasthenic syndromes. It is an autosomal-recessive disorder characterized by a limb-girdle pattern of fatigable weakness, typically presenting in childhood or early adult life.[125–131] It differs phenotypically from MG in that oculobulbar musculature is spared. Deep tendon reflexes may be normal or hypoactive. Awareness of this syndrome is important, as it is easily mistaken for a myopathy if appropriate EDX assessment is not performed.

LAMBERT–EATON MYASTHENIC SYNDROME

LEMS is the second most common NMJ disorder.[190–198] As in MG, LEMS is an autoimmune disorder. It is causally related to antibodies directed against voltage-gated calcium channels in the majority of afflicted individuals. LEMS is a paraneoplastic disorder in approximately two-thirds of cases. Small cell carcinoma of the lung is the underlying malignancy in approximately 90% of these paraneoplastic cases. Lymphoproliferative disorders, pancreatic, breast and ovarian carcinomas are other neoplasms reported to associate with LEMS.[199,200] The LEMS symptoms usually precede tumor recognition by about 10 months (range 5 months to 3.8 years). Approximately 84% of patients with LEMS are over the age of 40 years, with 54 years being the mean age at presentation. Patients with LEMS who are seronegative are clinically indistinguishable from their seropositive counterparts.[201]

In the other third of patients, LEMS occurs in the apparent absence of an underlying cancer. Such cases are more common in young females who commonly have other autoimmune disorders. Rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, primary biliary cirrhosis, and even MG may coexist.[202–210] Other than the risk factors of age and smoking, the paraneoplastic and nonparaneoplastic forms of LEMS are clinically and electrophysiologically indistinguishable.

Patients with the LEMS usually voice the same complaints as their MG counterparts, that is weakness and easy fatigability, thus explaining its designation as a myasthenic syndrome.[190,192,193,195–198,211,212] The morbidity and functional impairment associated with these complaints seem to be disproportionate to the severity of objective weakness in many patients. This may be in part due to the technique of muscle testing as described below. Regardless, it may contribute to the suspicion of a psychogenic disorder, particularly in young women with the nonparaneoplastic form of the disorder.

The majority of patients present with proximal lower extremity weakness. Proximal upper extremity weakness is noted in approximately 80% of patients during the course of the illness. A third of patients complain of muscle aching and stiffness during or following physical exertion. Approximately 20% of patients note that their weakness and fatigue are exacerbated by hot weather or baths. Ocular and bulbar symptoms are not as common or as severe as seen in MG but do occur and may be the initial manifestation.[213,214] In those with cranial muscle involvement, neck flexor, extensor, and facial muscles are among the most commonly affected. Ptosis and diplopia are often transient and mild. Some patients develop dysarthria or dysphagia. Xerostomia and xeroophthalmia may be contributory to these symptoms. Cholinergic dysautonomia manifesting in this way or with blurred vision, constipation, decreased sweating, and impotence are common.[200] Although pulmonary symptoms from lung cancer or associated chronic lung disease may occur, ventilatory issues are rare, although LEMS presenting with ventilatory

failure has been described.[50,215,216] Complaints of numbness and paresthesias in the distal extremities may occur on occasion.

As previously mentioned, erroneous assessments of muscle strength may result from the potentiation created by the manual muscle testing procedure. The patient's strength must be graded from the initiation of contraction, not several seconds later. For example, the patient may initially have difficulty maintaining hip flexion in the seated position but then demonstrate subsequent recovery. This phenomenon may contribute to the perception that the patients are stronger than their histories suggest. Potentiation occurs primarily in proximal hip and shoulder girdle muscles. The improvement usually dissipates with sustained muscle contraction. Repetitive squatting is another means to demonstrate initial weakness, improvement, and then subsequent decline after several minutes. Exercise may also be used to evaluate ptosis, which may be improved with sustained voluntary lid elevation in a manner opposite to MG.[217]

In advanced stages of the disease, muscle atrophy can be observed. Cholinergic dysautonomia may also be demonstrated by recognition of a sluggish pupillary light reaction or diminished sweating to a provocative challenge. Deep tendon reflexes may initially be diminished or absent but may amplify once a muscle has been contracted. A few patients with LEMS associated with anti-Hu antibodies (usually seen with small cell carcinoma of the lung) also have clinical findings suggestive of a sensory neuronopathy, cerebellar ataxia, and/or limbic encephalitis.[218] The former may explain the paresthesias or sensory loss that can occasionally be reported or recognized.

A small number of patients will present with what seems to be an MG/LEMS overlap syndrome.[149,219–227] Most MG cases overlapping with LEMS are based on the presence of AChR antibodies in patients who otherwise appear to have LEMS on a clinical and electrophysiological basis. As many as 13% of patients with LEMS have AChR-binding antibodies.[228] The anti-AChR antibodies may be epiphenomenal rather than pathogenic in at least some LEMS patients.[147,228] Nonetheless, rare patients may exhibit clinical features of both LEMS and MG.

BOTULISM

In an adult, the clinical presentation of botulism is similar, irrespective of whether the disease is acquired through a foodborne, wound, or hidden (i.e., suspected gastrointestinal) route.[113,229–236] The foodborne and infantile varieties are the most common forms of the disease. Statistically, different serotypes of *Clostridium botulinum* may have minor phenotypic differences, which are inconsequential in the evaluation of individual patients. Symptoms of botulism can be categorized as neurologic, gastrointestinal, or miscellaneous.

Dysphagia, xerostomia, diplopia, and dysarthria beginning acutely and progressing over the course of 12–36 hours are characteristic. Anxiety is a common symptom. The time course is dependent, in part, on the amount of toxin consumed. A careful history may allow documentation of upper cranial nerve involvement prior to the development of more rostral swallowing and speaking difficulties. In foodborne botulism, gastrointestinal symptoms of nausea, occasional vomiting, and initial diarrhea followed by constipation may occur just prior to or coincident with the neurologic symptoms. Associated complaints of abdominal cramps, undue fatigue, and dizziness may also be described during the disease's evolution. Subsequently, dependent on the degree of intoxication, patients develop progressive weakness affecting first the upper and then the lower extremities. The patient may begin to notice shortness of breath prior to extremity involvement. Occasional asymmetries may be appreciated. It has been speculated that the cranial muscles are affected prior to the limb muscles due to higher temperatures of the face compared to limbs. There is a distinct lack of sensory complaints, although an occasional patient may describe an alteration in sensation affecting either face or limbs.

Cranial nerve evaluation in botulism typically reveals ptosis, a diminished gag reflex, dysphagia, dysarthria, facial paralysis, tongue weakness, and occasionally nystagmus. Deep tendon reflexes may be normal or diminished initially, with progression to complete loss in severely affected individuals. The forced vital capacity is reduced in most cases, with ventilator support eventually being required in 32–81% of patients.[237,238] The duration of required mechanical ventilation is dependent on the severity of the illness and serotype of the infecting organism, with a mean of 58 days for type A and 26 days for type B botulism.[237,238]

Careful patient examination can reveal disturbances of autonomic function affecting both the sympathetic and parasympathetic systems. Specifically, there can be loss of vagal cardiac influence, ileus, hypothermia, and urinary retention. Hypotension without tachycardia may be present, and a lack of vasomotor responses to postural change may be observed. Pupils are often poorly reactive to light.

In wound botulism, the patient's symptoms are quite similar to the foodborne form of botulism with a few modifications. The patient may or may not relate to a history of a traumatic event, particularly individuals who use elicit, parenteral drugs. Botulism should enter the differential diagnosis of weak patients who are intravenous (IV) drug abusers. Gastrointestinal complaints are less common than foodborne botulism. Wound botulism is more likely to affect an individual as opposed to a group as might be anticipated in foodborne disease.

The incubation period is longer in wound botulism, typically 4–14 days in comparison to hours for toxin or spore ingestion. In cases of suspected wound botulism, the integument should be carefully searched, not only for gross disruption and wound contamination, but also for minor bruising with or without signs of infection. Culture of these areas should be performed for anaerobic organisms. The nasal mucosa should also be carefully evaluated.

The phenotype of infantile botulism can range from mild symptoms to sudden death. Constipation is a relatively constant and sometimes the sole symptom in mild cases. Affected children may appear listless with diminished spontaneous movements. Parents may note that the child has a diminished suck. In more severe forms of the disease, the child is hypotonic and "floppy." Excessive drooling accompanied by a weak cry is particularly worrisome. Ptosis and "smoothing" of facial expression may be noted. Repeatedly testing pupillary constriction may reveal fatigue of this response. Reduced head control and gag reflex may also be noted. Inserting one's finger into the infant's mouth reveals a weak sucking action compared to healthy infants. Deep tendon reflexes may be present or diminished. With disease progression, infants become areflexic.

Ventilatory function should be closely monitored, as approximately 50% of infants require assisted mechanical ventilation. Both ventilatory muscle weakness and airway obstruction from pharyngeal muscle weakness may be contributory. Several weeks may be required prior to patient recovery. Similar to adults, infants infected with botulinum toxin (BTX) A tend to have a more severe disease course than those infected with BTX B. During the recovery phase, the infants may continue to shed toxin and organisms from the stool. This does not implicate that the disease is refractory to treatment. Eventually, bowel flora returns to normal.

TICK PARALYSIS

Tick paralysis is a rare but fascinating cause of acute generalized weakness caused by a salivary toxin from selected species of ticks. Its classification is a matter of some controversy. It is discussed here in DNMT, as the pathophysiology of at least one species appears to involve neuromuscular blockade and as abnormal responses to repetitive stimulation have been suggested (see below). In all probability, it should be more accurately considered as a toxic neuropathy, as the majority of known varieties of this disorder appear to represent nerve channel poisons.

Children are three times as likely to be afflicted with tick paralysis as adults.[239–244] One hypothesis for this discrepancy is the added opportunities for attachment on the long hair of short-statured young girls. On the other hand, adult men are more likely to be affected than women presumptively because of increased exposure to wooded areas. Patients typically present with ascending weakness evolving over the course of a few hours or days to flaccid paralysis.[239–242,245–254] Children are often quite irritable. Cranial nerve involvement including internal and external ophthalmoplegia, facial weakness, dysarthria, and dysphagia occur commonly. Ventilatory muscle weakness is a common feature as well. Patients may complain of pain, numbness, and uncomfortable paresthesias, such as itching or burning in the extremities. Despite these complaints, objective sensory loss is mild and typically restricted to initial stages of the disease. Occasional patients may develop sensory ataxia, past-pointing, and decreased heel-to-shin and finger-to-nose ability. Deep tendon reflexes are diminished or absent. The onset and course are usually more abrupt on average than seen in most cases of Guillain–Barré syndrome, but this is of little value as a discriminator in individual cases.[255]

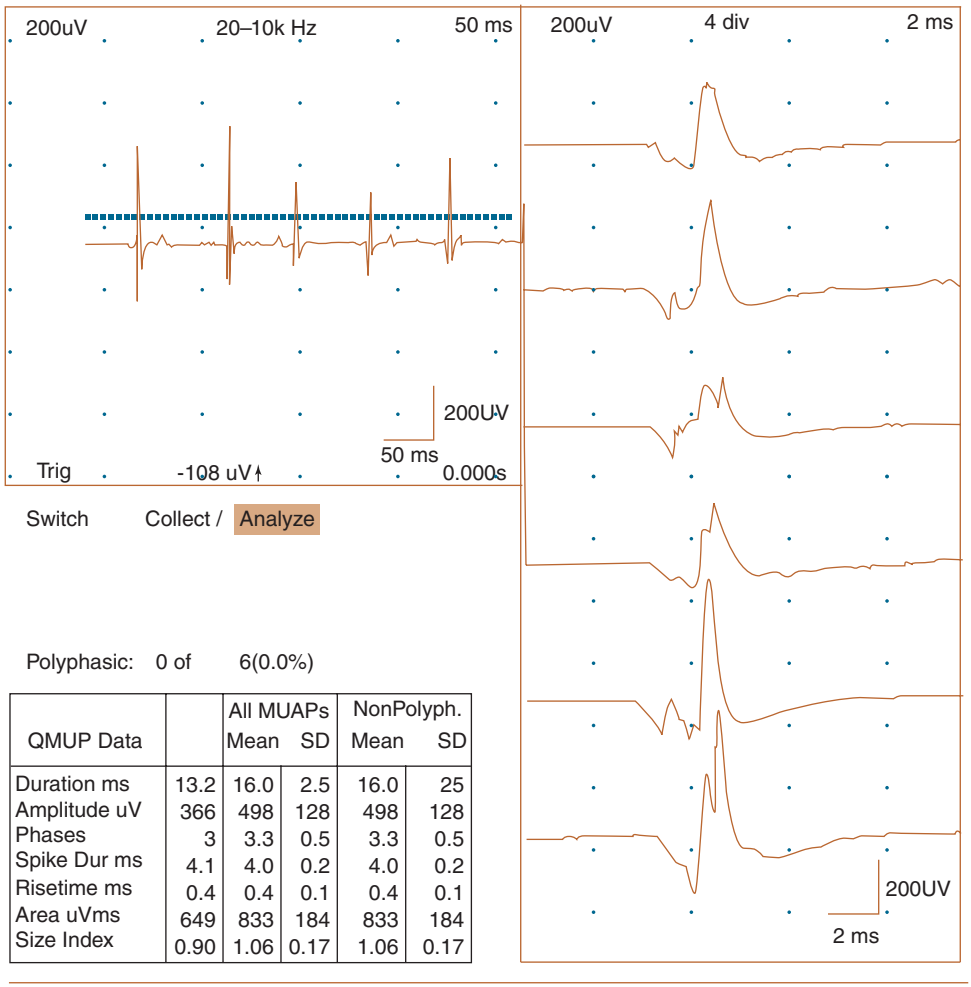
▶ LABORATORY FEATURES

MYASTHENIA GRAVIS

Electrophysiology

A detailed description of the electrodiagnostic EDX features of MG and other DNMT is provided in Chapter 2.[256] In summary, routine motor and sensory conduction studies are typically normal. Fibrillation potentials and positive waves are uncommon but may occur, particularly in paraspinal, bulbar, and proximal muscles.[257] Their prevalence increases in patients who are significantly affected by generalized disease.[258–260] Their presence may lead the electrodiagnostician away from a diagnosis of MG if unaware of this unusual finding. Short-duration, low-amplitude motor unit action potentials (MUAPs) associated with early recruitment may occur. This pattern results from neuromuscular blockade and an effective reduction in the number of functional myofibers within a given motor unit.[258–273] This pattern, i.e., fibrillation potentials and small MUAPs, is similar to the needle electromyography (EMG) findings in inflammatory myopathies. As a result, the possibility of a coexisting inflammatory myopathy may be overlooked. Serum CK values may aid in resolving this potential problem.

Demonstration of unstable MUAP variability (instability) is a very helpful EDX tool in MG (Fig. 23–2). MUAP variability can be easily demonstrated if sought for. To do so, a single MUAP is isolated and viewed repetitively using a delayed trigger line coupled with an increased low-frequency filter setting (500 Hz) and fast sweep speed (1–2 m/s). This MUAP variability is analogous to the decremental response to slow repetitive stimulation,



QMUP Data		All MUAPs Mean	All MUAPs SD	NonPolyph. Mean	NonPolyph. SD
Duration ms	13.2	16.0	2.5	16.0	25
Amplitude uV	366	498	128	498	128
Phases	3	3.3	0.5	3.3	0.5
Spike Dur ms	4.1	4.0	0.2	4.0	0.2
Risetime ms	0.4	0.4	0.1	0.4	0.1
Area uVms	649	833	184	833	184
Size Index	0.90	1.06	0.17	1.06	0.17

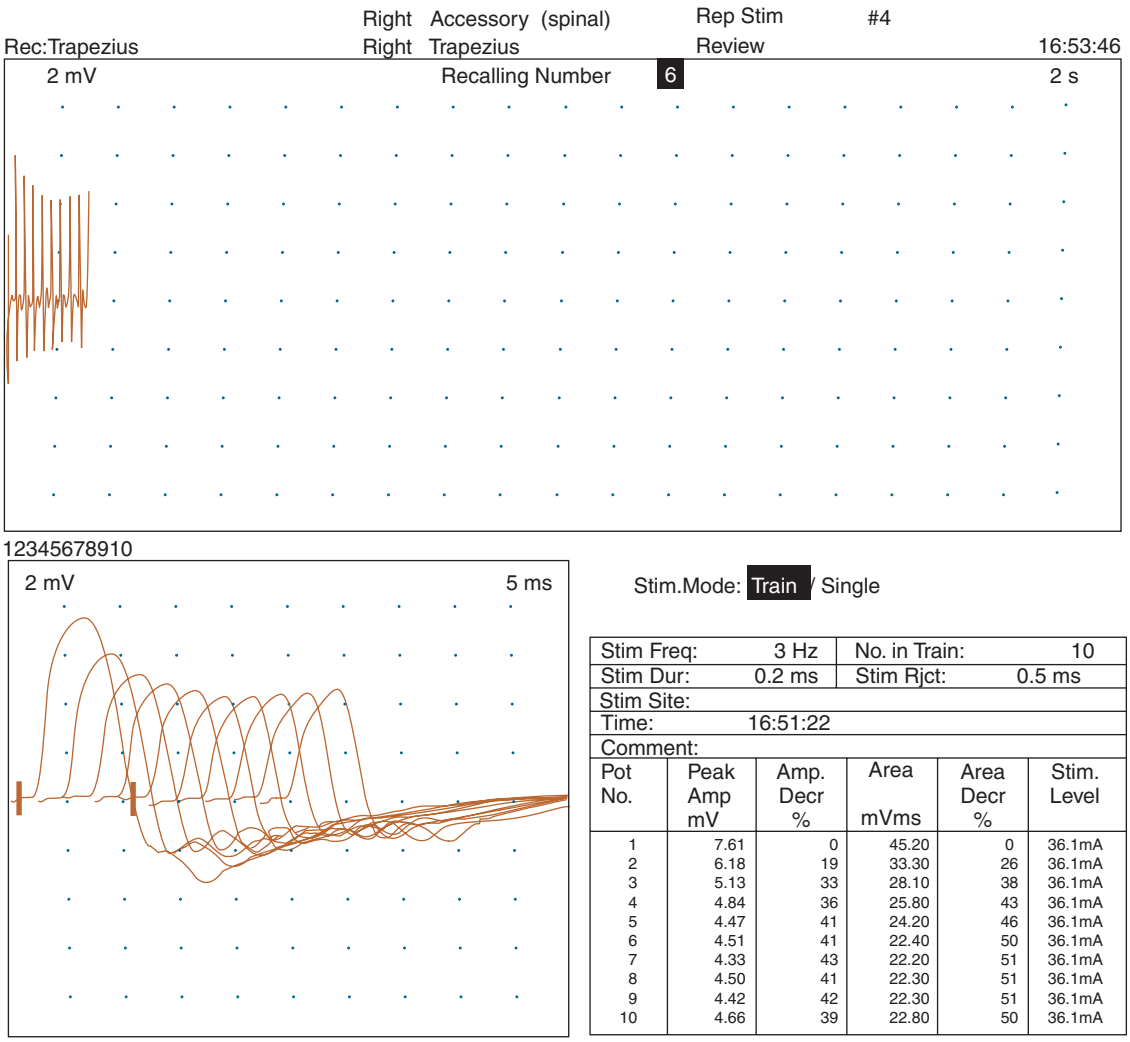
Figure 23–2. Motor unit instability—i.e., variable MUAP size and shape with consecutive firings.

blocking in single fiber electromyography (SFEMG), and the fatigable weakness experienced by the patient. Its value is that it provides the same information as a decremental response to slow repetitive stimulation in muscles that are not technically accessible to nerve conduction studies without the diagnostic rigor required for SFEMG evaluation.

The traditional EDX tool used to identify a postsynaptic DNMT is the decremental response to "slow" repetitive stimulation.[274–276] "Slow" repetitive stimulation refers to rates ≤5 Hz, with 2 or 3 Hz typically used. Under normal circumstances, compound muscle action potentials (CMAPs) of the same amplitude will occur indefinitely due to the safety margin of the endplate potential (EPP), which will be subsequently described. When the safety margin is lost by the combined stresses of "slow" repetitive stimulation and by presynaptic, synaptic, or postsynaptic dysfunction, NMT failure may occur at one or many myoneural junctions.

With slow repetitive stimulation, a train of five to 10 stimuli is delivered depending on laboratory preference. Five stimuli are adequate to identify the decremental response. Although 10 stimuli are more uncomfortable, these improve recognition of the typical pathological pattern and serve to reduce the possibility of a technically induced false-positive diagnosis. A decrement may not be evident in response to the initial stimulus train. In most traditional testing paradigms, the muscle tested is then exercised in an attempt to induce postexercise exhaustion and increase the diagnostic yield. Recently, this practice has been called into question in view of the time and discomfort associated with this approach in comparison to the relatively low additional diagnostic yield.[277] With this maneuver, only modest increases in the incidence and severity of decrement occur.

To elicit postexercise exhaustion, the tested muscle is exercised for 1 minute. Subsequent stimulus trains are delivered at 30-second intervals until a significant decrement occurs or 3–4 minutes elapse. The study is considered positive if a >10% decrement is identified by measuring either CMAP amplitude or area. Comparison is made between the first and the smallest (typically



Stim Freq:	3 Hz	No. in Train:	10
Stim Dur:	0.2 ms	Stim Rjct:	0.5 ms
Stim Site:			
Time:	16:51:22		
Comment:			

Pot No.	Peak Amp mV	Amp. Decr %	Area mVms	Area Decr %	Stim. Level
1	7.61	0	45.20	0	36.1mA
2	6.18	19	33.30	26	36.1mA
3	5.13	33	28.10	38	36.1mA
4	4.84	36	25.80	43	36.1mA
5	4.47	41	24.20	46	36.1mA
6	4.51	41	22.40	50	36.1mA
7	4.33	43	22.20	51	36.1mA
8	4.50	41	22.30	51	36.1mA
9	4.42	42	22.30	51	36.1mA
10	4.66	39	22.80	50	36.1mA

Figure 23–3. Typical pattern of a pathological decremental response to "slow" repetitive stimulation.

fourth or fifth) responses. The 10% criteria was historically chosen to minimize the chances of a false-positive result. This decision was made in an era where technical concerns pertaining to equipment were more of an issue. With the precision of contemporary equipment, a decremental response of 5–10% should be considered suspicious if it reproducibly conforms to the pattern described below.

Movement or other artifact sources may easily produce a false-positive response. A pathological decrement has a characteristic pattern, the absence of which should preclude an abnormal conclusion. This pattern consists of a steady decline in CMAP amplitude between the initial responses until the nadir is reached between the forth and the sixth responses. The greatest amplitude or area difference between consecutive waveforms occurs between the first and second responses. After the nadir of the decrement, somewhere between the forth and the sixth response, a steady increase in CMAP amplitude occurs. The CMAP amplitude of the ninth and 10th responses approach but never achieve the amplitude of the initial response. The resulting smooth curve defined by the peaks of these responses has a configuration that looks like a ski jump or a lopsided banana (Fig. 23–3). Any response curve with baseline movement, an irregular saw-toothed configuration, or whose configuration varies between consecutive trains without additional influence should be interpreted cautiously.

To further avoid the possibility of a false-positive result, repair of the decrement may be attempted. Typically, this is done by taking advantage of the principle of post-tetanic facilitation. This can be achieved either by brief (10–15 seconds) isometric exercise of the tested muscle (the preferred method in the cooperative patient) or by the delivery of a brief train of "fast" repetitive stimuli at a frequency of 10 Hz or more. The former technique is equivalent to repetitive stimuli delivered at approximately 20–30 Hz. With either method, the EPP is

transiently augmented by increased quantal release from the presynaptic terminal. As will be described in more detail below, this is a consequence of the increased calcium concentration within the presynaptic terminal that has not had a chance to dissipate between consecutive stimuli because of the short stimulus interval between stimuli. The facilitation of quantal release provoked by either exercise or fast repetitive stimulation is limited in duration and quickly replaced by exhaustion if either the stimulus train or the exercise exceeds 30–60 seconds.

It should be emphasized that patients with postsynaptic DNMT such as autoimmune MG have CMAP amplitudes that are typically normal at rest, which cannot be augmented by either of the facilitation techniques described above. The only role of postexercise facilitation in MG is to repair a decrement that has been previously created by "slow" repetitive stimulation. Although more cumbersome, a decrement may be repaired pharmacologically as well with the use of the cholinesterase inhibitor, edrophonium. Although not usually required for diagnostic purposes, the decrement can be readily recreated following repair by applying an additional 1 minute of isometric exercise followed by an additional train of slow repetitive stimulation.

The muscles chosen for this exercise represent a compromise between muscles that are technically easiest to study (better-tolerated, less movement artifact) and those that have the highest diagnostic yield. Intrinsic hand muscles may fail to demonstrate a significant decremental response in 50–68% patients with moderately severe MG.[272,276] Proximal muscles, e.g., the biceps, deltoid, and the trapezius, have higher yields. Erb's point stimulation with deltoid recording may be 80–90% sensitive in patients with myasthenia, but brachial plexus stimulation is both uncomfortable and technically difficult in view of the movement it creates. Accessory nerve stimulation has similar sensitivity and is usually better tolerated with an easier to establish stable baseline.[278] Movement artifacts may be averted by strategies that diminish actual body movement. An arm board can be used to immobilize the elbow with musculocutaneous nerve stimulation in the axilla. Patients can sit on their hands during axillary nerve stimulation. A belt or cloth loop connecting ipsilateral hand with the foot of the extended leg may provide additional stabilization for trapezius recordings. With stimulation of the common peroneal nerve while recording from the tibialis anterior, stabilizing the ankle with an ankle foot orthosis may improve the quality of the result. Facial nerve activation with recordings from the orbicularis oculi or nasalis muscles has a higher yield than limb muscles. Movement can be a significant problem in some patients. In view of the proximity of the stimulating electrode to the contracting muscles, there is a significant potential for movement of the stimulating electrodes. Using electrodes securely taped to the angle of the jaw over the facial nerve with a plastic pen or pencil applying pressure to the middle of the bar electrode is one way to minimize this problem.

Historically, regional applications of both ischemia and d-tubocurarine curare were used in addition to "slow" repetitive stimulation, in an effort to increase diagnostic yield in MG. As these are cumbersome and potentially risky maneuvers, SFEMG represents the preferred EDX alternative in most EMG laboratories where "slow" repetitive stimulation is nondiagnostic.

"Slow" repetitive stimulation is estimated to be abnormal in 37–62% of individuals with MG.[43,258–260,262,274,279–286] Stimulation of a proximal muscle increases the percentage of abnormal responses to 62–77%. In patients with ocular MG, repetitive stimulation of a distal upper extremity nerve yields positive results in only up to 35% of patients. Adding a proximal nerve increases the yield slightly to 45%. Patients who are MuSK antibody positive tend to have both a lesser incidence and a lesser degree of decrement in limb muscles compared to other MG populations.[73,85] A higher yield of abnormal decrement will be found in facial muscles in the anti-MuSK patient population.[82] Estimates of incidence of abnormal decrement in these patients range from one-third to one-half in limb muscles as opposed to 50–85% in facial muscles.[88]

All of the aforementioned information pertaining to the EDX assessment of NMT applies to children and adults alike. In normal infants, the limited data available suggest that with stimulation rates between 1 and 2 Hz, there is no alteration in the CMAP.[287–289] Repetitive stimulation at rates between 2 and 5 Hz yields variable results, with some normal infants demonstrating a decrement and others revealing no change. At 5 Hz, most term infants should not demonstrate an alteration in the sequentially recorded CMAPs, although a few may demonstrate a mild (11–17%) increment with an occasional decrement being noted. If a 10-Hz train of stimuli is applied for 15 seconds, about half of children examined who are 39 weeks or older may reveal an increment approaching 14%. When a 15-second 20-Hz stimulation train is applied, most children reveal a decrement of about 24%, while premature infants (<38 weeks) have a larger decrement (about 32%). A few term infants may demonstrate an initial increment for several responses followed by the anticipated decrement. If repetitive stimulation is delivered at 50 Hz for 15 seconds, all term as well as premature infants demonstrate a decrementing CMAP response of approximately 50% with premature infants having larger decrements of about 77%. These findings suggest that term infants and especially premature infants have a reduced NMJ reserve capacity, especially at the higher rates of stimulation. It is certainly possible to examine infants with repetitive stimulation techniques as long as the above findings are kept in mind. This is particularly relevant following 50 Hz

stimulation when attempting to define the presence of postactivation exhaustion.

SFEMG is a more precise and quantitative way of assessing motor unit variability.[290] Either a special SFEMG electrode or a standard concentric needle may be used. A muscle(s) is studied that is anticipated to have a high diagnostic yield (e.g., the frontalis or obicularis oculi in a patient with isolated ptosis) and for which normative data exist. SFEMG, like MUAP variability and slow repetitive stimulation, is capable of identifying failure of NMT, which in SFEMG parlance is referred to as blocking. SFEMG has a twofold advantage over these former techniques. First, it is more sensitive, as it can demonstrate failed NMT in single muscle fibers rather than in single motor units (MUAP variability) or entire muscles ("slow" repetitive stimulation). More importantly, unlike the other techniques, it can identify abnormal NMT prior to actual failure. It does so by measuring jitter, i.e., the variability in the interpotential interval between consecutive action potential discharges of two or more single muscle fibers belonging to the same motor unit.

This variability stems from the basic principle that the time between EPP initiation and myofiber action potential generation is inversely proportionate to the EPP amplitude. As described in the "Pathophysiology" section below, EPP amplitude varies with each consecutive myofiber activation due to variable acetylcholine (ACh) quantal release, efficiency of cholinesterase metabolism, or availability of ACh receptors. This EPP amplitude and resultant timing of muscle fiber action potential variation are the physiologic bases of jitter. Jitter is an inherently normal property of NMT, i.e., abnormal only when values are excessively high or low.[270,279] The actual technique of SFEMG is described in more detail in Chapter 2.

Stimulated SFEMG is another method of assessing jitter and blocking. Its major benefit is that it requires minimal patient cooperation and has its greatest utility in patients incapable of providing a consistent effort, that is children or encephalopathic, extremely weak or unresponsive adults.[291–298] The technique can be performed by inserting a stimulating monopolar needle into the muscle near the motor end plate. The anode is typically a surface electrode placed nearby. The stimulation frequency can range from 2 to 10 Hz, while duration of the stimulus should be 0.05 millisecond. The intensity of the current should be low to start and be gradually increased until a visible twitch in the muscle is apparent. The current should never exceed 20 mA. If large currents are necessary, the stimulating electrode is too far from the end plate. The single fiber needle is placed where the muscle twitching is apparent. The needle is adjusted so that recorded potentials have a rise time <200 microseconds and amplitudes of at least 200 μV. The jitter of the recorded potentials is measured in relation to the triggered stimulus.

With the axonal stimulation provided by stimulated SFEMG, it is often possible to record two or more potentials at any given position of the recording single fiber needle. Consequently, stimulated SFEMG is much faster than volitional SFEMG. A major pitfall of the procedure that clinicians need to be aware of is direct stimulation of the muscle fiber itself rather than the axon innervating it. Direct stimulation of the muscle fiber bypasses the NMJ, and therefore the measured "jitter" is abnormally short (i.e., 5 microseconds or less). Data obtained from these recordings should be discounted and the stimulating monopolar needle repositioned.

Jitter values when properly obtained by either voluntary or stimulated SFEMG are reported as the mean consecutive difference. These values are less with the stimulated technique than with volitional SFEMG by a factor of approximately 20%, as the variability of one rather than two NMJs is being measured.[294] Normal values for mean consecutive difference during axonal stimulation of the extensor digitorum communis are <40 microseconds for individual potentials and <25 microseconds for the mean of 20 potentials. Normal mean consecutive difference during axonal stimulation of the orbicularis oculi is 30 microseconds for individual potentials and <20 microseconds for 20 potentials.[140]

The diagnostic yield of all of these tests varies. As weakness in DNMT results from failure of NMT, the inability to demonstrate the electrophysiological correlates, i.e., MUAP variability with routine needle EMG, a decremental response to "slow" repetitive stimulation, or blocking in SFEMG, in a clinically weak muscle, is incompatible with a DNMT diagnosis. SFEMG is the most sensitive of these tests and is capable of documenting abnormalities of jitter in 77–100% of patients, depending on disease severity and the muscle chosen.[258–260,268,271,272,281,285,286,299–301] SFEMG abnormalities in the frontalis or obicularis oculi are found in 87–99% of patients with oculobulbar weakness.[302] Studying the frontalis as opposed to a limb muscle will increase diagnostic yield from the 22–66% range to the 54–100% range.[258,259,262,272,285] SFEMG abnormalities, like every other aspect of MG, can be patchy. In 433 potential pairs from 32 patients with MG, normal jitter was apparent in 9%, increased jitter in 38%, and abnormal jitter with blocking in 53% of the potentials.[268,271] Blocking does not typically occur until jitter values are increased into the >80 microseconds range. The severity of jitter measurements and the incidence of blocking correlate with the severity of muscle weakness. Although jitter measurements improve following successful treatment,[258–260,281,286,303] jitter abnormalities may persist even in those in clinical remission.[258–260,286,304] As in "slow" repetitive stimulation, SFEMG abnormalities in patients who are anti-MuSK are more likely to be found in facial or proximal muscles rather than in distal

limb muscles such as the extensor digitorum communis, with a lower yield in limb muscles in general than expected in other MG populations.[83,87]

The diagnostic yield in any patient suspected to have MG studied electrodiagnostically can be improved upon by withdrawing cholinesterase inhibitors for 12 hours or more prior to testing and by warming tested limbs adequately. It must be emphasized that none of the aforementioned electrophysiological tools are specific for either MG or any other DNMT. Any of them can be abnormal in any nerve disease in which active reinnervation and immature NMJs occur. ALS is a notable example of this.[305]

The electrical findings in transient neonatal MG are analogous to those found in adults.[102,105,306] A decremental CMAP response is typically demonstrable at low rates of stimulation, which can be minimized with postactivation excitation and augmented with postactivation exhaustion. Frequently, a decrement occurring at high rates of stimulation occurs as well, depending on the severity of the disease. Tapering anticholinesterase medication and assessing the degree of decrement can be used in an attempt to determine safe medication withdrawal. The absence of a decrement indicates adequate (and permanent) recovery.

Serological Testing

AChR antibodies are detected in the majority but not in all patients with MG.[307] There are three types of detectable antibodies directed specifically at the AChR receptor. These are also described in more detail in Chapter 2. AChR-binding antibodies, AChR-modulating antibodies, and AChR-blocking antibodies are all commercially available tests.[228,308] Elevation of one or more of these three antibody levels identifies 80–90% of patients with all grades of MG. The sensitivity is estimated at 70–80% in MG clinically restricted to extraocular muscles. In patients who have generalized disease, a sensitivity of over 90% is expected. There does not appear to be significant differences in phenotype, EDX signature, natural history of disease, or response to treatment between patients who are seropositive and seronegative.[66] AChR-binding antibodies are the most frequently tested and identified. Most patients have both the binding and the modulating antibodies present, but approximately 8% will have only one of these antibodies detected.[71,228,308] AChR-modulating antibodies also have value as a surveillance tool for thymoma, as 73% of patients with thymoma and MG will have modulating antibodies producing a >90% receptor loss.[71] AChR-blocking antibodies are present in approximately half of patients with generalized MG but only 30% of patients with ocular disease.[228,308] As <1% of patients will have blocking without detectable binding or modulating antibodies, this particular test has limited pragmatic value.

AChR-binding antibodies are highly specific for MG, but these can also be detected in patients with autoimmune liver disorders, approximately 13% of patients with LEMS, and about 3% of patient with lung cancer without an apparent neurological disorder.[228] It is important to emphasize that the value of any of these tests is strictly in initial diagnosis, or in the case of modulating antibodies, as a potential marker for thymoma. The serum titer of any of these antibodies does not correlate with disease severity. Following titers is generally not considered an accurate means to judge treatment response, although in some patients, a falling antibody titer following thymectomy seems to correlate with clinical improvement.[309]

In 2001, the first report of antibodies directed against MuSK antibodies in MG was published.[310] Currently, it is estimated that 40% of patients with MG who do not have one or more of the aforementioned AChR antibodies will be found to be MuSK seropositive. Most studies have suggested no overlap between MuSK and AChR antibodies in patients with MG,[85,310] although exceptions to this rule at least in Japanese patients occur.[118] Unlike AChR antibodies, there appears to be a correlation between anti-MuSK titers, disease severity, and the application of immunomodulatory therapy.[311] On the other hand, thymectomy does not significantly alter anti-MuSK levels.

Striated muscle antibodies refer to a class of antibodies directed against components of skeletal muscle including titin, the ryanodine receptor, myosin, and α-actinin.[312] These are discoverable in approximately 30% of adult patients with MG without thymoma, 24% of patients with thymoma without MG, and 70–80% of patients who have both.[71,228,313,314] These antibodies may also occur in high titer in individuals who do not appear at the time of testing to have either MG or thymoma. Their ultimate significance in these situations is unknown. In some patients, striated muscle antibodies may be the only serological marker of autoimmunity in patients with MG. Unlike AChR antibodies, striational antibodies can be of value in monitoring the disease course. Persistence or recurrence of high titers of these antibodies may suggest incomplete resection or recurrence of thymoma, respectively.

There is also a known association between MG and certain HLA genotypes. Some studies have noted a predilection for HLA types A1, A3, B7, B8, and DRw3 in patients with MG.[315] These HLA subtypes may somehow predispose patients to autoimmune diseases. HLA genotyping is not routinely used in the evaluation of patients suspected to have MG.

Antibodies directed against the Kv1.4 subunit of voltage-gated potassium channels have been described to occur in a percentage of patients with MG but not in patients with thymoma, inflammatory myopathy, or in healthy controls.[93] These were found exclusively in

patients who were also AChR-binding antibody positive and are not commercially available. Their role in the diagnosis of MG, if any, has yet to be defined.

Pharmacological Testing

The edrophonium (i.e., Tensilon) test can be helpful in diagnosing MG.[28,30,316] Edrophonium is a short-acting anticholinesterase, the administration of which will result in a transient increase in ACh availability at the NMJ sufficient to transiently improve strength. To perform the edrophonium test, a butterfly needle is placed in an accessible vein. A 2 mg (0.2 mL) test dose of edrophonium is administered initially, as some patients are extremely sensitive to such low doses. Giving a full 10 mg dose initially may result in a false-negative conclusion in these individuals. If there is no response after 30 seconds, the remaining 8 mg are administered in 2 mg increments every 10–15 seconds. If the patient has an objective improvement or a severe side effect, the rest of the injection is aborted.

Performance of edrophonium testing should only be done in patients in whom an objective improvement can be documented. In this regard, evaluating improvement of ptosis or ophthalmoparesis is most useful. A test is not considered positive if the patient states that they feel stronger. Unfortunately, false-negative edrophonium testing is not rare in patients with MG. A modest response to edrophonium may be seen in other disorders as well. LEMS,[196] overlap MG/LEMS,[219] amyotrophic lateral sclerosis (ALS),[317–319] CMS,[177] botulism,[320] and Guillain–Barré syndrome[321] are notable examples. Accordingly, a positive edrophonium test indicates abnormal NMT and does not specify a singular disease entity.

Edrophonium testing is reported to be positive in 50–70% of MuSK antibody-positive cases. In general, false negative results are more common than with AChR seropositive patients.[73]

Edrophonium testing is not without risk. Many patients will be aware of the drug effect through the development of fasciculations, borborygmi, and eructation. Some patients are overly sensitive to the anticholinergic side effects of edrophonium and develop nausea, vomiting, increased tearing, and lacrimation. Syncope from bradycardia and transient heart block have occurred. Testing should be done with atropine, an EKG machine, and an individual skilled in resuscitation available. Clinicians should monitor the pulse and blood pressure of patients and be prepared to administer atropine to counteract the cholinergic effects of edrophonium.

Edrophonium has also been used in an attempt to distinguish myasthenic from cholinergic crises or in an attempt to determine whether respiratory difficulties are due, at least in part, to myasthenic-induced ventilatory weakness. As currently available treatments rarely require the doses of anticholinesterase medications used historically, the question of cholinergic crises rarely arises today.

The relative sensitivities of different tests used to support the clinical diagnosis of MG have been estimated and are summarized in Table 23–2.[43,283] AChR antibodies are estimated to occur in 70% of patients with ocular MG and between 70% and 90% of patients with generalized disease proportionate to the severity of their disease. Slow repetitive stimulation will identify a significant decrement in <35% of patients with ocular disease when distal muscles are tested, with the yield increasing to 45% if proximal muscles are selected. In more generalized disease, the yield is as low as 60% if distal muscles are tested in mildly affected individuals and approaches 100% in either distal or proximal muscles in severe generalized disease. In general, the yield is the greatest when proximal muscles are tested or the disease is more severe. SFEMG has the greatest sensitivity of all testing modalities even when the extensor digitorum communis was tested, with a yield of 80% in ocular cases and 90–100% of generalized disease.

▶ TABLE 23–2. DIAGNOSTIC YIELD OF TESTS COMMONLY USED IN THE DIAGNOSIS OF MYASTHENIA GRAVIS

Type	AChR			Distal Rep Stim (%)	Prox Rep Stim (%)	SFEMG (%)
	Binding (%)	Blocking (%)	Modulating (%)			
Remission	81	19	75			
Ocular	71	30	72	0–35	45–50	59–63
Mild generalized	88	52	89	55	76	91
Moderate–severe Generalized	93	66	91	86–99	96–99	99
All	86	52	86	37–62	62–77	86–92

AChR, antiacetylcholine receptor; SFEMG, single fiber electromyography.
With permission from Dumitru D, Amato AA. Neuromuscular junction disorders. In: Electrodiagnostic Medicine, 2nd edn, Chapter 25. Philadelphia: Hanley & Belfus, 2002, p. 1165.

CONGENITAL MYASTHENIC SYNDROMES

The evaluation of a patient with a suspected CMS can be a specialized undertaking that exceeds the capabilities of most institutions. AChR antibodies, anti-voltage-gated calcium channel antibodies, and potentially other serological tests to address and exclude autoimmune DNMT should be considered. Demonstrating a decremental response to "slow" repetitive stimulation will support the existence of a DNMT. It will not, however, distinguish CMS from other NMT disorders, nor will the absence of a decrement exclude a CMS from consideration. Identification of an afterdischarge(s) as described in Chapter 2 (Fig. 23–4) is not specific for AChE deficiency or the slow channel syndrome but is very suggestive in the appropriate clinical context. MUAP variability may be difficult to demonstrate in an uncooperative child and has the same limitations as a "slow" repetitive stimulation. SFEMG, a sensitive but nonspecific test, is usually reserved for patients in whom a decremental response cannot be demonstrated. In children, SFEMG is usually performed by the stimulated rather than the voluntary technique.

Ultimately, the identification of the existence and likely subtype of CMS may depend on a very specialized testing, which includes in vitro electrophysiological analysis such as patch-clamp experiments on single AChR channels, ultrastructural and immunocytochemical synaptic imaging, and potential genetic analysis in research laboratories.

Electrophysiology

Choline Acetyltransferase Deficiency

A decremental response to "slow" repetitive stimulation may be demonstrated in proximal muscles and is more likely to occur following serial trains of stimuli delivered after 1 minute or more of exercise. Motor unit variability may be seen on needle electromyography. No abnormal spontaneous activity is expected.

Paucity of Synaptic Vesicles and Reduced Quantal Release

A decremental response to "slow" repetitive stimulation may be demonstrated. Routine nerve conduction studies are normal. Facilitation at rapid rates of stimulation has not been demonstrated.

AChE Deficiency

In both this disorder and the slow channel syndrome described below, afterdischarges may be noted, similar to, if not identical to, those seen in organophosphate poisoning, Issac's syndrome, or envenomation with potassium channel poisons (Fig. 23–4).[172,173,180–184] These repetitive CMAPs are separated by 6–10 milliseconds, are small, and can be easily overlooked. These afterdischarges may decrement or disappear with repetitive stimulation delivered at the rates of 0.2 and 2 Hz. A decremental response may occur at both "slow" (e.g., 2 Hz) and "fast" (e.g., 40 Hz) rates of stimulation. The administration of edrophonium does not alter the decrement. Routine needle electromyographic examination demonstrates MUAP instability. Abnormal spontaneous activity is absent.

AChR Deficiency

Routine conduction studies are normal.[322–327] Repetitive stimulation at 2–3 Hz reveals a decremental response. There is no abnormal spontaneous activity. SFEMG analysis demonstrates increased jitter and blocking.

Primary Kinetic Defect with Slow Channel Syndrome

The magnitude of the CMAP may be normal or slightly reduced, depending on the severity of the disease. Afterdischarges as in AChE deficiency may occur.[165–167] Following a brief voluntary contraction, this afterdischarge disappears only to return following a brief rest period. A decrementing response to "slow" repetitive stimulation is usually observed only in clinically weak muscles. Routine needle electromyographic analysis reveals MUAPs with variable amplitudes, polyphasia, and decreased durations, which may suggest a myopathic disorder. Rarely, positive sharp waves, fibrillation potentials, and fasciculation potentials can be observed.

Primary Kinetic Defect with Fast Channel Syndrome

Repetitive stimulation demonstrates a mild decrement with 3 Hz stimulation.

Dok-7

A decremental response to "slow" repetitive stimulation is seen in the majority of cases.[188]

The anticipated findings in familial limb-girdle MG are also essentially identical to autoimmune MG. Sensory and motor nerve conductions are normal, decremental responses are common in response to "slow" repetitive stimulation in clinically weak muscles, small and unstable MUAPs are demonstrable on needle EMG, and increased jitter values and blocking are found on SFEMG.[125–128,130,131] Fibrillation potentials and positive waves have not been reported.

Other

Edrophonium testing is positive in most CMS including the presynaptic disorders, AChR deficiency, and the fast channel syndromes. End-plate AChE deficiency, occasional cases of the slow-channel syndrome, and Dok-7 syndromes are notable exceptions.

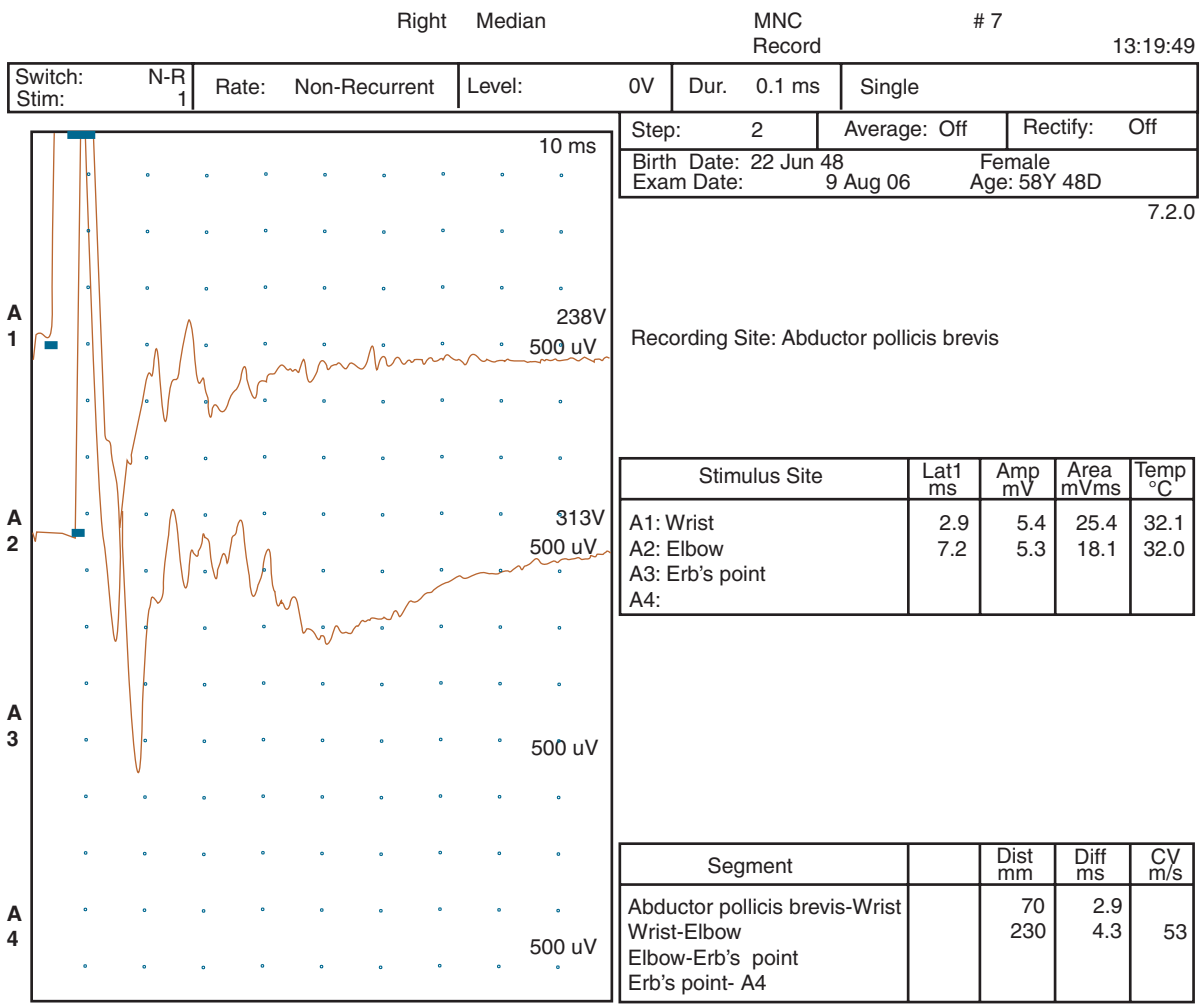


Figure 23–4. Afterdischarges, i.e., multiple small CMAPs resulting from a single supramaximal stimulus delivered to a motor nerve as might be seen in certain CMS syndromes, organophosphate toxicity, neuromyotonia, or envenomation with potassium channel toxins. CMS, congenital myasthenic syndrome. (Photo courtesy of Drs. Alpa Shah and Steven Vernino, University of Texas Southwestern.)

LAMBERT–EATON MYASTHENIC SYNDROME

Electrophysiology

As in all DNMT, sensory conductions are normal in LEMS unless paraneoplastic sensory neuropathy, chemotherapy-induced neuropathy, or another confounding disorder coexist. H-reflexes may be absent upon initial attempts at elicitation but may appear following muscle contraction.[328–330] F-waves have been reported to occasionally be larger than anticipated, although the reason for this occurrence is unclear.[331] Neither of these latter observations holds major diagnostic significance.

In LEMS, the CMAP amplitudes are significantly and usually uniformly reduced. This is the key EDX feature that initially distinguishes presynaptic from postsynaptic disorders of NMT. The responses to exercise and/or repetitive stimulation as described below provide supplemental evidence that both identify and characterize the nature of the NMT disorder.[45,131,191,192,194,196,225,226,258–260,295,296,297,332–347]

As a result of the differing baseline CMAP amplitudes, MG and LEMS are usually readily distinguished by the experienced electrodiagnostician. Occasionally, a patient with LEMS will be confused with MG electrophysiologically. If a patient with LEMS is seen early enough in their illness, their CMAP amplitudes may fall within population norms. In this situation, the incremental response characteristic of a presynaptic deficit may not be either evident or sought for. The demonstration of a decrement, characteristic of both LEMS and MG, without demonstration of an increment may lead to misdiagnosis. If LEMS is suspected but cannot be proven electrodiagnostically or by the presence of voltage-gated

calcium channel antibodies, repeating the nerve conduction studies at regular intervals over the course of the next several months may be enlightening.[332,333,348]

As previously stated, the majority, if not all, of CMAP amplitudes are reduced in a given patient with LEMS. In a large study of 73 patients with LEMS (42% with lung cancer), the CMAP amplitude was reduced in the abductor digit quinti in 95%, abductor pollicis in 85%, extensor digitorum brevis in 80%, and in the trapezius in only 55% of cases.[346]

The combination of diffusely reduced CMAP amplitudes and preserved SNAPS should always prompt a search for an incremental response. In a cooperative patient, this is rapidly and easily performed by isometric exercise of the tested muscle for 10–15 seconds followed immediately by a second, supramaximal stimulus. In normal individuals, there may be a mild increase in CMAP amplitude (<40%) associated with a shorter duration and similar area under the curve (pseudofacilitation). The actual basis of this phenomenon is poorly understood. It has been postulated to represent improved motor unit synchronization due to a disproportionate increase in the conduction velocity of the slowest conducting muscle fibers.[105,270] In the majority of patients with LEMS, brief exercise will produce an incremental response of 100–400%. Following maximum voluntary contraction for 10–15 seconds, an increase in the CMAP amplitude over 100% from the baseline recording was noted in the abductor digiti minimi (ADM) in 77%, abductor pollicis brevis (APB) in 62%, extensor digitorum brevis (EDB) in 59%, and trapezius in 10% of patients.[346] It is important to recognize that patients with end-stage LEMS may fail to mount a significant increment.[349] In those individuals who cannot cooperate with isometric exercise for whatever reason, "fast" repetitive stimulation of 20 Hz or higher represents a more uncomfortable means by which to demonstrate the characteristic increment (Fig. 23–5).

Repetitive nerve stimulation at low rates (2–3 Hz) performed on LEMS patients often yields a decremental response that is identical to that described in MG.[338,341,345,346,350] It is sometimes difficult to appreciate the decrement if the baseline amplitude is too low to begin with. Decrement on 3 Hz stimulation has been demonstrated in the abductor digiti quinti (ADQ) in 98%, APB in 98%, EDB in 84%, and trapezius in 89% of cases.[346] Following a brief maximal exercise period of 10 seconds, there is a blunting of the decrement in response to 2–3 Hz stimulation, resulting in increased amplitudes of the initial as well as subsequent responses. This postexercise facilitation effect lasts approximately 20–30 seconds. If the muscle is exercised for 1 minute, i.e., postexercise exhaustion, 2–3 Hz repetitive stimulation produces a decrement that peaks at 3–5 minutes and exceeds that observed in the resting state. Rarely, postactivation exhaustion may last for up to 20 minutes.[351] There is no correlation between patients with respect to severity of disease and magnitude of decrement, increment, or amplitude of the CMAP at rest. In other words, if patients have a CMAP amplitude of 300 μV at rest that increments to 8 mV, they do not have more or less severe disease than a patient who has a resting CMAP of 1 mV that increments to 6 mV.

Insertional activity in LEMS is normal or slightly reduced. Positive sharp waves and fibrillation potentials are usually absent in patients with LEMS. Minor membrane instability may be observed.[131,192,194,211,258–260,332,333,334,337,343] Abnormalities of MUAP morphology are apparent in weak muscles if carefully assessed. An effective loss of muscle fibers per motor unit due to neuromuscular blockade results in shorter-duration and lower-amplitude MUAPs. As a consequence of this effective reduction in MUAP size, the twitch tension of individual motor units decline and compensatory early recruitment may occur. Additionally, fewer active muscle fibers produce less overlap or synchrony of component single fiber action potentials, increasing the percentage and severity of polyphasic MUAPs. Motor unit instability is readily evident if sought for. With continued contraction, the amplitude of the interference pattern increases and the amount of MUAP variability declines as NMT improves in response to the same postexercise facilitation phenomenon described above.

Predictably, both volitional and stimulated SFEMG evaluations of patients with LEMS yield abnormal results.[45,196,225,226,230–232,258,259,260,295–297,334,335,338–340,340,344,347] Jitter values in patients with LEMS are significantly elevated and statistically exceed that observed in MG. In essentially all NMJs examined, irrespective of muscle chosen, markedly abnormal jitter values are evident. This is disparate from MG where a spectrum of jitter values from normal to highly abnormal exists within and between individual muscles. Unlike MG, the jitter in patients with LEMS is not dependent on the degree of weakness in a particular muscle. Blocking is often more prevalent and severe in LEMS in comparison to

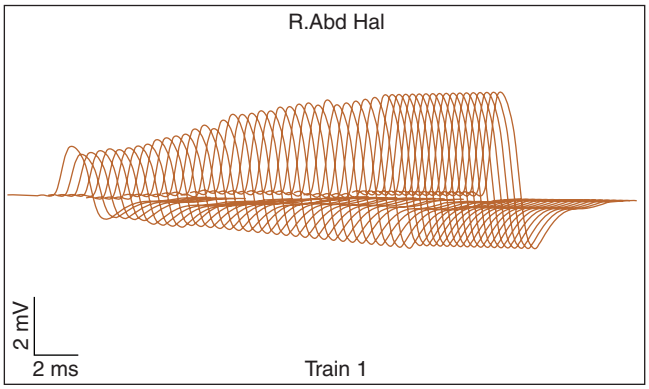


Figure 23–5. Incremental response in response to 20 Hz "fast" repetitive stimulation in a patient with LEMS.

MG. Some of the highest percentages of documented blocked potentials occur in LEMS.

Frequency-dependent alterations in jitter and blocking are also observed in LEMS if sought for. Specifically, at low rates of voluntary firing, 5–10 Hz for example, jitter and blocking can be quite impressive. Further activating the muscle and increasing the rate of motor unit firing to 20–30 Hz result in a reduction of the jitter value as well as a decrease in the number of blockings. An attempt can be made to quantify these observations by using stimulation SFEMG.[293–297,335,344,352] Stimulating an intramuscular neural branch and recording a single muscle fiber potential allow jitter measurement with varying stimulus rates. One study of patients with LEMS demonstrated that the jitter decreased from a mean of 150 microseconds at a stimulation rate of 2 Hz to about 90 microseconds at a firing rate of 15 Hz.[295–297] Similarly, when changing the stimulus frequency from 2 to 15 Hz, the percent of blockings noted decreased from 70% to fewer than 10%.

Distinguishing MG from LEMS by contrasting stimulated SFEMG responses is theoretically possible but impractical in most circumstances. With stimulation rates of <10 HZ, patients with MG reveal a gradual increase in jitter and blocking. In contrast, patients with LEMS demonstrate a continuous decline in both jitter and percent blocking. For any given patient, both jitter values and blocking frequencies may look quite similar, depending on the severity of the disease. This type of pattern recognition may be of value in attempting to electrophysiologically distinguish between these two diseases in questionable cases.

Muscle temperature variation affects EDX responses in LEMS as well.[353–355] Decreasing muscle temperature results in an improvement in the CMAP amplitude at rest, reduces the magnitude of decrement at low rates of stimulation, and prolongs the duration of postactivation facilitation.

As dysautonomia in LEMS is commonplace, abnormal autonomic nervous system testing is anticipated. In a large series of 30 patients with LEMS, autonomic testing revealed abnormalities of sudomotor function in 83% of patients, abnormal cardiovagal reflexes in 75%, decreased salivation in 44%, and abnormal adrenergic function in 37% of tested individuals.[200]

Serological Testing

Antibodies directed against the P/Q-type voltage-gated calcium channels of the motor nerve terminals are detected in the serum in over 85–90% of patients with both paraneoplastic and nonparaneoplastic LEMS cases.[200,201,228] In addition, antibodies directed against the N-type calcium channels, which are located on autonomic and peripheral nerves as well as cerebellar, cortical, and spinal neurons, are present in 74% of patients with LEMS and lung cancer and 40% of patients without cancer.[200,228] Antibodies directed against various epitopes of the calcium channel, including the α1A- and β-subunits have been identified. Some patients with paraneoplastic LEMS also have anti-Hu antibodies and an associated sensory ganglionopathy, cerebellar degeneration, and/or encephalopathy.[200,218,228] AChR-binding antibodies are found in as many as 13% of patients with LEMS. This is a potential source of diagnostic confusion if inadequate attention is paid to phenotypic and EDX detail.[147,228,356–359] These anti-AChR antibodies are not necessarily pathogenic in patients with LEMS and may just represent an epiphenomenon. Nonetheless, rare patients may exhibit features of both LEMS and MG as mentioned above.

Pharmacological Testing

Edrophonium testing in LEMS produces variable results and is not normally employed.

BOTULISM

According to the Center for Disease Control criteria, a patient is classified as having botulism if the reported illness has neurologic manifestations of descending paralysis and clear sensorium associated with at least one of the following: identification of the offending *C. botulinum* organism in the stool or wound; documentation of BTX in the serum, wound, stool, or portions of suspected contaminated food; or a clinical presentation compatible with other reported cases of foodborne illness.

Electrophysiology

The electrophysiologic findings in botulism are clarified by awareness of the disease's underlying pathophysiology. In human botulism, microphysiologic techniques reveal a significant reduction in the EPP amplitude and frequency of miniature end-plate potentials (MEPPs) but not in MEPP amplitude.[113,234] This implies that the content of each vesicle is normal, but the frequency of quantal release is reduced. It has been demonstrated that on average a total of seven quanta are released in response to 100 nerve terminal activations.[360] The mathematics of this suggests production of an EPP far below the 7–20 mV necessary to bring the myofiber from its resting membrane potential to action potential threshold. Understandably, if this effect is pervasive within a muscle or the organism as a whole, there will be wholesale failure of NMT and resultant loss of muscle strength and stamina.

Sensory conductions are normal in the vast majority of patients with documented botulism. There have been a few reported exceptions to this rule.[329,330,361,362] The known pathophysiology of BTX does not provide an adequate explanation for this finding. In general,

abnormal sensory studies should prompt consideration of an alternative or superimposed diagnosis.

As with other "presynaptic" disorders, the major EDX abnormality with botulism is CMAP amplitude reduction seen in 85% of cases.[236,320] On average, CMAP amplitudes are several millivolts in size (normal values being typically >5 mV in the majority of limb muscles commonly tested) and thus not as severely affected as the average patient with LEMS where CMAP amplitudes are often 2 mV or less.[363] The speed of motor nerve conduction measured as either velocity, or distal, F-wave or H-reflex latencies is with rare exception normal.[222,223,234,236,329,330,364–372]

Several patterns in response to repetitive stimulation may be observed, depending on patient age, site, and severity of disease. As outlined below, there may be considerable variation in patient responses, from muscle to muscle and patient to patient. Both decremental and incremental responses are helpful when present. Their absence within a given muscle or even a given patient does not preclude a diagnosis of botulism, particularly in patients with less severe disease.

In infants, the initial-evoked CMAP from a rested intrinsic hand muscle is usually reduced to approximately 110–4000 μV, with 88% of patients having amplitudes <2000 μV and 52% of patients with amplitudes below 1000 μV.[373] At "slow" rates of repetitive stimulation, the response is variable. An estimated 56% of infants will demonstrate a decremental response with a mean of 14%, comparing the first response to the nadir of the decrement (range 5–41%). Approximately 24% of patients do not reveal a change with "slow" repetitive stimulation, while 20% will increment with a mean increase of 37% (range 5–116%) from the first to fifth response. Repetitive stimulation at 20 Hz and 50 Hz for 10 seconds results in incremental change in 92% of children with botulism averaging 73% (range 23–313%). If an increment is not found at 20 Hz, then 50 Hz stimulation should be performed. The diagnostic sensitivity quoted above represents the expected responses in severely afflicted children.

The most reliable finding in infants with botulism is postactivation facilitation that exceeds 20–40% and has prolonged persistence (4–20 minutes) in comparison to other DNMT.[367,373–376] In infants, postexercise testing is impractical and 20–50 Hz stimuli delivered for a minimum of 10 seconds to multiple muscles are typically required for the detection of postactivation facilitation.[377] The duration of this facilitation is strongly suggestive of botulism. In LEMS and MG, postactivation facilitation characteristically lasts for approximately 30 seconds. Rarely, this prolonged effect may be witnessed in patients with LEMS and hypermagnesemia.[349] Following the demonstration of postactivation facilitation, single stimuli delivered at regular intervals are delivered to determine the duration of this effect.

In adults, similar although characteristically less robust abnormalities are noted. Abnormalities are more apparent in those patients with more severe disease.[234,236,262,320,364,366–371,378–384] The diagnosis of serotype A disease may be particularly elusive at onset from an EDX perspective.[385] The reduced CMAP amplitude at baseline, incremental response to brief exercise or "fast" repetitive stimulation, and decremental response to "slow" repetitive stimulation that characterize presynaptic DNMT may be absent early on. These features may reveal themselves at the peak of the disease and return to normal after several months. Patients with relatively mild disease may demonstrate normal to low normal baseline CMAP amplitudes, no decrement with "slow" repetitive stimulation, and an increment to "fast" repetitive stimulation or brief exercise. In contrast to LEMS, the increment is usually <100% and more prevalent in proximal muscles.[235,386,387] In more severe disease, reduced baseline CMAP amplitudes are expected. A decrement to "slow" repetitive stimulation may occur, and, paradoxically, the incremental response to "fast repetitive stimulation or brief exercise is not as significant as in milder cases. Rarely, a decremental response to "fast" repetitive stimulation may be seen.[388] This may be a result of significant reinnervation subsequent to a large number of functionally denervated muscle fibers, with immature NMJs blocking in response to the high stimulation rate. With continued recovery this abnormal decrement resolves.

In patients with primarily bulbar disease, EDX involvement is not likely to be detected until the limbs become clinically involved. Decremental responses are, in general, less commonly observed than in the adult patient with generalized disease. Facilitation is common in adults but needs to be carefully distinguished from pseudofacilitation by attention to CMAP duration and area as well as amplitude measurements. In contrast to LEMS where EDX abnormalities tend to be ubiquitous, they can be quite patchy in botulism. Particular attention should be given to clinically weak muscles. A combination of distal and particularly proximal and cranial muscles should be sampled.

The needle electromyographic examination of individuals with botulinum intoxication can be somewhat variable, depending on the time of examination.[234,236,329,330,365,367,370,371,373,378,384,389–393] Early in the course of the disease, there is usually normal insertional and spontaneous activity. Fibrillation potentials and positive sharp waves may be found in severely affected muscles but, as in most DNMT, are more typically absent. The MUAPs are typically a mixture of normal and low-amplitude, short-duration morphologies. There is often an abnormal early recruitment pattern characteristic of disorders that effectively reduce the number of muscle fibers in motor units. This is coupled with a reduced interference pattern of

relatively low amplitude, during attempts at maximal voluntary contraction. The latter may mimic a nascent pattern seen in severe denervation and early reinnervation. Careful observation may demonstrate a slight increase in the overall amplitude of the electrical activity with prolonged muscle activation, but this is a difficult impression to quantitate. As with repetitive stimulation, the same panoramic selection of muscles should be tested including proximal and distal muscles in both upper and lower extremities as well as those innervated by cranial nerves. As the bulbar muscles (e.g., masseter, orbicularis oculi and nasalis, hypoglossus, and trapezius muscles) are usually affected first, these tend to demonstrate greater degrees of abnormality than their limb counterparts. Pathological MUAP changes in these muscles may be difficult to detect, however, as MUAPs in facial muscles are small under normal circumstances as a result of their low innervation ratio. With symptom progression and increasing time from disease onset (greater than 10 days), there may be a significant reduction in both the numbers and the duration/amplitude of MUAPs and an increased prevalence of positive sharp waves and fibrillation potentials. This is especially true for profound disease in the proximal limb and cranial muscles. After several months, there tends to be a rather complete electrophysiologic recovery with respect to MUAP parameters.

The morphological changes of MUAPs in botulism are explained by mechanisms similar to many myopathies or other DNMT. As NMT fails in muscle fibers that are in close proximity to the needle electrode, their contribution to the amplitude of the MUAP diminishes. As NMT fails in myofibers belonging to that same motor unit but at the periphery of the recording radius of the needle electrode, their contributions to the duration of the MUAP are lost. As the synchrony between all of the single muscle fiber action potentials contributing to that MUAP is altered by NMT failure in random fibers, MUAP polyphasia may occur. As NMT failure in a myofiber may effectively denervate it, abnormal spontaneous activity in the form of fibrillation potentials and positive waves may occur.

The small number of patients studied with SFEMG allow only a cursory description of what is "typical" for botulism.[363,369,378,387,393–395] Predictably, abnormal (increased) jitter values and blocking can be observed early in the disease in 40–50% of SFEMG studies. It would appear that, unlike MG, the degree of blocking is somewhat independent of the severity of jitter. The mechanism for this is uncertain, although it has been hypothesized that it may be related in part to the acuity of disease onset and the associated impaired quantal content. A finding in botulism that is similar to LEMS is the tendency for jitter values to decline in association with an increased frequency of muscle fiber action potentials. This in all probability due to the same physiological factors that lead to electrophysiologic increment and postexercise facilitation described above.

Fiber density may be relatively low on the initial SFEMG study and may increase as the patient's condition improves.[396] This is likely a result of the reduced probability of fiber pair detection due to failure of NMT in one or both members of a pair that may otherwise be captured under normal conditions. As a result, voluntary SFEMG may become more time consuming, and stimulated SFEMG may represent a more efficient means to assess jitter and potential blocking. There have been a few reported cases of increased fiber density coincident with patient recovery, which appear to persist, at least for the relatively limited reported period of follow-up.[262,286,397] Both the severity of the disease and the method of NMJ recovery in botulism may explain these two disparate findings. Reduced fiber density may be seen in relatively mild cases of disease where a limited number of NMJs are affected. The abnormality is sufficient to reduce the probability of finding two single fiber action potentials belonging to the same motor unit within the recording radius of the needle. Disease severity may be insufficient to provoke significant motor unit remodeling or what is effectively a denervating and reinnervating disorder that may occur in more severe cases. In this latter situation, recovery of the more severely affected NMJs leads to a more significant loss of multiple NMJs. Substantial nerve terminal sprouting may be required to restore NMJ transmission. This provides a potential explanation for the histological changes of denervation atrophy previously described, the increased fiber density measurements that represent one of their EDX correlates, and the reduced MUAP recruitment with vigorous attempts to activate a muscle.

The value of SFEMG is similar to that of other DNMT, i.e., an increased sensitivity in the detection of minor changes in NMT before CMAP amplitude reduction or responses to repetitive stimulation become evident. In patients with suspected botulism, SFEMG is usually reserved for individuals in whom routine conduction studies and repetitive stimulation and postexercise techniques are nondiagnostic. Again, it should be emphasized that the enhanced sensitivity of SFEMG comes with the price of diminished specificity. SFEMG abnormalities are therefore at best supportive and not diagnostic of botulism.

Other Testing Methods

Isolated cases of foodborne, wound, or inadvertent botulism may escape diagnosis. This is, in part, due to its relative rarity and the lack of a single, readily available test that has adequate sensitivity and specificity. The diagnosis should be considered in any adult with an acute onset of symptoms suggesting cholinergic dysautonomia, impaired GI motility and weakness, particularly

affecting cranial muscles. In infants >3 months of age, hypotonia, impaired sucking, crying, and/or breathing difficulties should raise a similar suspicion.[398]

Edrophonium testing is of limited value. A positive response is rarely dramatic and occurs in only a quarter of affected individuals.[361,399,400] Lumbar puncture may disclose an elevated protein level but its value, like edrophonium testing, is limited by its lack of specificity. More specific evidence of intoxication is sought by analyzing and culturing specimens of serum, gastric contents, stool, wound aspirate, or suspected foods for toxin and organism, respectively. Blood should be collected prior to the administration of antitoxin. BTX assay is an indirect bioassay that involves injecting mice with one or more of the aforementioned samples. If the mouse dies, the injection is repeated with the addition of specific antitoxins. This implicates not only BTX as the cause of death but serves to specify the exact strain.

The diagnostic yield varies depending on a number of factors including method of inoculation and duration between symptom onset and testing. The yield of toxin detection is understandably higher early in the disease, whereas the yield of culture increases with disease duration in untreated patients. In general, toxin tests have a yield of approximately 1/3 and are higher in blood and stool than in gastric aspirates. Positive cultures may be obtained in a half to two-thirds of cases. Unfortunately, these tests are time consuming and costly, typically available only from state laboratories and the CDC. Rapid confirmation of toxin detection or culture result does not typically occur.[398,401,402] Newer, potentially more expeditious and accurate assays are in development. Problems associated with their in vivo application have kept them from supplanting the mouse toxin bioassays and anaerobic culture as the diagnostic tests of choice.

TICK PARALYSIS

Electrophysiology

Our knowledge of EDX in tick paralysis is limited. Sensory nerve conduction parameters have been reported to fall within population-based norms but often demonstrate faster speeds and higher amplitudes when studied again following recovery.[240,241,403–407] The implication is that tick paralysis may produce a mild sensory neuropathy. The EDX detection of this neuropathy may well be obscured by the wide range of population-based norms. Normal premorbid values for sensory nerve action potential (SNAP) amplitudes in these typically otherwise healthy young people may be considerably higher than population norms, thereby precluding the detection of mild sensory axon loss or dysfunction. The recovery of electrical parameters appears to follow the physical resolution of paralysis, implicating channel dysfunction or impaired NMT as opposed to axonal loss or demyelination as the primary disease mechanism.

Motor conduction velocities and CMAP amplitudes are typically mildly reduced in paretic upper and lower extremities.[240,241,403–407] Removal of the tick within several days of clinical presentation results in the prompt resolution of both size and speed of motor and sensory conduction responses. Repetitive nerve stimulation at both low and high rates does not reveal either a significant decrement or a pathologic increment in the majority of cases, although there have been a few reported cases of an incremental response. On closer inspection, these increments probably represent pseudofacilitory responses. This phenomenon may also have contributed to the classification of tick paralysis as a DNMT in many writings.

Needle electromyographic evaluation of individuals with acute tick paralysis performed within several days of onset of weakness or after tick removal usually demonstrates only abnormalities of recruitment, reminiscent of any acute neurogenic disorder. As such, it supports that tick paralysis, at least in some cases, is more of a disorder of nerve than of NMT. Positive sharp waves and fibrillation potentials are notable for their absence. In one apparently outlier case of a child with apparently 50 or more attached ticks, abnormal spontaneous activity in the form of fibrillation potentials and positive waves appeared within several days of paresis onset.[405] These abnormal spontaneous potentials persisted for the 6 months this patient was followed.

Other

Unlike Guillain–Barré syndrome, CSF protein concentration is usually normal in tick paralysis.

MISCELLANEOUS DNMT

Organophosphate Poisoning

The electrophysiologic presentation of acute organophosphate intoxication is rather unique.[230–232,408,409–414] Motor and sensory nerve conduction velocities are essentially normal within the first 24–48 hours. Mild conduction slowing may develop subsequently. CMAP amplitudes are decreased in severe intoxication with limited effects in milder exposures. In about 60% or more of patients, an afterdischarge(s) as described above may be seen (Fig. 23–4). This is believed to be the most sensitive EDX indicator of early toxicity.[230–232]

A rather unique feature of organophosphate toxicity is a decrement–increment pattern to repetitive stimulation observed either early in the course of the disorder or in later stages of recovery. Specifically, there is an

initial decrement to repetitive stimulation, with a subsequent increment to the baseline CMAP at high rates of stimulation. During repetitive stimulation, the afterdischarges evoked during single stimulation are absorbed into the subsequent CMAPs and are no longer observed. Patients with significant intoxication reveal a decrement to repetitive stimulation at low rates of stimulation, while those with moderate-to-mild intoxication only reveal a decrement at rates >10 Hz. With slow repetitive stimulation, edrophonium chloride administration, in contrast to MG, results in a marked worsening of the decremental response, which returns to the resting level within about 30 seconds.[229] Application of d-tubocurarine, an AChR-blocking agent, repairs the decrement by decreasing the number of AChRs available to the excess ACh. Needle electromyographic examination does not reveal positive sharp waves or fibrillation potentials during the initial stages of the disease. The only abnormality is a reduction in the number of voluntary MUAPs. In patients who develop an axonal neuropathy as a result of delayed or chronic organophosphate exposure, a typical length-dependent EDX neuropathy pattern eventually develops.

In patients given nondepolarizing neuromuscular blocking agents, there is a reduced CMAP that is expected to decrement with "slow" repetitive stimulation. The results are similar to those observed in MG. The MUAP can be seen to decline in magnitude as single muscle fibers belonging to a particular motor unit serially block with increasing dosages of curare.[415] As might be expected with SFEMG analysis, doses of curare that do not produce weakness may nevertheless produce an increase in jitter values.[416]

▶ HISTOPATHOLOGY

MYASTHENIA GRAVIS

Histopathology is not part of the routine evaluation in the majority of patients with MG. Routine light microscopy may reveal mild, nonspecific abnormalities on muscle biopsy including type 1 fiber predominance, mild fiber type grouping, or type 2 fiber atrophy.[233] Focal interstitial inflammatory infiltrates, so-called lymphorrhages, are not uncommon, particularly at the end plates.[230–232,417]

Ultrastructural abnormalities are more evident. Immunoelectron microscopy of the postsynaptic membrane region in patients with myasthenia demonstrates IgG and complement precipitation on the membrane, an increased synaptic space, reduced postsynaptic membrane complexity with fewer postjunctional folds, and decreased numbers of AChRs. Many of the remaining AChRs are bound with IgG.[181,182,233,418–422] In contrast, the presynaptic portion of the NMJ appears completely normal. To date, there have been no convincing morphological changes of the NMJ attributed to MuSK antibodies. Muscle biopsies in these latter patients have demonstrated minor simplification of some end plates. The density and distribution of AChR in patients with MuSK are essentially normal in the studies reported to date. Complement deposition or other markers of an immune-mediated disease has not been identified.[423,424]

CONGENITAL MYASTHENIC SYNDROMES[1]

The histologic changes of the CMS are, in large part, limited to those detectable by ultrastructural analysis. This evaluation is a very specialized undertaking done at a limited number of centers. Light microscopic analysis of muscle is not routinely performed in patients with suspected CMS. In most of these disorders, routine muscle biopsy findings are normal or nonspecific in nature.

- Choline acetyltransferase deficiency has limited morphological change. Synaptic vesicles are smaller than normal. Postsynaptic structure is normal.
- Light microscopic analysis from patients with end-plate AChE deficiency demonstrates normal-appearing muscle tissue or type 1 fiber predominance.[172,173,180–184] Electron microscopic analysis reveals a reduction in the size of the nerve terminals that do not cover the entire end-plate region and an AChR number that varies from muscle to muscle. There is an atrophy of presynaptic terminals in an apparent compensatory attempt to limit quantal release and prevent AChR overstimulation. Despite this, there is degeneration of synaptic folds with a reduced number of secondary synaptic clefts and diminished postsynaptic area. Immunocytochemistry studies reveal the presence of fetal AChR that contain the γ-subunit instead of the ε-subunit.
- Paucity of synaptic vesicles and reduced quantal release is associated with a decreased density of synaptic vesicles in the immediate release zone of the presynaptic terminal.
- Slow channel syndrome reveals light microscopic changes unlike most CMS. These include type I fiber predominance with associated isolated grouping of atrophic type I or type II fibers, fiber size variation, tubular aggregates, fiber splitting, endomysial fibrosis, and vacuolization near the NMJ.[165–167,172,173,185,425,426] Ultrastructural examination reveals degeneration of the junctional folds of the end plate. Apoptotic nuclei and degenerating organelles may also be observed.

There is an abnormal distribution of end plates over an excessively large portion of the muscle tissue, particularly in more profoundly affected muscles.

- AChR deficiency syndromes are characterized by an increased number of scattered end-plate regions, each of which contains fewer AChR than normal. Junctional folding is preserved but may be attenuated. Light microscopic analysis of muscle tissue may demonstrate type 1 fiber predominance. Immunocytochemistry studies reveal the presence of fetal AChR, which contains the γ-subunit instead of the ε-subunit.
- Plectin deficiency in muscle results in degenerating organelles and structural alterations in end plates with multiple but small synaptic contacts.
- Dok-7 mutations are characterized by a reduction in end-plate size and variable junctional fold architecture, some of which are well developed and some of which are degenerated.
- AChR subunit mutations may also include a number of ultrastructural alterations. There may be junctional-fold degeneration, loss of AChRs, apoptotic nuclei, degenerating organelles, junctional vacuolar change, and an end-plate myopathy similar to AChE deficiency.
- There are no morphological abnormalities associated with CMS with paucity of synaptic vesicles and paucity of quantal release and the fast channel form of primary kinetic defect.[178,427]

In familial limb-girdle myasthenia, muscle biopsies may reveal tubular aggregates along with nonspecific myopathic changes.[126]

LAMBERT–EATON MYASTHENIC SYNDROME

Muscle biopsies are not routinely performed on patients with suspected LEMS. When performed, nonspecific type II fiber atrophy is an uncommon and isolated light microscopic finding.[196] On quantitative electron microscopic analysis, nerve terminals appear normal in both their size and the number of synaptic vesicles they contain.[419,428] Similarly, the postsynaptic membrane is intact but with an increase in the postsynaptic fold area and number of secondary synaptic clefts, presumably as a compensatory mechanism in response to reduced quantal release. The total number and activation properties of the AChRs appear normal. Freeze-fracture analysis of the presynaptic membrane demonstrates a marked decrease in the number of intramembranous proteinaceous particles, which are assumed to be P/Q voltage-gated calcium channels. These presumptive channels are disorganized and aggregated in clumps.[165–167,429,430–432]

BOTULISM

Histological studies in botulism are primarily researched based and are not a routinely used clinical tool. Structural changes produced by BTX are similar to those that result from nerve sectioning and denervation. These include bouton loss, a decreased number of retracted dendritic profiles, astrocytic proliferation, and sprouting of motor nerve endings from the original terminal arborizations.[433,434] Motor nerve growth-simulating factor(s) released by denervated muscle may promote this sprouting.[435,436] The new NMJs that are formed may be near or at some distance from the original NMJ. New NMJ formation enlarges the end-plate region and may result in multiple end plates on individual muscle fibers from the same or different motor units. The ultrastructural changes of nerve terminals are limited to the distribution of vesicles that have a "log-jam" appearance, suggesting impaired vesicle fusion with the presynaptic membrane.[437] Neurogenic muscle atrophy has also been noted in humans with inadvertent [438] and wound botulism.[234]

▶ PATHOGENESIS

Suspecting, diagnosing, and managing patients with DNMT are greatly enhanced by knowledge of both the anatomy and the physiology of normal and abnormal NMJs. This unique component of the neuromuscular system represents the interface between the terminal twigs of motor nerves and the muscle fibers that they innervate in mammalian skeletal muscle. The NMJ serves to transduce and amplify the peripheral nerve's relatively small electrical current into a chemical signal. This chemical or neurotransmitter, in turn, creates a current of sufficient intensity and proper location such that it initiates a propagating action potential in the substantially larger muscle fiber. Alterations in the structure and consequently the function of the various subcomponents of the NMJs are the basis of the disorders described in this chapter.

Regardless of the species or muscle chosen, NMJs can be subdivided into three major components: (1) the presynaptic region (2) the synaptic space or cleft, and (3) the postsynaptic region (Fig. 23–6).[439] DNMT arise from abnormalities in each of these locations. Presynaptic DNMT may result from the reduced release of normal quanta due to impaired calcium entry into the presynaptic nerve terminal, defective synthesis or packaging of ACh into synaptic vesicles, or the diminished probability of ACh release. Synaptic DNMT relate primarily to reduced or dysfunctional AChE. This may occur pharmacologically or due to a genetic alteration in AChE in at least one form of congenital myasthenia. Weakness in these disorders may be promoted by either continuous

depolarization or desensitization of the AChR channel. Postsynaptic DNMT occur as a result of a reduced number or reduced reactivity of receptors. The former may result from the complement-mediated destruction of receptor sites in MG. The latter may result from hereditary AChR subunit mutations, which may affect the normal mechanics of channel opening and closing. Regardless of the cause, the final common pathway is a reduction of the muscle EPP amplitude to the extent that NMT fails in one or many muscle fibers.

The bulbous nerve terminal of the presynaptic region contains a number of subcellular components, the most notable of which are the multiple synaptic vesicles containing the neurotransmitter acetylcholine (ACh) (Fig. 23–6). Presynaptic function can be summarized by a number of sequential steps. These include

1. packaging of ACh into synaptic vesicles;
2. clustering of synaptic vesicles in the vicinity of the active zone;
3. docking of the synaptic vesicle at the active zone;
4. calcium-triggered fusion pore opening with exocytotic release of ACh into the synaptic cleft;
5. endocytosis and refilling of vesicles with migration back to the active or mobilization sites.

The synaptic vesicles tend to cluster close to the presynaptic membrane in small groups in membrane-dense regions referred to as active zones.[418,440–442] Although there are non-calcium-dependent mechanisms of ACh release, the efficient function of these active zones is dependent on calcium entry into the distal motor nerve terminal. The P/Q type calcium channels integral to this process are distributed along the active zones at the sites of vesicle fusion on the presynaptic membrane. Calcium influx through these channels greatly facilitates vesicle fusion and subsequent exocytotic release of the ACh-containing vesicles known as quanta into the synaptic cleft. In mammalian systems, 50–300 vesicles are typically released in response to a single nerve action potential, referred to in the aggregate as quantal content.[1] It is estimated that 75–100 microseconds are required between arrival of the nerve action potential at the nerve terminal and quantal release.[357,443,444]

There are approximately 200–400 $\times$ 10^3 individual synaptic vesicles contained in the average nerve terminal. In mammalian NMJs, approximately 20% of these are positioned for immediate release in the active zones.[445,446] Within each vesicle, there are between 5×10^3 and 10×10^3 molecules of ACh.[447–452] The mobilization pool or reserve pool is estimated to contain 300×10^3 vesicles that can be moved readily to the active zone region.[450,453] Following vesicle fusion with the presynaptic membrane and exocytosis, ACh resynthesis and repackaging (endocytosis) take place. Experimental data suggest that the rate of resynthesis parallels the rate of ACh release under normal physiological conditions and is capable of increasing to keep pace with neuromuscular activation.[454]

The process of ACh synthesis and resynthesis, vesicle packaging, migration, docking, and exocytotic release into the synaptic cleft is extremely complex and dependent on >1000 functional presynaptic proteins (Fig. 23–6). Detailed description of this obviously complex system is incompletely understood and beyond the scope of this chapter. The soluble NSF attachment receptor (SNARE) proteins, characterized by a homologous 70-residue sequence, are major components of this process. Synaptobrevin (vesicle-associated membrane protein), syntaxin 1, and SNAP-25 are three of the major SNARE proteins. The first is located on the surface of the synaptic vesicles and the latter two on the presynaptic plasma membrane. These proteins facilitate vesicle binding and fusion as well as the creation of fusion pore, which will subsequently allow the exocytic release of quanta into the synaptic cleft. SNARE complex formation is dependent of other proteins, notably Munc 18-1 which must dissociate in order for this process to proceed. The synaptophysins, which bind to synaptobrevin, appear to have a critical function in vesicle fusion and release as well. The synaptotagmins appear to play the critical role of acting as calcium sensors. As such, these facilitate the interaction between calcium entry into the presynapse and the aforementioned components of vesicle fusion and exocytic ACh release.[1,455–457]

The delay between calcium entry into the nerve terminal, interaction with these proteins, subsequent fusion of vesicles, and release of quantal content is estimated to be about 100 microseconds.[443] There are a number of apparent mechanisms by which calcium is handled subsequent to its uncoupling with quantal release proteins. It may freely diffuse away from the active sites, be removed from the nerve terminal by a coupled sodium/calcium exchange mechanism, sequestered in the smooth endoplasmic reticulum or in mitochondria.[458–465]

The synaptic space or synaptic cleft is that region through which quanta traverse, located between the pre- and postsynaptic membranes of the nerve terminal and muscle, respectively (Fig. 23–6). The morphology of the synaptic space may be subdivided into the major or primary gap (cleft) between the nerve terminal and muscle and multiple secondary clefts formed by the postjunctional folds extending into the postsynaptic region.[466] This folding increases the surface area of the postjunctional membrane by 10-fold in comparison to the presynaptic membrane.[419,422,467] This allows for an increase in the density of AChRs/channels, thereby improving the efficiency of NMT. The synaptic cleft is narrow with an average distance of 50 nm between the presynaptic membrane and the summits of the postsynaptic folds.[1] This narrow gap facilitates rapid NMT. The primary synaptic space is in direct communication with all of the secondary synaptic clefts.

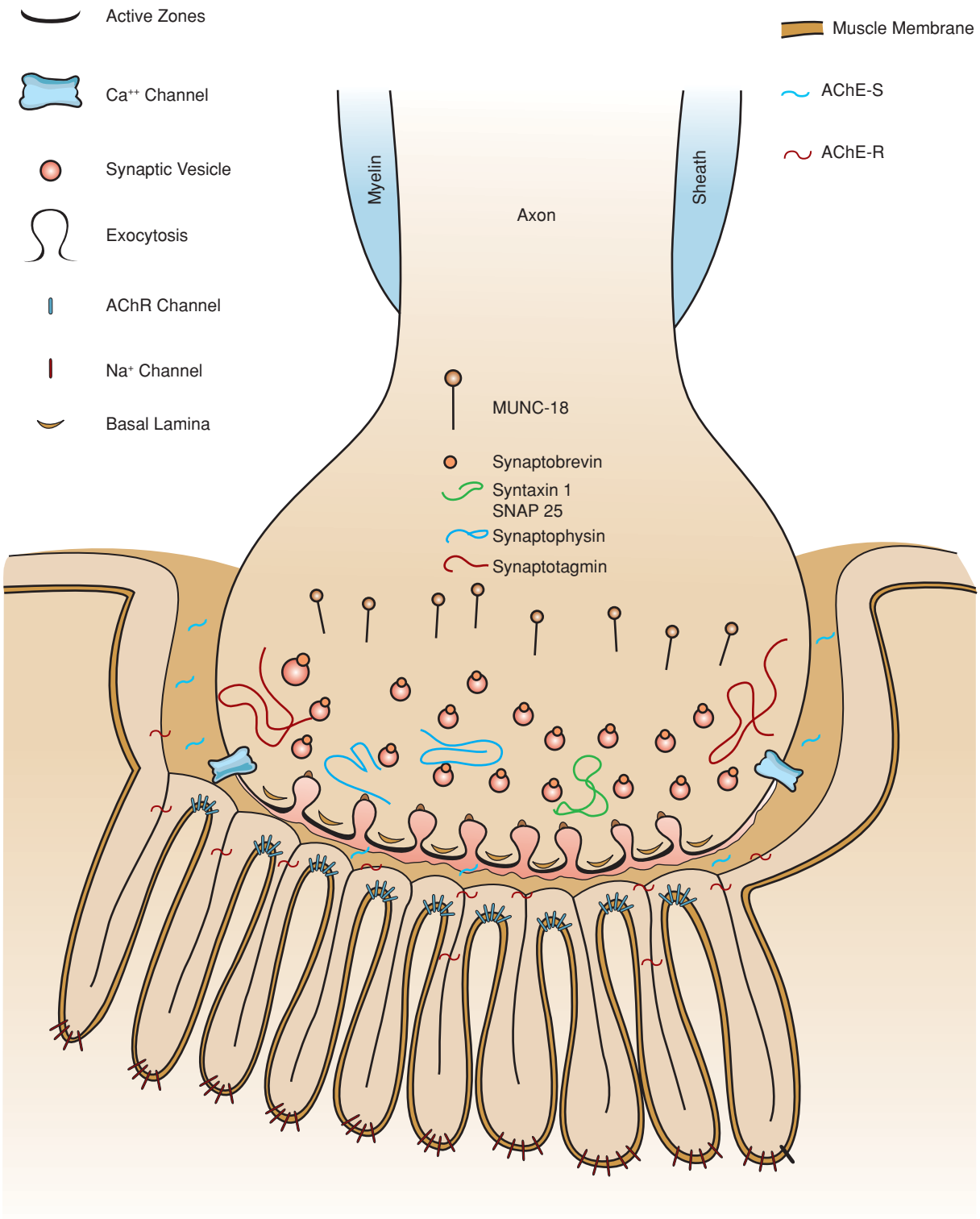


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Figure 23–6. (Continued)

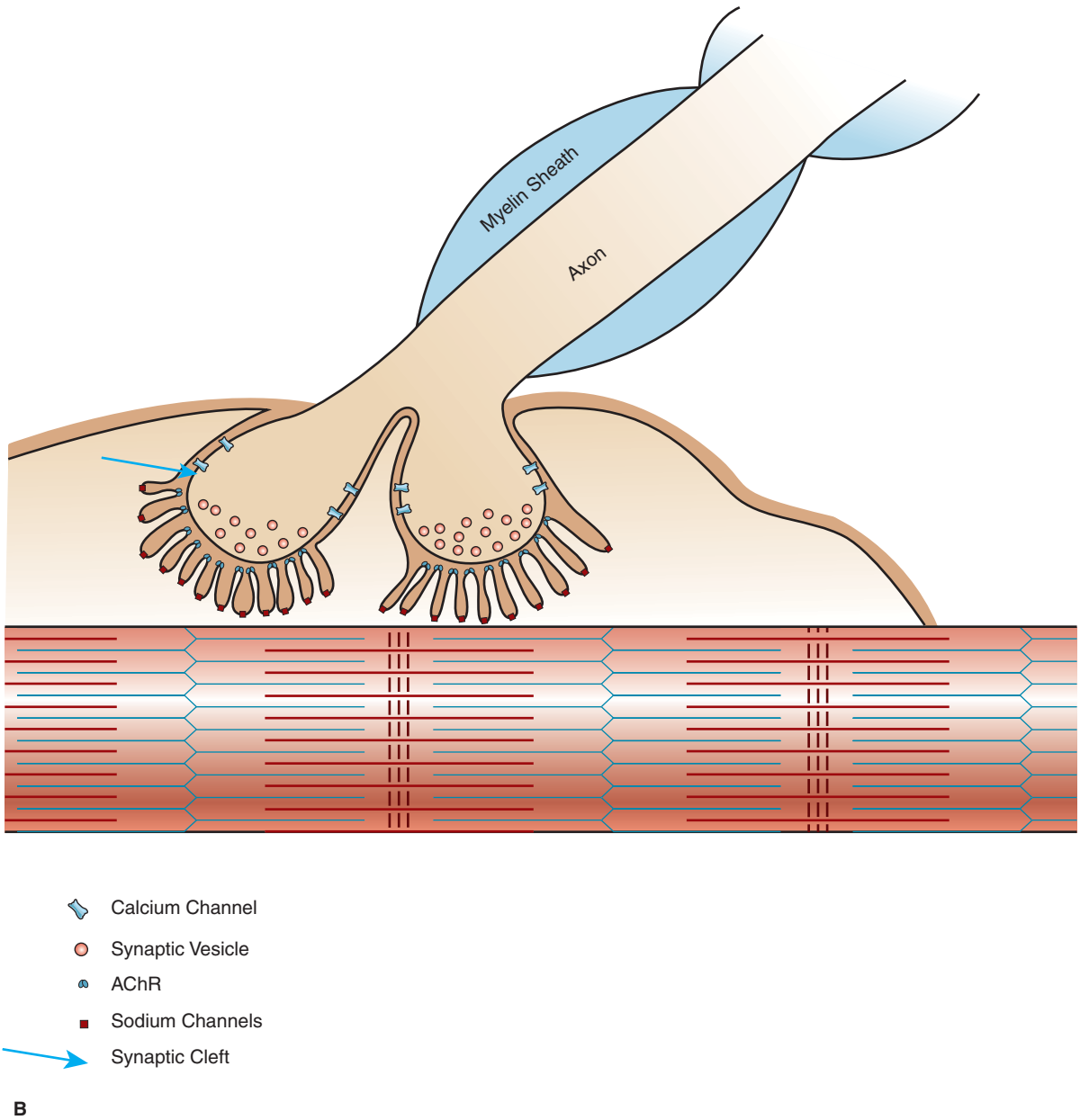

Figure 23–6. (Continued) Schematic representation of a normal presynaptic terminal with constituent proteins, synaptic vesicles and depiction of vesicle fusion with exocytotic ACh release, junctional folding, localization of AChR, acetylcholine receptor and sodium channels.

The lateral boundary of the synaptic space is a porous basement membrane, which permits communication between the synaptic space and the extracellular region. Communication also exists between the muscle fiber's transverse tubules and the secondary synaptic clefts.[468,469]

The synaptic cleft is not empty but filled with an extension of the basement membrane covering the external surface of both the terminal nerve and the muscle fiber. Of particular importance in mature NMJs is AChE, the enzyme responsible for degrading ACh into acetate and choline. AChE is attached to the basement membrane through a collagen tail (ColQ) and is present only in the synaptic region.[470] This process of ACh catalysis is one of the fastest enzymatic processes known and occurs at a rate of five ACh molecules per millisecond.[471,472] Despite this, ACh enjoys a competitive advantage as the density of AChR (15–30K × m^2) is 5–10 times greater than the molecular density of AChE (2–3 × $10^3/m^2$).[473–475] This allows 50–75% of the quantal content to achieve successful interaction with AChR under normal circumstances.[333,476] Temperature changes have effects on a number of different aspects of NMT. Reduced temperature slows the rate of AChE hydrolysis

of ACh, prolonging the duration of EPPs by allowing ion channels to remain open for longer periods of time and enhancing end-plate responsiveness to ACh.[468,477–480] The net effect is for reduced temperature to enhance NMT, which has both electrophysiological and clinical significance.

AChE exists in at least two isoforms: AChE-S and AChE-R (Fig. 23–6). AChE-S plays a critical role in terminating the action of ACh on the AChR. It is anchored on the basement membrane via its collagen tail. Mutations of the AChE gene produce one form of congenital myasthenia. Weakness in this disorder results from excessive depolarization in a manner similar to the effects of succinylcholine. The AChE-R isoform differs from its S counterpart in that its levels are more variable and change in response to external influences, and it is soluble as it lacks an anchoring domain. Its function is apparently to limit ACh access to the AChR. Overexpression of AChE-R impairs NMT.[443] Suppression of AChE-R synthesis may provide a novel means of treating DNMT.[481] There are two other forms of cholinesterase present in the synaptic cleft: butyryl cholinesterase (pseudocholinesterase) and eserin-resistant carboxylic esterase. Neither is felt to play a role in the normal physiology of NMT.[453,471,482–484]

Postjunctional folds are not well formed at birth but develop with age.[485] Their summits assume a perpendicular orientation to the synaptic cleft and presynaptic terminal (Fig. 23–6). Generally, fast twitch muscle fibers have more pronounced and extensive junctional folds than slow twitch muscle fibers.[486] The summits of the junctional folds are thicker than the recesses due to the presence of small particles, 6–12 nm in diameter, with a spatial density reaching 10,000 particles/m^2. The density of these membrane structures decrease by >95% as one proceeds into the recesses of the secondary synaptic clefts.[487] Alpha bungarotoxin specifically and irreversibly binds to the AChR. When this toxin is radiolabeled and exposed to NMJs, it demonstrates a very good geographic correlation between toxin and intramembranous particle location. As a result, it is generally accepted that the AChR and above-noted particles are identical structures.

The topographical distribution of AChR and related proteins are integral components of normal NMT (Fig. 23–7). The AChRs are anchored to the sarcolemma and induced to cluster by the protein rapsyn located in the immediate subsarcolemmal region. Rapsyn is, in turn, bound to the transmembrane protein β-dystroglycan, which is linked to the intracellular cytoskeleton by utrophin.[1,443,488] This complex is similar to the dystrophin–glycoprotein complex. In addition, The AChR–utrophin–glycoprotein complex is connected to the extracellular matrix by agrin, a basement membrane protein, which is also thought to be responsible for AChR aggregation. Agrin colocalizes with MuSK and AChRs in the sarcolemmal membrane. MuSK is thought to facilitate agrin-induced AChR clustering. Knockout of the MuSK gene in mice prohibits both NMJ development and animal survival.[1] Not all mammalian muscles possess the aforementioned NMJ anatomy and physiology. The extraocular muscles, the tensor tympani, stapedius, laryngeal muscles, and tongue all possess muscle fibers that are innervated by terminal nerve twigs from multiple fibers, the so called en grappe, as opposed to en plaque NMJ configurations. In addition, these muscles may normally contain fetal-type AChRs whose physiological properties may differ from their en plaque counterparts.[1]

These AChRs are actually channels that regulate cation entry through the sarcolemma and into the muscle fiber. Although potassium, calcium, and sodium ions are all capable of traversing the channel, sodium conductance is most dynamic due to favorable size, concentration, and electrical gradient considerations. The AChR is a transmembrane complex consisting of four different types of glycoprotein subunits, designated α β, δ, and ε (Fig. 23–8).[489–493] The adult AChR consists of five subunits, two α subunits, and one each of the remaining subunit types. In fetal AChRs, in AChRs in certain oculomotor and bulbar muscles, and in certain pathological conditions such as denervation and specific congenital MG syndromes, a γ subunit replaces its ε subunit counterpart. These five subunit constituents of the normal ACh channels are believed to fit together in a manner similar to the staves of a barrel turned inside out with the concavity oriented externally. This creates a hydrophilic central channel with a nuclear cooling tower configuration oriented with its long axis perpendicular to the sarcolemmal membrane. An ACh-binding site is thought to be located on the extracellular surface of each subunit.[494–496] In the resting state, the central narrow region or waist of all five subunits meet in opposition, effecting channel closure. Channel opening is dependent on the simultaneous binding of two molecules of ACh with each channel, which then leads to a conformational change, allowing transient opening of the channel pore and, as a result, ion movement.

In response to a nerve action potential and the subsequent events described above, the 50–300 ACh vesicles released result in a nonpropagating muscle EPP, which usually exceeds 50 mV.[497] In health, an EPP of this magnitude far exceeds that which is required to adequately depolarize and transit the muscle fiber from its typical resting membrane potential of approximately –80 mV to action potential threshold. This threshold may be achieved by a change in voltage of only 10–15 mV, thus providing the three- to fourfold safety margin that exists in normal NMT transmission. As implied, this EPP is graded, unlike the all or none action potential it subsequently promotes. The EPP is decreased by repetitive stimuli occurring at a frequency of 5 Hz or less, which, at least initially, deplete ACh-containing vesicles in the

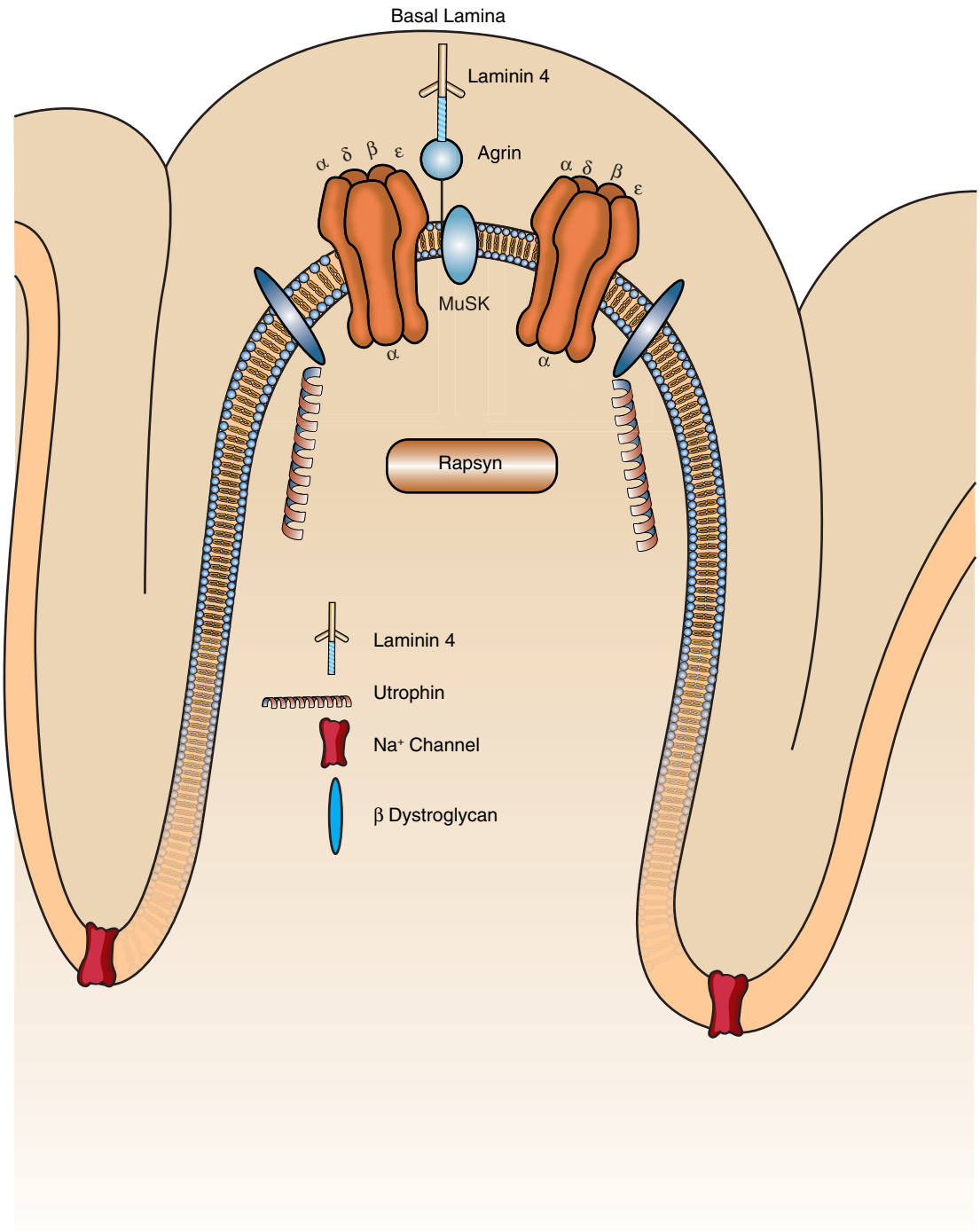

Figure 23–7. Schematic representation of a normal adult AChR channel imbedded in the postsynaptic membrane with key associated proteins. AChR, antiacetylcholine receptor.

active zone. Because of the aforementioned safety margin, this effect has no significance in the normal individual. The decline in the EPP in response to "slow" repetitive stimulation does not persist indefinitely. After the fourth or fifth stimulus, the EPP begins to increase, attributed to increased ACh arriving from the mobilization pool. Conversely, and perhaps counterintuitively, the EPP may be augmented substantially by repetitive stimuli, which occur at frequencies of 5 Hz or more. This phenomenon of post-tetanic facilitation is attributed, in large part, to enhanced quantal release related to lingering calcium effects within the

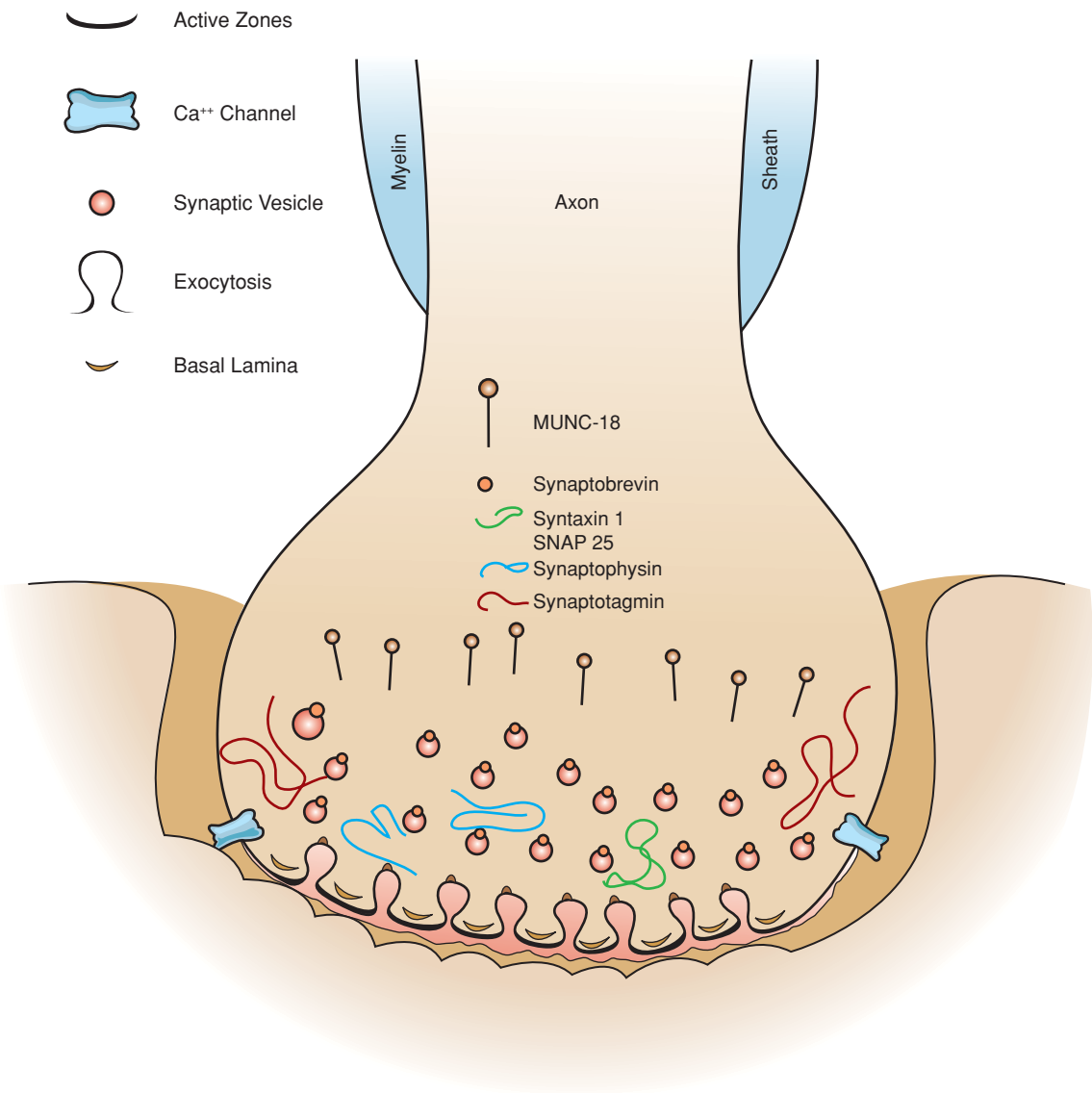

Figure 23–8. Schematic representation of neuromuscular junction affected by myasthenia gravis with a normal density of presynaptic vesicles, simplification of postjunctional folding, and a reduced density of AChR. AChR, acetylcholine receptor.

presynaptic terminal. Again, this phenomenon bears no consequence in the normal individual, as action potentials are already occurring in each muscle fiber in response to each and every stimulus. This EPP response does not last indefinitely, and the EPP will begin to decline after approximately 1 minute in normal people due to declining Ach availability. This subsequent decline in the EPP is known as post-tetanic or postexercise exhaustion.[103,104] In disease, the loss of the EPP safety margin is the basis by which NMJs fail and weakness ensues, regardless of a presynaptic, synaptic, or postsynaptic disease focus. Altering the EPP by either fast or slow repetitive stimulation, as mentioned above and described in detail in Chapter 2, is the primary electrophysiologic means by which these disorders can be both identified and characterized.

Voltage-gated sodium channels (Nav1.4) are also located on the postsynaptic muscle membrane with a density that is five- to —10-fold higher in the end plate than in other regions of the sarcolemma.[443] Their location tends to be the polar opposite of AChRs, being concentrated in the depths rather than pinnacles of the secondary folds. Sodium ingress at the NMJ facilitates the EPP generated by ACh channel opening and adds to the safety margin of NMT. Ultimately, the EPP activates the Nav1.4 sodium channel. Mutation of Nav1.4 is one of the numerous mechanisms underlying the CMS described elsewhere in this chapter.

Vesicle release also occurs in a singular and spontaneous fashion, unrelated to a nerve action potential stimulus. This occurs at a frequency of about 0.2–0.03 times per second, resulting in the activation of 1–2 × 10^3 AChR channels and the generation of a nonpropagated MEPP with a magnitude of 0.5–1 mV.[358,498] The EPP amplitude generated by a nerve action potential is dependent on the number of quanta released and the amplitude of each MEPP. The latter is determined by the number of ACh molecules per vesicle, and indirectly to the efficiency by which ACh can be resynthesized and repackaged. Measuring the content, number, and frequency of MEPP with in vitro recordings of myoneural junctions has provided many of the seminal insights regarding the pathophysiology of both acquired and inherited DNMT.

The half-life of an AChR in the junctional membrane is about 8–10 days.[499] This rapid turnover is a major reason why DNMT are more treatment responsive than other neuromuscular disorders where damaged components heal more slowly or incompletely. The "old" receptors are internalized by the process of endocytosis and transported to lysosomes for degradation through an intricate network of intracellular tubules. The AChR are not recycled but are replaced by newly synthesized receptors. The cross-linking of the AChR by antibodies in patients with MG accelerates the internalization of the receptors and shortens their half-life, as described below.

Ultimately, effective NMT is dependent on a series of events, each of which is a potential rate-limiting factor. ACh must be resynthesized and repackaged in a timely fashion into vesicles that need to be positioned to release themselves with sufficient numbers in response to a nerve action potential. This process is facilitated by the ingress of calcium as well as the existence of a number of nerve terminal (SNARE) proteins, which promote the fusion of vesicles with, and subsequent release through, the presynaptic membrane. This quantal release must then negotiate the synaptic cleft without either the inadequate or the excessive influence of AChE, to bind with an adequate number of correctly positioned and functioning AChR. In turn, these AChR must interact with Nav1.4 sodium channels, which have the same characteristics described as their AChR counterparts. If all of this proceeds without a hitch, a muscle EPP sufficient to trigger a muscle fiber action potential will occur in response to each and every stimulus in each and every muscle fiber.

Both the anatomy and the physiology of NMT are codependent on the distal motor nerve terminal. Schwann cells produce proteins such as neuregulins, nerve growth factors, and calcitonin gene-related protein that are capable of inducing AChR gene transcription in nearby muscle fibers and are necessary for motor neuron survival and growth.[1,443] Neuregulins are yet another group of proteins that contribute to the clustering of AchR at the NMJ.

A small region of the muscle fibers' sarcoplasm, the junctional sarcoplasm, overlies the myofibrils and extends into the junctional folds.[500] Clusters of five to 10 myonuclei are also found here and serve the purpose of coding messenger RNA for the construction of AChRs.[501–503] The junctional sarcoplasm's function is to manufacture and degrade AChRs, to maintain an appropriate ionic balance for the sacroplasmic constituents, and to synthesize AChE for the synaptic space.

Temperature is an important clinical and electrophysiological consideration in NMT. In patients with MG, a reduction in muscle temperature results in a number of well-documented findings.[19,20,24,25,353–355,504,505] The magnitude of a decremental response during repetitive stimulation at a muscle temperature of 34°C can be significantly reduced or repaired by cooling muscle by only a few degrees. The exact mechanism(s) of the diseased NMJ's response to alterations in temperature is only partially understood. The duration and amplitude of the nerve action potential at the presynaptic terminal are increased by cooling.[203,506,507] This may result in prolongation of the calcium channels' open time and subsequent augmentation of ACh release.[359,497,508–510] In addition, NMT is enhanced at cooler temperatures as the hydrolytic capability of AChE is significantly reduced at temperatures below 34°C, with an increased probability of ACh–AChR interaction.[477] Reducing the affected muscle's temperature is known to increase the AChR's open time as well.[479] Finally, a reduction in muscle temperature leads to a lowering of the resting membrane potential, bringing it closer to threshold, thus requiring less of a stimulus for a single muscle fiber action potential to take place. These four factors and perhaps others as well serve to improve NMT in response to cooling and to potentially result in a false-negative EDX conclusion if the tested muscle is not adequately warmed.

Temperature-dependent changes in jitter can also be seen in persons with normal or abnormal NMJs with differing responses.[21,273] Jitter is <50 microseconds in persons with no known neuromuscular disease and is dependent on patient age and muscle selected. Lowering the intramuscular temperature several degrees below 35°C increases jitter by 2–3 microseconds per degree, while further decreases in temperature toward 30°C result in a increase of jitter values by 6–8 microseconds per degree change. In other words, the jitter increases from 50 to 60–70 microseconds and may even reach 100 microseconds at the temperature of 25°C.[270] The EPP's increased rise time and variability of all the factors necessary to facilitate ACh release may explain this. Conversely, in patients with DNMT of any type but particularly those of the postsynaptic membrane, the jitter may actually improve with a reduction in muscle temperature. Additionally, block present at 34°C may no longer occur at an intramuscular temperature of 30°C. At reduced temperatures in patients with markedly abnormal

jitter (>80–100 microseconds), the increased quantal content results in an EPP of larger magnitude. This subsequently results in a faster rise time approaching, but not reaching, normalcy with less inherent variability and an increased safety factor. This leads to a reduction in the jitter. With abnormal NMJs, the increased ACh release offsets the prolongation effect of temperature on rise time and variability. The above-discussed processes are equally applicable in pre- as well as postsynaptic disorders. In a presynaptic disease process where fewer quanta are released per nerve impulse at slow rates of stimulation, a reduction in temperature leads to more quanta being released in addition to more ACh reaching the postsynaptic membrane secondary to the reduced hydrolytic action of AChE. This effect is likely sufficient to correct the reduced quantal content problem in effect at warmer muscle temperatures. Larger EPPs occur in presynaptic disorders not only because of enhanced quantal release in response to cooler temperatures but due to prolonged opening of AChRs as well. The net effect is an improvement in the safety factor, thus reducing the amount of neuromuscular block and hence an improvement in both clinical strength and fatigue.

A cogent explanation as to why circulating antibodies in MG may produce weakness that is asymmetric and in which certain muscle groups are selectively vulnerable is hard to provide. The preferential involvement of the external ocular muscles may be related to the elevated temperature of the head compared to limbs, specific anatomic and physiologic aspects of these muscles, different antigenic AChR subtypes, firing rates, and/or other poorly understood factors.[511,512]

MYASTHENIA GRAVIS

Despite multiple insights into the pathogenesis of MG, the actual cause(s) remains unknown. There are suggestions that a genetic predisposition exists, at least in some patients.[513,514] Studies of asymptomatic relatives of patients with MG who undergo SFEMG demonstrate that a third will have abnormal jitter values.[269,514] A role has been suggested for infectious agents as a precipitating cause as well.[515] The thymus has always played a central role in MG disease theories. As many as 40–70% of patients with autoimmune MG have thymic hyperplasia and about 10–15% of patients have a documented thymoma.[516–519] The observation that some patients with MG apparently respond clinically to the removal of the thymus gland lends further support to this hypothesis. One potential explanation involves the recognition that the thymus contains myoid cells and other types of stem cells that may serve as autoantigens by the expression of AChRs or AChR antigens on their surface.[520] There are also AChR-specific B lymphocytes within the thymus that generate antibodies to AChR in culture. T lymphocytes specific to AChRs are also found in patients with myasthenia.[207,452,521,522]

The following is an event sequence proposed in an attempt to explain both the initiation and the maintenance of MG. Macrophages and dendritic cells activated for as of yet unknown reasons act as an antigen-presenting cell.[16,18,230,231,233,523] This macrophage may phagocytize and degrade AChRs into peptide subcomponents, which are then linked with a class II major histocompatibility complex (MHC; e.g., HLA-B8, DR3, and DQw2), the molecule required for reactivity to "self-antigens."[524] This AChR antigenic fragment and MHC complex are transported to the macrophage's and dendritic cells' surface. There, specific helper T cells, in cooperation with the CD3 complex and CD4 molecular T-cell receptor site, recognize this antigenic complex.[525–529] Additionally, specific receptor sites on the T cells recognize cytokines secreted by the macrophage and dendritic cells. The activated helper T cells begin to secrete substances, which act to stimulate specific B lymphocytes. The activated B lymphocytes grow and differentiate into plasma cells. These differentiated plasma cells manufacture IgG anti-AChR antibodies that bind to NMJ AChRs. These AChR antibodies are polyclonal, including multiple IgG subclasses directed at different but specific sites on the AChR.[111,123,529–532]

There are a number of mechanisms by which antibodies adversely affect NMT. This includes not only a decreased number of AChRs as described below, but also a diminished postsynaptic membrane area associated with fewer postjunctional folds and, as a result, increased synaptic space.[180–182,418,419–421] A number of antibodies belonging to the IgG class are directed against the main immunogenic receptor as well as other sites on the AChR (Fig. 23–5).[122,533–535] Once bound to the AChR, these antibodies initiate a number of irreversible processes, all of which are directed at the AChR and postsynaptic membrane. In addition to the complement-mediated AChR destruction, the antibodies, by binding to a nearby site, may physically block the ACh-binding site by steric hindrance.[536] It is also possible that antibody binding may prevent the necessary conformational change required to open the ion pore.

The antibodies not only bind to the AChR but also cross-link with other antibodies.[537,538] When the AChRs are cross-linked in this manner, these are reabsorbed by the postsynaptic membrane by a process known as endocytosis. This degradation process occurs up to three times faster than unlinked AChRs. The AChR population is diminished as a result.[539–541] The normal NMJ AChR half-life of 5–10 days is dramatically reduced.[539,540,542] Synthesis of new AChRs remains unchanged, thus resulting in the net reduction of total AChRs per NMJ.

Finally, the antibodies are believed to result in activation of the complement cascade that is directed at the postsynaptic membrane.[165–167,172,173,180–182,543,544,545] Destruction of the postsynaptic membrane has several adverse consequences. Simplification of the postsynaptic membrane reduces the surface area available for AChRs. Widening of the synaptic cleft has the effect of increasing the diffusion time of ACh from the pre- to postsynaptic membranes, thus increasing ACh's exposure to AChE. All these factors act in concert to reduce the NMJ's safety factor by reducing the probability of ACh–AChR interaction. Less ACh will get to the receptor (longer diffusion times, increased exposure to AChE, and greater chance to diffuse out of the synaptic space), and fewer AChRs will be available and responsive to the ACh that eventually arrives.

Regardless of mechanism, impaired ACh binding renders the AChRs whose numbers are reduced or function impaired unable to contribute in a normal fashion to the generation of an EPP. The reduced number of activated AChRs per unit region of postsynaptic membrane translates into a reduction of EPP amplitude. In addition to its primary effects of the AChR channel, MG also reduces the EPP by affecting the number of end-plate voltage-gated sodium channels.[546]

Support for the above hypotheses in MG is provided by (1) the documentation of IgG complexed with AChRs, (2) identification of IgG localized to the postsynaptic membrane,[180–182,420] (3) circulating IgG antibodies that are found in over 90% of patients with MG,[420] and (4) approximately 70–90% reduction in the total numbers of AChRs identifiable at the postsynaptic membrane.[547] Purified immunoglobulins from patients with not only seropositive but also seronegative MG reversibly block currents through nicotinic AChR in patch-clamp experiments.[548] In normal muscle tissue, it is possible to block approximately 75% of functioning AChRs and reduce EPP currents by only 60% of their normal amplitude, with maintenance of essentially normal NMJ transmission.[476,549,550] In MG, however, the confluence of all of the aforementioned factors means that blocking only a small number of the remaining AChRs is all that is required to transform a marginally functioning NMJ into one that is no longer capable of generating a muscle fiber action potential and myofiber contraction.

A cause and effect relationship between anti-MuSK antibodies and MG is based, in large part, on their apparent specificity for patients with myasthenic phenotypes. To date, there are at best modest morphological and electrophysiological data to support a direct role of anti-MuSK antibodies in the pathogenesis of MG. MuSK knockout mice develop normally in utero but die perinatally with a virtual absence of postsynaptic differentiation.[551] Experimental MG has been produced in mice by immunization with one MuSK component. In one patient who underwent an intercostal muscle biopsy, in vitro electrophysiology did disclose reduced MEPP amplitudes.[424]

The pathophysiology of transient neonatal myasthenia results from the passive transplacental transfer of the mother's IgG AChR antibodies. The reason why this disorder does not happen with greater frequency is unknown. The pathophysiology and the genetics of familial limb-girdle MG are unknown. It is presumed to be a postsynaptic disorder in view of its electrophysiological behavior.

CONGENITAL MYASTHENIC SYNDROMES

Our understanding of the complex pathophysiology of the CMS has evolved over the past 30 years. Although many have contributed, much of our knowledge derives from the efforts of Andrew Engel and colleagues at the Mayo Clinic.[163,174,185,426] In vitro electrophysiological recordings from motor points of intercostal muscle including patch-clamp experiments of single AChR channels have allowed analysis of their kinetic properties. Ultrastructural imaging of nerve terminals, the synaptic cleft, and the muscle end plates have provided insight into normal and abnormal structure of the NMJ in these disorders. Formulation of the knowledge gained by these interventions has translated into the identification, location, and function of the proteins involved in normal and abnormal NMT. In some cases, this has provided the insight allowing identification of the genes responsible for a number of these CMS. In the past 20 years, the number of recognized CMS has expanded from three to at least 10.[163]

Understanding the pathophysiology of at least some of the CMS syndromes requires an explanation of the phenomenon of AChR desensitization. This phenomenon refers to AChR unresponsiveness developing in response to excessive temporal and spatial ACh exposure with resultant failure of EPP generation.[356,552–555]

A general overview of the pathophysiology of specific CMS syndromes follows.

Presynaptic Disorders

- Choline acetyltransferase deficiency—This enzyme is responsible for ACh synthesis, resynthesis, and repackaging. Defects result in the inability to maintain a normal ACh content within individual vesicles in response to the stress of repetitive stimulation, typically delivered at a frequency of 10 Hz. MEPP and EPP amplitudes are normal initially but decline in time as resynthesis is

required to replenish ACh stores.[556] Further support for this mechanism comes from similar synaptic responses to hemicholinium whose action is to block choline reuptake into the presynaptic terminal.[191,557]

- Paucity of synaptic vesicles and reduced quantal release—The underlying cause of this syndrome is unknown. Ultrastructural imaging reveals a synaptic vesicle population that is reduced by a factor of 4 in comparison to normal and a proportionate reduction in quantal content.

Synaptic Disorders

- End-plate AChE deficiency—One identified mechanism of this syndrome is a mutation of the ColQ gene on chromosome 3p24.2.[558,559] This protein anchors the AChE within the synapse. The resultant decrease in AChE prolongs the half-life of ACh within the synapse, which has a number of adverse effects on NMT. The EPP duration is prolonged, which can exceed the refractory period of muscle and produce multiple discharges in response to a single nerve action potential. The cationic overloading of the end plate that occurs results in a series of anatomic and physiologic events. There are structural end-plate alterations and compensatory atrophy of the nerve terminal in an apparent attempt to minimize receptor to ACh overexposure. Physiologically, this results in reduced quantal content, loss of AChR, and AChR desensitization as described above.

Postsynaptic Disorders

- Primary kinetic defect +/– AChR deficiency—The slow (to close) channel disorders refer to dominantly inherited kinetic defects that prolong the duration of AChR channel opening as a result of different mutations of the AChR α-, β-, or ε-subunits.[168,174,560] This, in turn, leads to an increased half-life of MEPP and EPP decay. The mechanisms may involve an accelerated rate of channel opening, a delay in channel closing, or an enhanced affinity of ACh for the AChR. Again, increased cationic migration through these prolonged channel openings leads to degeneration of junctional folds, decreased AChR synthesis, a resultant reduction in AChR numbers, as well as depolarization block. The latter is a result of sequential stimuli arriving at a time of a refractory period that also has a prolonged duration.

  Fast (to close) channel disorders due to α-subunit mutations of the AChR are recessively inherited, whereas mutations of the ε-subunit occur in heterozygotes.[174,186] The potential mechanisms are the opposite of those that occur in the slow channel syndromes. There may be a decreased rate of channel opening, an accelerated rate of channel closing, or a decreased affinity of ACh for AChR. Any of these actions may result in a reduction in the duration of channel opening. The EPP safety margin is reduced as a result of the reduced duration of channel open time or reduced frequency of channel opening.

- Primary AChR deficiency +/– kinetic defect—This is an autosomal-recessive disorder caused by homozygous or heterozygous mutations of the ε-subunit of the AChR.[174,561,562] There are a decreased density and an abnormal distribution of AChRs. This, in turn, diminishes the number of successful ACh–AChR interactions and, as a result, the EPP amplitude.
- Rapsyn deficiency—Rapsyn is a protein responsible for concentrating the AChR in the postsynaptic membrane. Deficiency of this protein results in an abnormal density and distribution of AChR, which may, in turn, impair the ACh to AChR-binding process.
- Sodium channel myasthenia—Mutation of the Nav 1.4 sodium channels at the depths of the junctional folds renders them unexcitable in the resting state and therefore thwarts the development of the muscle action potential despite an adequate AChR function.
- Plectin deficiency—Plectin is a protein that is found at numerous locations within the muscle fiber and seems to correlate with areas that receive mechanical stress. Plectin depletion in muscle results in structural changes to organelles and muscle end plates.
- MuSK mutations—Agrin, Dok-7, muscle-specific kinase, and rapsyn are all proteins that interact to promote normal AChR concentration and synaptic organization and maintenance. MuSK is not only the apparent target of an autoimmune response in acquired MG, but mutations of MuSK have been associated with CMS.[563] In identified patients with MuSK mutations, AChR aggregation was impaired, providing a situation similar to AChR deficiency.
- Dok-7 myasthenia—Dok-7 is a protein that activates muscle-specific kinase, a transmembrane protein that, like agrin and rapsyn, appears to be involved in AChR clustering and appears to be essential in maintaining the structural integrity of the NMJ. Smaller end plates scattered on

simplified junctional folds diminish both MEPP and EPP amplitude.

LAMBERT–EATON MYASTHENIC SYNDROME

LEMS is an acquired, autoimmune disorder caused by antibodies directed against P/Q type voltage-gated calcium channels and to a lesser extent the N-type voltage-gated calcium channels and synaptotagmin on and in the presynaptic motor nerve terminals.[200,202,207,209,210,228,431,432,564,565] Passive transfer of IgG from patients with paraneoplastic and nonparaneoplastic LEMS to animals induces all of the morphologic and electrophysiologic features of the disease.[201] In addition, passive transfer experiments in seronegative LEMS suggest that this is an autoimmune disorder in which the culprit antibody has yet to be identified. The trigger for initiating the afferent limb of the autoimmune response is unknown. In patients with cancer, it is speculated that the tumor cells express an embryonic-type calcium channel or calcium channel protein subcomponent that provokes the production of autoantibodies capable of cross-reacting with presynaptic neuronal calcium channels in persons genetically predisposed.[566] The antigenic substrate located on the tumorous calcium channels is believed to be the same, or share a similar antigenic signature, as the neuronal calcium channels.[165–167,430,431,432] A common antigenic relationship between small cell carcinoma and calcium channels is supported by observations of the polypeptide neurotoxin α-conotoxin secreted by the marine snail *Conus geographus*. These effects will be subsequently described in the last paragraphs of this chapter, which discuss drug and toxin effects on NMT.

By whatever mechanism, the immune system is activated to produce antibodies directed against these nerve terminal calcium channels.[200,228,270,567] The antibodies bind to the voltage-gated calcium channels and inhibit the entry of calcium into the nerve terminal. Additionally, the antibodies may cross-link neighboring calcium channels, thus precipitating the process of internalization and degradation of the calcium channels. Complement does not appear to be involved in this process because the nerve terminal maintains a grossly normal appearance without evidence of lytic destruction.[419]

Antibody binding with the calcium channels act to reduce the amount of calcium entry during an action potential. The reduced nerve terminal calcium concentration limits vesicular release from the nerve terminal's internal cytoskeletal bridgework. There is some indication that calcium serves to cleave the bonds holding the vesicles to this intraneural framework. The net result is less availability of vesicles to fuse with the membrane. Cross-linking and internalization of calcium channels have the same net result of reduced calcium entry and hence hinder the vesicle's ability to attach or dock with recognition proteins at the active zones.[568]

In patients with LEMS, intracellular microelectrode recordings reveal potentially paradoxical findings. The MEPP's magnitude in LEMS is quite similar to that recorded in normal muscle, implying that the amount of ACh per vesicle is normal. The frequency of MEPP production, however, may be normal or somewhat greater than that of normal muscle, i.e., 0.57 vs. 0.24/s, respectively.[192,204,569] This increased frequency of quantal release appears to be incompatible with the concept of antibody binding to the synaptic vesicle and fusion hindrance. If this mechanism were true, it would be anticipated that the frequency of MEPPs should decline and should not increase. The reason for the increased MEPP frequency is unknown, although it could be postulated that the spontaneous synaptic release is not calcium dependent to the extent that vesicle release prompted by a nerve action potential is.

The nerve terminal response to depolarization is of interest. The mean quantal content in LEMS is roughly 8 (3.3–15), while a normal terminal releases approximately 56 (24–106) quanta. This finding of diminished quantal release is quite similar to what is observed when the extracellular fluid bathing the nerve terminal is deprived of calcium, and/or the magnesium concentration is dramatically elevated, i.e., reduced quantal release to neural depolarization. The hypothesis of reduced calcium entry secondary to immune-mediated channel dysfunction, disorganization, or destruction is compatible with the physiologic findings of reduced quantal release. Decreasing calcium entry serves to decrease the probability of ACh release, thereby decreasing the amount of ACh released per nerve terminal depolarization and decreasing the muscle EPP.

The histologic and physiologic findings appear to be concordant. In LEMS, normal-appearing vesicles contain normal amounts of ACh. If sufficient amounts of ACh are released, the postsynaptic membrane responds normally, as evidenced by EPPs more than capable of reaching threshold. The reduced quantal content is evidenced by subthreshold EPPs, which reach threshold following rapid rates of stimulation, which were described in the laboratory evaluation setting. This effect is most likely due to the residual calcium overwhelming the binding/sequestering mechanism, thereby increasing the probability of vesicle release. The increased amounts of residual nerve terminal calcium compensates for the diminished amount of calcium entering the terminal in response to each nerve stimulus. The cumulative effect of calcium is necessary for the appropriate amounts of ACh to be released and generate suprathreshold EPPs. All of these physiologic effects directly impact on what

is observed during the EDX examination of patients with LEMS.

BOTULISM

Botulism is a potentially fatal disease caused by one of several protein neuro-exotoxins produced by the bacterium *C. botulinum.* There are eight immunologically distinct types of botulinum neurotoxin (BTX) designated alphabetically by their order of discovery: A, B, C1, C2, D, E, F, and G.[570] The clostridial neurotoxins (botulinum and tetanus toxins) are proteases that selectively degrade the SNARE proteins and, by doing so, inhibit the release of neurotransmitters. The differences in the clinical manifestations and pathophysiology of botulinum and tetanus intoxication are related to the selectivity of the toxins, determined by their heavy chains, for different neurons of the peripheral and central nervous systems (CNS), respectively.

The organism responsible for causing botulinum intoxication is a Gram-positive (Gram negative with maturation), spore-forming, rod-shaped bacterium. This bacterium is only one of more than 100 anaerobic species belonging to the genus *Clostridium.*[34,570,571] The majority of strains can produce only one type of toxin. BTX produced by the organism is released only after the infected cell has undergone lysis. This is somewhat puzzling from a teleologic perspective, as it serves no obvious offensive or defensive purpose. All of the BTXs consist of a heavy (H) chain and a light (L) chain joined together end to end. Immediately upon bacterial lysis, the toxin has modest toxicity. A proteolytic enzyme contained either within the bacterium or in the intoxicated organism is required to cleave the bond joining the two chains, thus activating the molecule into its highly toxic form. This toxin is one of the most poisonous substances known. The minimal lethal dose in man is estimated to be approximately 1.4×10^{-2} μg/kg bodyweight.[572]

Once enterically located, the toxin is readily absorbed and transported hematogenously as is the toxin introduced through a contaminated wound. The toxin produces its physiologic effects at cholinergic, presynaptic terminals. NMJs, autonomic ganglia, postganglionic parasympathetic nerves, postganglionic sympathetic nerves, and adrenal glands are all susceptible.[573–575] The former is the basis of the neuromuscular morbidity and most of the potential for associated mortality. While BTX is primarily a disorder of NMT, the symptoms attributable to cholinergic dysautonomia are of clinical and diagnostic significance.

After binding to the nerve membrane, the toxin becomes internalized by receptor-mediated endocytosis.[35] At low temperatures, there is little if any transport of toxin into the nerve terminal. At normal temperatures, substantially more toxin is transported into a more active nerve terminal, resulting in a more rapid toxic effect. As mentioned above, several distinct SNARE proteins are necessary for docking and fusion of ACh synaptic vesicles in the motor nerve terminal.[455–457,576] The toxic intracellular activity of the different forms of BTX are mediated by zinc-dependent specific proteases, which target these specific polypeptides. BTX B, D, F, and G specifically recognize and cleave vesicle-associated membrane protein (VAMP)/synaptobrevin. BTX A, D, and E cause specific hydrolysis of SNAP-25 (synaptosomal-associated protein), while BTX C cleaves syntaxin. BTX D and F cleave cellubrevin.

Botulism, derived from the Latin word for sausage, is well known by the general public because of the occasional well-publicized outbreaks associated with contaminated restaurant or home-canned foods.[577] The relative rarity of this disease places it low on the list of potential differential diagnoses in patients presenting to emergency facilities. Five clinical forms of botulism have been described: (1) classic or foodborne botulism, (2) infant botulism, (3) hidden botulism, (4) wound botulism, and (5) inadvertent botulism.[236] Types A, B, and E account for the majority of reported food-poisoning cases. Toxin type C affects animals and not humans.

Classic or Foodborne Botulism

Perhaps the earliest description of an outbreak of foodborne botulism occurred as early as in 1897, in which members a music club became ill and several died as a result of eating contaminated ham.[578] Foodborne botulism is not an infection but an intoxication secondary to the consumption of preformed toxin present in the consumed food. From 1899 to 1977, 766 outbreaks of foodborne botulism were reported in the United States.[579] From 1976 to 1984, there were 124 reported outbreaks of the disease.[580] Roughly two-thirds of these reported cases affected only a single person. The mean number of persons per outbreak is 2.7. Approximately 54% of patients are male, with a median age of all affected patients being 44 years. Reported incidence rates suggest that the top three states are Alaska (8.6/100,000), Washington State (0.43/100,000), and Oregon (0.41/100,000).[580,581]

In the United States, the BTX A accounts for about 60%, BTX B responsible for 30%, and BTX E for only 10% of documented botulinum intoxication. Of interest, the majority of BTX A intoxication occurs at the west of the Mississippi River, whereas BTX B cases tend to cluster in the East, particularly in the Atlantic states.[582,583] The reason for this geographic association is the prevalence of specific toxin-producing organisms in certain soil conditions. The BTX E outbreaks are primarily, but not exclusively, found in Alaska and felt to be secondary to the consumption of particular marine organisms indigenous to this region. BTX is usually transmitted through poorly prepared home-canned vegetables. The risk is greater in

higher altitudes where longer cooking times and higher temperatures are required to kill the spores. Outbreaks of BTX associated with restaurants account for a small portion of the total number of outbreaks but tend to involve larger number of people.

The percentage of fatal outcomes resulting from foodborne botulism has declined from about 50% prior to 1950 to approximately 7.5% from 1976 to 1984.[579,580] This decline in mortality is attributed to heightened physician awareness, improvements in the delivery of prompt emergency care, expeditious institution of mechanical ventilation, and possibly the administration of antitoxin in early diagnosed cases.[236,371,584,585] Those persons over 60 years of age are particularly prone to a higher mortality rate.[586–588] Individuals who are the first or only affected patient in an outbreak have a higher (25%) mortality rate. The reason is unknown. It may be related to a shorter incubation period, greater consumption of toxin, or perhaps a low index of suspicion by an unsuspecting physician. Once a diagnosis is made in an index case, other individuals presenting with similar symptoms may be recognized more quickly.

The best medical approach is public education and preventative measures. Individuals canning their own foods should use properly manufactured jars with containment seals as well as using a pressure cooker to kill botulinum spores. Importantly, the bacterial spores are resistant to heat and may survive home-canning techniques at temperatures below 120°C. Boiling food prior to canning at high altitudes should include acidification with vinegar, thus ensuring a pH <4.6, which is known to inhibit the growth of *C. botulinum*.[585] Boiling quickly inactivates the toxin produced by the bacteria but may facilitate bacterial growth by readily producing an anaerobic environment.

Infantile Botulism

Infantile botulism is the most common form of botulism in the United States, with an incidence of 1/100,000 live births.[589] The mortality rate among recognized infants inoculated with botulinum spores is under 4%.[590] BTX A and B are the most common serotypes. There are occasional cases of infantile botulism from BTX E and BTX F, particularly in Europe.

The pathophysiology of infantile botulism is related to enteric spore inoculation rather than ingestion of preformed toxin.[236,244,589,591–593] Spores produced by the *C. botulinum* bacteria inadvertently enter the infant's intestinal tract, germinate, colonize this region, and intoxicate the child. Infantile botulism occurs in children <1 year old, particularly those between 6 and 8 months of age. Botulism spores are ubiquitously found on foods grown in soil and are undoubtedly ingested by young and old alike. It is unknown why older individuals seem resistant to botulism from spore ingestion. One postulate holds that infants <6 months of age are preferentially breast fed, which produces a relatively inhospitable milieu for *C. botulinum* colonization in comparison to formula-fed children.[594,595] It has been hypothesized that infantile botulism may be one of the causes for the so-called sudden infant death syndrome.[31,596,597] Others have discarded this theory.[598] Epidemiological studies reveal risk for botulism in infants consuming honey with as many as 25% of tested honey products containing clostridia spores.[244,599]

Hidden Botulism

Hidden botulism is believed to be in essence a form of "infantile" botulism, occurring in individuals over the age of 1 year.[236,585,600] Patients have a typical botulism phenotype with supportive EDX findings but do not have an obvious food or wound source for the disease. The disorder usually manifests in individuals who have preexisting gastrointestinal problems that allow for the colonization by *C. botulinum*, often facilitated by antimicrobial administration.[580,601–605] Normal flora is believed to have an inherent ability to suppress *C. botulinum* growth. Colonization of the gut by *C. botulinum*, an abnormal event in normal children of this age, leads to the in vivo production of the toxin.[606,607] A and B are once again the most common serotypes involved with F rarely being responsible.

Wound Botulism

This form of botulism is caused by wound inoculation with the *C. botulinum* organism, with the subsequent production of toxin in that location. Of all forms of botulinum intoxication, wound botulism is the least common. There have been increasing reports of wound botulism occurring in IV drug abusers.[96,234,608] In the non-drug user, the typical insult is some types of focal trauma to a limb with or without a compound fracture. Needle injection sites and maxillary sinusitis related to the nasal sniffing of cocaine have been implicated. BTX A is more commonly implicated than type B.[383] A mortality of 12.5% is associated with the disease.

Inadvertent Botulism

This is the most recently described form of botulism related to the introduction of BTX as a therapeutic agent.[236] BTX is now commonly used to treat focal dystonias and other movement disorders. Rarely patients may develop distant or generalized weakness or autonomic dysfunction following focal injections of BTX.[438,609,610] SFEMG studies in patients treated with focal BTX injections have demonstrated increased jitter and blocking at muscle sites distant from injected muscles.[204,286,611]

Less specifically, abnormalities on muscle biopsies have been shown at distant sites.[609] The mechanism is likely hematogenous spread of the toxin.

TICK PARALYSIS

The mechanism(s) by which tick bites produce paralysis is not fully understood.[592] In all cases, the paralysis appears to result from toxins found in the saliva of engorged ticks. The toxin may work directly or indirectly by the provocation of an autoimmune response. Tick paralysis is classified here as a DNMT transmission, as early studies implicated the NMJ as the primary target[252,612] and as ixovotoxin released by the Australian tick *Ixodes holocyclus* affects paralysis by reduction in ACh release at presynaptic terminals.[241] It is speculated that in North American cases of tick paralysis, the toxin may block the sodium channel at the nodes of Ranvier and the distal motor nerve terminals, thus potentially explaining the sensory as well as motor symptoms in some cases.

Ticks are blood-consuming (hematophagous) parasites, which belong to the insect class Arachnida (possessing eight legs) that include spiders and scorpions.[613–615] There are three major families of ticks: Ixodidae (hard-body ticks), Argasidae (soft-body ticks), and Nuttalliellidae. Ticks belonging to the first two families are responsible for causing human paralysis through toxins found in their saliva. Ticks are found worldwide primarily in rural and wilderness areas. In North America, the common wood tick, *Dermacentor andersoni*, usually causes the disease, and, to a lesser frequency, *Dermacentor variabilis* (dog tick). Occasionally, ticks such as *Amblyomma americanum*, *Amblyomma maculatum*, as well as others have been implicated in human paralysis. A particularly notorious tick in Australia, *I. holocyclus* (Australian marsupial tick), causes especially severe disease in humans.[241,616,617] Gravid female ticks are usually implicated in the production of human paralysis because these feed for considerably longer time periods (days). Peak occurrences of paralysis caused by ticks are in the spring and summer months. Their breeding season coincides with peak human outdoor exposure.

Ticks transmit more of a variety of infectious agents than any other type of arthropod and are second only to the mosquito as a human vector of illness. Ticks usually climb to the upper most aspect of tall grasses and weeds waiting for their hosts to walk through the high vegetation. These latch onto the animal's fur or person's clothes and then attempt to climb to the highest place on the victim. In the case of the human, that is frequently the scalp. The slow progression and delicate insertion of its mouth parts into its victim quite frequently take several hours and often goes unnoticed.

▶ DRUGS, TOXINS, AND NMT

There are many drugs, and toxins that augment or, in some cases, create disordered NMT.[618,619] These substances may have scientific, industrial, military, and forensic, as well as therapeutic and diagnostic applications. This section will discuss many of these agents, some of which are exotic. Although an attempt will be made to be fairly comprehensive, the emphasis will be focused on those agents whose applications are most relevant to the practice of clinical neuromuscular disease. Of these, drugs that cause, aggravate, or uncover DNMT in general and MG in particular are the most relevant (Table 23–3). There are many tables that attempt to weight the relative potency of these agents in regard to their likelihood of affecting NMT to a clinically relevant extent. As there are many potential variables that can impact the natural history of MG, it is difficult to objectively weight the magnitude of clinically relevant neuromuscular blockade for most of these agents. Knowing this limitation, in Table 23–2 we attempt both to be comprehensive and to identify those drugs that

▶ TABLE 23–3. DRUGS THAT MAY ADVERSELY AFFECT NEUROMUSCULAR TRANSMISSION

1. Drugs that may unmask or exacerbate myasthenia gravis
   a. Antiarrhythmic agents—lidocaine, quinidine, quinine, procainamide, and trimetaphan camsylate
   b. Antimicrobial agents including aminoglycosides, polymyxin B, colistin, clindamycin, ciprofloxacin, netilmicin, azithromycin, pefoxacin, norfloxacin, and erythromycin
   c. Corticosteroids
   d. Magnesium (parenteral)
   e. Neuromuscular blocking agents—depolarizing and nondepolarizing
2. Drugs potentially implicated in unmasking or exacerbating myasthenia gravis
   a. Anesthetics—diazepam, ketamine, propanedial ether, and proparacaine
   b. Anticonvulsants—phenytoin, mephenytoin, ethosuximide, barbiturates, carbamazepine, and gabapentin
   c. Antimicrobial agents—tetracyclines and ampicillin
   d. Antirheumatics—chloroquine
   e. Beta blockers—propanolol, oxprenolol, timolol, practolol, and betaxolol
   f. Drugs of abuse—cocaine
   g. Gastrointestinal—cimetidine
   h. Miscellaneous—D–L-carnitine, tropicamide, iodinated radiographic contrast, and trihexiphenidyl
   i. Ophthalmics—echothiophate
   j. Psychotropic drugs—phenothiazenes and lithium
3. Drugs that cause myasthenia gravis
   a. D-Penicillamine
   b. Alpha-interferon
   c. Case reports: trimethadione, riluzole, ritonavir, chloroquine, statins, and beta-interferon

probably exacerbate abnormal NMT as opposed to those that might. Support for a cause–effect relationship in disease exacerbation appears to be the greatest for the antibiotics in general and for the aminoglycosides in particular. It is generally accepted that both penicillamine and alpha-interferon are capable of inducing, not simply exacerbating, seropositive MG.

For the sake of completeness, drugs that influence the nerve action potentials that ultimately lead to successful NMT will be discussed. Tetrodotoxin and saxitoxin are two of the most potent toxins known. These produce generalized weakness including ventilatory paralysis by blockade of nerve sodium channels.[620] Tetrodotoxin is found in the visceral organs of the fish of the Tetraodontiformes, the Japanese puffer fish being the most notable example. Saxitoxin is produced by dinoflagellates and are retained in the various tissues of shellfish that consume these organisms. Under certain conditions, these organisms can rapidly multiply to discolor the ocean accounting for the name red tide.

A number of naturally occurring toxins can produce paralysis by the opposite effect, i.e., by facilitating ACh release by prolonging inactivation or directly activating sodium channels on nerve. Ciguatoxin is a potent toxin produced by dinoflagellates that is consumed by and accumulated in various reef fish.[621] Individuals who consume such fish develop characteristic symptoms of abdominal pain, dyspepsia, extremity and circumoral paresthesias, feeling hot, arthralgias/myalgias, and other generalized symptoms. Affected individuals may be considered to have Guillain–Barré syndrome, porphyria, or heavy metal intoxication. Other toxins that promote nerve sodium channel overactivation include a toxin produced by the sea anemone (*Anemonia sulcata*),[622] the Brazilian scorpion (*Tityus serrulatus*),[623] and the spider *Phoneutria nigriventer*, which may result in spastic paralysis, muscle pain, abdominal cramps, seizures, and cardiovascular disturbances resulting from nerve terminal sodium channel activation.[624]

Blockade of nerve terminal potassium channels with associated prolongation of the action potential and enhanced ACh release can arise from envenomation from the black and green mamba snake venom (dendrotoxin) and a particular type of scorpion sting (*Pandinus imperator*).[625] The net result is an increase in EPP amplitude and repetitive EPPs. Cramps, fasciculations, and death may occur in individuals who are particularly sensitive or who receive large amounts of the venom. The Australian Tiger snake produces a lethal mouse venom (notexin) that acts by blocking potassium channels, thus decreasing the release of ACh from the nerve terminal.[626]

Different types of calcium channels exist with specific affinities for the various calcium channel inhibitors. Although these drugs do not typically affect NMJ transmission in most persons, it is possible for patients with MG to experience a worsening of their weakness following the administration of the drugs verapamil and diltiazem.[76,627,628] Antibiotics (particularly the aminoglycosides) also have the ability to adversely affect the nerve terminal entry of calcium.[629,630] Neomycin and polymyxin B can have especially profound NMJ transmission effects.[631–634] Both clindamycin and oxytetracycline have a comparatively reduced ability to prevent voltage-dependent calcium entry.

The administration of magnesium salts can adversely affect NMJ transmission by competitively inhibiting calcium entry into the nerve terminal.[208,635–638] Serum levels of >5 meq/L may abolish deep tendon reflexes, with generalized weakness typically present with levels >9–10 meq/L.[639] This is particularly important in preeclamptic women who have either a reduced ability to eliminate the drug or an occult DNMT. The results of EDX studies are similar to patients with other presynaptic disorders of NMT, i.e., low-amplitude CMAPs that facilitate with brief exercise or "fast" repetitive stimulation.

There are four toxins produced by the marine snail (*C. geographus*), at least two of which adversely affect NMT. ω-Conotoxin works presynaptically to bind to voltage-dependent calcium channels, thereby preventing calcium entry and hence ACh release.[640–642] By radiolabeling this toxin and allowing it to bind to the nerve terminal, it is possible to physically identify the calcium channels. Of the several different types of calcium channels known, this toxin specifically binds irreversibly to those voltage-sensitive channels present in the presynaptic nerve terminal. By radiolabeling the snail toxin and exposing it to tumor tissue, it is possible to collect a radiolabeled toxin–channel complex.[643–650] Exposing this complex to serum of patient with LEMS results in antibodies attaching to the radiolabeled toxin–channel complex.

There are a number of additional drugs that appear to impair NMT through incompletely understood mechanisms. Corticosteroids are believed to directly affect the nerve terminal membrane by causing depolarization, eventually depleting ACh, and altering MEPPs and intracellular potassium concentrations.[651,652] These mechanisms may be one or more of the reasons for the initial worsening of patients with MG treated with these drugs. Azathioprine, theophylline, and papavaerine are thought to inhibit phosphodiesterase, which is responsible for the hydrolysis of cyclic AMP. Increased amounts of cyclic AMP potentiates ACh release.[653,654] Conversely, imidazole indirectly reduces ACh release by augmenting phosphodiesterase activity.

There are several snakes and arthropod toxins that have the capability of impairing ACh release from the nerve terminal. One such toxin is β-bungarotoxin, a phospholipase constituent of the multibanded krait (*Bungarus multicinctus*) venom.[624,626,655] Crotoxin from

the Brazilian rattlesnake (*Crotalus durissus*) initially increases and then depresses the amount of ACh released from the nerve terminal. Many snake venoms contain postsynaptic as well as presynaptic toxins. Local pain and swelling in addition to mild cranial nerve palsies and variable degrees of respiratory paralysis constitute common symptoms experienced by most patients.

Both the black widow (*Latrodectus mactans*) and brown widow spiders (*Lactrodectus geometricus*) produce a number of toxins, one of which has been studied rather extensively and is known as α-latrotoxin.[656–658] This toxin's effects include an initial surge (500–1000×) in the spontaneous MEPP frequency for the first several minutes of exposure. MEPPs then decline and disappear over the next 30 minutes. Ultrastuctural imaging reveals a swollen nerve terminal devoid of synaptic vesicles. Patients at first experience pain at the site of the bite followed by pain in the extremity, which then migrates to other large muscle groups. Muscle cramps and abdominal rigidity can also be observed. Within 2–4 hours, the patients become hypertensive and may demonstrate mild cardiac arrhythmias. Additional signs of autonomic instability can occur with opisthotonus rarely observed in severe envenomations.

BTX, the most notorious of the presynaptically oriented neuromuscular agents, has been discussed previously. As mentioned in the subsequent sections on treatment of LEMS and some of the CMS, the aminopyridines are a group of voltage-gated potassium channel-blocking agents that facilitate NMT and improve strength. These do so by delaying the egress of potassium from the nerve terminal, prolonging the duration of the action potential, and, by doing so, allowing additional calcium ingress into the presynaptic terminal and enhancing quantal release.[1,659]

Guanidine enhances NMT by inhibiting calcium egress from the postsynaptic terminal and thereby increasing the probability of vesicle fusion and quantal release. Hemicholium-3 blocks the reuptake of choline into the presynaptic terminal and interferes with NMT by reducing ACh resynthesis.

Substances that work within the synaptic space to alter NMT have had numerous applications. Anticholinesterase agents bind with AChE to act as a surrogate substrate, thereby impeding the hydrolysis of the natural substrate ACh. From a therapeutic standpoint, anticholinesterases augment ACh–AChR interactions, thus augmenting the EPP and the safety factor of NMT in disease states. Three anticholinesterases have clinical utility in neuromuscular disease: neostigmine bromide, pyridostigmine bromide, and the short-acting edrophonium chloride.[660] Their effects are reversible, as they are eventually hydrolyzed by AChE in a similar manner to ACh. Physostigmine has similar properties but has limited application in neuromuscular disease, as it is capable of crossing the blood–brain barrier to cause largely unwanted CNS side effects.

The organophosphate compounds are considered anticholinesterase toxins.[660–663] These bind in a relatively irreversible manner with AChE. In reality, a number of these compounds are eventually hydrolyzed, but the rate is so slow that the damaging effects of continuous depolarizing amounts of ACh at the nerve terminal are potentially fatal prior to the toxic substance being eliminated from the system. Organophosphate agents are used primarily as weapons or as insecticides/pesticides. The nerve agents tabun, sarin, and soman are some of the most potent neurologic poisons known. Parathion is the agent responsible for many human intoxications.

Human intoxication with these agents usually takes place through accidental pulmonary or dermal exposure. Oral consumption is usually intentional, as an act of homicide or suicide.[664,665] Acute exposure to these substances usually begins with the muscarinic effects of miosis, wheezing (bronchoconstriction plus increased bronchial secretions), and diaphoresis When ingested, there may be prominent gastrointestinal symptoms including abdominal cramping, nausea and vomiting, salivation, and involuntary defecation. Incontinence of urine, bradycardia, and hypotension reflect adverse cholinergic effects of the bladder and heart. Nicotinic symptoms affecting the neuromuscular system such as skeletal muscle weakness, fatigue, and fasciculations leading to ventilatory muscle paralysis may be observed. An altered sensorium secondary to cholinergic CNS effects may occur as well. Depending on the agent, the amount of exposure, the route of administration, and the delay in treatment initiation, death can occur in <5 minutes to 24 hours or more. Atropine in appropriate dosages, an AChE reactivator (e.g., pralidoxime), and supportive ventilatory/respiratory management are the mainstays of treatment along with attempted toxin elimination. Patients with chronic organophosphate exposure may develop a prototypic length-dependent, sensory motor, axonal neuropathy. Recovery from this is typically prolonged and may be incomplete.

The most notorious agent affecting postsynaptic NMT is curare (d-tubocurarine), which is a naturally occurring derivative of the plant *Strychnos toxifera*.[660] It is used medically, as a poison, and historically to improve the diagnostic yield of repetitive nerve stimulation testing. Curare binds to the AChRs, effectively prohibiting NMT through competitive blockade. Related compounds used in anesthesia for neuromuscular block and relaxation of skeletal muscles are pancuronium, vecuronium, atracurium, and gallamine.[666]

Of particular interest is the syndrome of critical illness paralysis, a syndrome that may represent a neuropathy, a myopathy, a DNMT, or a combination of the above.[667–669] For unclear reasons, certain persons are

particularly prone to developing dysfunction of the neuromuscular systems after the prolonged administration of the short-acting neuromuscular blocking agents vecuronium or atracurium usually combined with corticosteroid administration. This syndrome(s) is mentioned here for the sake of completeness and is covered in detail in Chapters 18 and 32.

Succinylcholine and decamethonium also act on the AChR as depolarizing rather than nondepolarizing agents.[660] These substances persistently bind to the AChR and maintain the postsynaptic membrane in a constantly depolarized state. The net result is a brief flurry of muscular overactivity such as fasciculations with subsequent neuromuscular block and flaccid paralysis. Nicotine is a powerful drug with the ability to bind to the AChR with an initial depolarization (facilitation effect) and subsequent inactivation of the AChR (paralysis).

Several drugs act exclusively at the postsynaptic membrane. Others, including some of the antimicrobial agents mentioned previously, work at both the pre- and postsynaptic level.[632,633,651,660,670,671] Polymixin B, polymixin E, netilmicin, and colistin are capable of producing significant primarily postsynaptic neuromuscular effects, particularly in patients susceptible to this type of dysfunction (see above). Tetracycline, oxytetracycline, and rolitetracycline can produce postsynaptic blockade but to a less severe degree than those medications noted above. A number of the aminoglycosides can act both pre- and postsynaptically. Lincomycin and clindamycin have primarily a postsynaptic effect at low concentrations but can also disturb ACh release from the nerve terminal in large dosages.[672] The exact mechanism of how these drugs produce their effects remains to be more fully elucidated. Procainamide can act to worsen symptoms in patients with NMJ disorders through unknown pre- and postsynaptic effects.[75] There are a few reports of verapamil impeding NMJ transmission.[673] It is also possible for persons taking excessive amounts of thiamine to experience an alteration in the kinetics of the AChR with an associated elevation in jitter, as documented by SFEMG.[674]

A unique syndrome clinically indistinguishable from autoimmune MG may be initiated by the use of two agents: penicillamine [56,169,170,314,618,675–684] and alpha-interferon.[618,685–689] Rare patients exposed to these agents develop in most cases the clinical, serological, and EDX features of MG. Onset is within days to months after initial exposure, although cases delayed by years have been reported.[680] The syndrome resolves within 2–6 months of drug withdrawal as does the seropositivity in those patients who develop anti-ACh antibodies.[690] The mechanism of antibody induction is unclear. Case reports of myasthenic syndromes associated with beta-interferon, riluzole, chloroquine, trimethadione, ritonavir, and statins have been published.[690]

The majority of naturally occurring toxins work postsynaptically by binding to AChR, at times irreversibly. These are most frequently found in the venom of snakes belonging to the families Elapidae or Hydrophiidae.[655] Postsynaptic blockade is also provided by the α-conotoxin produced by the marine snail. Each of the snake venoms is referred to as curarimimetic because each of them mimics the actions of curare. The best known of these are α-bungarotoxin and α-cobratoxin, which are contained in the venoms of the banded krait and the Siamese cobra, respectively.[624,626] The ability of these toxins to tightly bind to the AChR allows them to be radiolabeled and serve as markers for AChRs. These have become valuable research tools as have many other toxins. Additional toxins exist in snake venoms, but these have been less well characterized and act in concert with the above toxins to render the AChR effectively blocked. The clinical manifestations of snake bites are varied, depending on the amount of toxin injected, and the patient's size and natural tolerance. The combination of pre- and postsynaptic toxins eventually produces respiratory paralysis and death. Additional hemolytic and autonomic signs and symptoms are usually present.

▶ DIFFERENTIAL DIAGNOSIS AND RECOMMENDED EVALUATION

The differential diagnosis of DNMT includes other disorders in which signs and symptoms fall predominantly if not exclusively within the motor domain. Any disorder that produces painless weakness, in a regional, multifocal, diffuse, or even a seemingly focal pattern, represents a potential DNMT. Motor neuron disease, myopathy, or the uncommon motor neuropathies are the other major disease categories to be considered in this patient population. At times, disorders such as diabetic radiculoplexus neuropathy, acute brachial plexus neuropathy, the inflammatory demyelinating polyneuropathies may produce a predominantly motor syndrome despite an anatomic localization that would predict paresthesia or sensory loss. Ultimately the differential diagnostic considerations of DNMT will be weighted by patient's age as well as other potential risk factors, the associated signs and symptoms not attributable to skeletal muscle weakness, the chronological course of the illness, and the pattern of weakness.

Autoimmune MG is most closely mimicked by other disorders that have a similar affinity for the oculobulbar musculature. In children, CMS need to be strongly considered in any seronegative MG suspect so as to avoid unnecessary and potentially harmful immunomodulating therapies. Along the same lines, CMS need to be considered in any child with an undiagnosed myopathy that a number of CMS phenotypes may mimic. Repetitive

stimulation should be performed in most if not all undiagnosed childhood myopathies to address this potential diagnostic pitfall. There are rare motor neuron disorders of childhood that may present as a prominent bulbar or oculobulbar syndrome (see Chapter 4).

In adults with bulbar weakness, considerations other than DNMT include but are not limited to the progressive bulbar palsy form of ALS, Kennedy disease, and both acquired and hereditary myopathies. As the presence of ptosis or ophthalmoparesis essentially excludes motor neuron disease or inflammatory myopathy from consideration, detection of these abnormalities provides valuable diagnostic insight. A number of inherited muscle diseases may affect the oculomotor system as well as the "bulbar" functions of swallowing and speaking. These include oculopharyngeal muscular dystrophy, the mitochondrial myopathies, myotonic muscular dystrophy, and rare adult-onset cases of congenital myopathy such as centronuclear myopathy. Other differential diagnostic considerations include subacute neoplastic, inflammatory or infectious diseases producing a chronic meningitis with cranial nerve or brainstem parenchymal involvement, or the brainstem parenchyma.

As mentioned above, weakness in MG uncommonly begins and remains (at least initially) confined to limb muscles. ALS, multifocal motor neuropathy, and inclusion body myositis are more common causes of this phenotype. Poliomyelitis or other enteroviral infections would readily distinguish themselves in most cases but require consideration due to their pure motor characteristics in any acute–subacute-onset case. The anti-MuSK and Dok-7 phenotypes with their predilection for neck and proximal limb muscles would be readily confused with a myopathy from both an EDX and a clinical perspective.[85,188]

The differential diagnosis of the CMS is that of the floppy infant syndrome.[691] Most floppy infants will have CNS disorders. Within the neuromuscular system, infantile spinal muscular atrophy, congenital hypomyelinating neuropathy, neonatal myasthenia, congenital myotonic and congenital muscular dystrophy, and the congenital, mitochondrial, lipid, and glycogen storage myopathies are the primary considerations. If ptosis is present, the list focuses on congenital myotonic dystrophy, centronuclear and nemaline myopathy, and mitochondrial disease.

In view of the typical limb-girdle pattern of weakness in LEMS, the entire list of acquired, subacute myopathies and the far less common pure motor forms of chronic inflammatory demyelinating neuropathy are the major considerations along with MG.

As a consequence of its acuity, botulism and tick paralysis are more likely to be confused with Guillain–Barré syndrome or its variants. Both should be considered in more fulminant cases of MG, with tick surveillance, as described above, being carefully carried out. Infectious polycranial neuropathies such as Lyme or, in patients who are nonvaccinated, diphtheria are considered as well in acute–subacute bulbar syndromes.

Evaluation strategies for MG vary. This is, in part, due to the individual biases and preferences of clinicians. It is also, in part, due to the varying differential diagnostic considerations that arise from different topographic presentations of MG. Even in the most clinically straightforward cases, the authors believe that diagnostic confirmation should be sought. The most sensitive test for MG is SFEMG (92–100%) followed by repetitive nerve stimulation of distal and proximal nerves (77–100%). AChR antibody testing is slightly less sensitive (73–90%). Nonetheless, in view of their combined sensitivity and excellent specificity, AChR-binding antibodies may be the first and only test obtained. If positive, no further confirmation is required if the clinical context is compatible with MG. Unless there is diagnostic urgency, testing for modulating and MuSK antibodies may be delayed until binding antibody results are reported. Testing for AChR-blocking antibodies has limited utility. In some laboratories, EDX is performed in addition to or prior to serology, in order to establish baseline values in the event that issues related to treatment arise.

EDX has a major role to play in any patient with painless weakness, particularly the suspected myasthenic who is seronegative. The goal is to establish the existence of a DNMT and, if possible, to categorize it as being a pre- or postsynaptic disorder. Alternatively, EDX is the primary means to identify or exclude other neuromuscular disorders from consideration. In most laboratories, "slow" repetitive stimulation is performed prior to SFEMG, but the patients' ability to cooperate with either of these tests and the skill set and individual preferences of physicians undoubtedly come into play in this decision. In all probability, edrophonium testing is used less frequently now than was the case historically. Despite both safety concerns and the possibility of both false-positive and false-negative results, edrophonium "Tensilon" testing can still provide valuable insights in the appropriate clinical context if performed with the appropriate cautions.

Other testing for DNMT other than MG, other neuromuscular diseases that enter into the differential diagnosis of MG, and comorbid disorders that have an increased prevalence in patients with MG are determined by the index of suspicion for each of these specific disorders. In patients who are seronegative for AChR-binding antibodies, serological testing for modulating, MuSK, striated muscle, and voltage-gated P/Q calcium channel antibodies should be considered. Elevated serum creatine kinase levels are atypical in DNMT and should suggest the presence of a myopathy or motor neuron disease. In the former situation, the myopathy may occur as either an alternative or an additional diagnosis. In patients in whom a diagnosis of autoimmune MG has been established

or is strongly suspected, chest imaging, baseline measurements of vital capacity, and blood work testing for striated muscle antibodies and TSH are recommended. Striated muscle antibody testing should be considered as a complimentary rather than surrogate test for chest imaging in patients with potential thymic abnormality if for no other reason than the location of thymic tissue is not always predictable.[692]

▶ TREATMENT

MYASTHENIA GRAVIS

There are various treatment modalities employed for MG: (1) AChE inhibitors, (2) immunomodulating medications, (3) plasma exchange (PEX), and (4) thymectomy.[15,18,539,540,693–699] Treatment regimens are individualized depending on the severity of the myasthenia (e.g., Osserman classification), patient age, thymic status, concurrent medical issues, and individual physician preference and experience.[700]

Whether patients with purely ocular symptoms benefit from treatment is controversial, either in terms of symptom relief or altering the natural history of the disease.[701,702] The evidence basis to aid in this decision making is limited.[703] Some have suggested that electrophysiological evidence of generalized disease justifies more aggressive treatment. It is the philosophy of the authors to manage the patient not the disease. Conservative symptomatic treatment with pyridostigmine or nonpharmacological measures is generally the initial recommendation. If patients are still symptomatic on pyridostigmine, a trial of eye crutches for ptosis or patches/prism lenses in an attempt to minimize diplopia may be considered. Unfortunately, these treatments are either not tolerated or sufficiently beneficial to satisfy most patients. Prisms cannot adequately correct diplopia that varies in intensity and direction. Eye patches are rarely tolerated for prolonged periods. Tarsorraphy should be undertaken cautiously if at all as concomitant weakness of eye closure may lead to exposure keratitis if the eyelid position is raised excessively. In our opinion, immunomodulating treatment of ocular myasthenics is a reasonable approach for patients who are refractory to conservative measures, whose quality of life is impacted by disease symptoms, and who can understand and accept the risks and uncertainties associated with this undertaking. In such cases, a short course of prednisone is prescribed in a slowly incrementing fashion. Initially, patients are started on prednisone 20 mg daily and the dose is increased by 5 mg every 3–5 days until the symptoms have resolved. They are kept on this dose for a month and then the dose is slowly tapered (no faster than 5 mg every 2 weeks down to 20 mg daily and then by 2.5 mg every 2 weeks). Most patients seem to require long-term immunosuppressive therapy to control their ocular symptoms. In such cases, an attempt is made to maintain them on the lowest possible dose of prednisone (preferably alternate day) and/or a second-line immunomodulating drug.

In patients who present with generalized symptoms, one approach would be to initiate pyridostigmine, prednisone, as well as a second immunomodulating agent (e.g., azathioprine) simultaneously. The strategy is to provide symptomatic control acutely with pyridostigmine, achieve better and more durable control within a few weeks by use of prednisone, and then to eventually maintain long-term control while "steroid-sparing" with azathioprine. Once the patient achieves a clinical remission with prednisone, the dose is slowly weaned on an every other day basis (e.g., 10 mg every 2 weeks) hoping that the delayed onset of azathioprine will "kick in" by the time the patient arrives at a "chronically acceptable" steroid dose (20 mg qod or less). If there is any question about the patient's ability to swallow, breath, or avoid aspiration, the patient is hospitalized and a course of PEX or intravenous immunoglobulin (IVIG) is considered in addition to the aforementioned treatments.

Patients in myasthenic crisis (severe respiratory distress or bulbar weakness) represent the opposite end of the spectrum from patients presenting with isolated oculomotor symptoms.[704,705] These patients should be admitted to an ICU and followed closely, particularly in regard to pulmonary function. When the forced vital capacity declines to <15 mL/kg or negative inspiratory pressure is <30 cm H_2O, intubation is recommended for airway protection. Mechanical ventilation is initiated to reduce the work of breathing, and improve respiration (gas exchange) by preventing atelectasis and reducing the A-a gradient. PEX is initiated and continued on an every-other-day basis until the patients has had a significant return of strength and can be weaned off the ventilator. PEX is also discontinued if 2 weeks pass without a meaningful response. IVIG may be an alternative or subsequent treatment if PEX fails, although it is our impression that its effect is more variable and slower in onset than PEX. While the patient is intubated, we typically avoid anticholinesterase medications in an attempt to minimize secretions. In addition to starting PEX, we usually begin corticosteroids at or around the same time. Although regimens are varied, IV methylprednisolone at a dose of 500–1000 mg/d for 5 days may be used followed by 0.8 mg/kg IV daily until the patient is capable of taking steroids by mouth. Although the steroids may initially exacerbate the patient's myasthenia, this is less of an issue in a patient already intubated and in the ICU. Improvements from both PEX and corticosteroids are related to regrowth of AChR, which may occur as early as 10 days in responding individuals. A long-term, second-line, disease "consolidating" agent

like azathioprine, cyclosporine, or mycophenolate may be initiated as well.

In juvenile MG, treatment options are identical to adults with a somewhat altered emphasis. As in adults, the efficacy of thymectomy has not been proven. Arguably, the potential value of this treatment is the hope of a drug-free cure. Arguably, this has even greater importance in this population than in adults. Considerations of medication effect on growth and procreation and the potential long-duration effects of immunosuppression are all of particular concern in children and adolescents. In a large retrospective series of 149 patients with juvenile MG, 85 patients had a thymectomy while 64 patients were managed medically.[97] In the thymectomy group, 82% of patients improved, while 48% went into remission compared to a 63% improvement rate and a 34% remission rate in the patients who are nonthymectomized.[97] In another retrospective series of 79 patients with juvenile MG, 65 patients (82%) underwent thymectomy. Of the patients who were thymectomized, remission occurred in 60% compared to 29% in the nonthymectomized group.[96] However, neither of these studies controlled for baseline severity or medical therapy, and, thus, the role of thymectomy in juvenile MG is unclear as it is in adults.[706] Thymic hyperplasia is common in juvenile myasthenic gravis, although thymomas are not. Importantly, removal of the thymus in children does not appear to have any deleterious effect on immune system development.[707] PEX[94,96] and IVIG appear to be effective in this population.[95,98] As in adults, immunotherapy is avoided if possible. Children are started on pyridostigmine at a dose of 1.0 mg/kg and then titrated to an effective dose. Patients with moderate-to-severe generalized disease are started on oral prednisone 1 mg/kg/d and switched over to alternate-day prednisone after 2–4 weeks and then tapered after strength is stabilized by subtracting first from the odd-day dose until zero and then from the even day until a minimally effective dose is achieved. The rate of dose reduction varies depending on patient response and the total daily dose but would rarely exceed 5–10 mg every 2 weeks (on an every-other-day basis) unless significant complications or lack of steroid efficacy developed. Other immunosuppressive agents are avoided when possible, although azathioprine and cyclosporine have been used in this age group with satisfactory results.[94,96]

Infants with neonatal myasthenia and weakness may be treated with anticholinesterase medications until such time the antibody levels have diminished and the child's breathing, swallowing, and movements are satisfactory. Those infants with severe weakness may require mechanical ventilation and treatment with PE. IVIG does not appear to be effective.[708,709] Frequent suctioning may be needed to prevent respiratory infection. The morbidity and mortality from this disease has improved markedly with the institution of the above-noted simple medical interventions.

Specific Treatments

Anticholinesterases

The AChE inhibitor, pyridostigmine bromide (Mestinon), usually improves weakness in patients with MG. By transiently inhibiting AChE from metabolizing ACh, the amount of ACh and the duration of its effect at the NMJ increase. This permits ACh to interact with sufficient numbers of AChRs to generate suprathreshold EPPs at NMJs. Elevation of subthreshold EPPs results in reversal of neuromuscular blockade at some muscle fibers, resulting in at least some amelioration of muscle weakness and fatigue. Importantly and unfortunately, pyridostigmine does not beneficially affect the junctional pathology of MG. Predictably, patients with severe generalized weakness, particularly those with bulbar and respiratory involvement, require more than just pyridostigmine for treatment. It is also common for the beneficial effects of anticholinesterases to diminish with time as NMJs may become increasingly damaged.

Pyridostigmine is initiated in adults at a dose of 30–60 mg every 6 hours. In children, pyridostigmine is started at a dose of 1.0 mg/kg. It is available in a liquid form at a concentration of 12 mg/mL. The dosage is gradually titrated as necessary to control myasthenic symptoms without producing undesirable side effects. Most adults require doses in the 60–120 mg every 4–6 hours range. Dosing should typically not exceed 600 mg/d in adults and 7 mg/kg in children. Dosing a half hour before meals may aid in swallowing and reduce aspiration risk. There is a timed-released form of pyridostigmine (180 mg), which is typically used when the patient is symptomatic at night or upon awakening. In patients with only mild or moderate weakness, it is equally efficacious to have the patients set their alarm 30 minutes before they need to arise from bed and take regular pyridostigmine dose at that time. Although desensitization and worsening MG from excessive anticholinesterase use is rarely considered or recognized, it is probably prudent to limit the exposure of time span specifically and pyridostigmine in general when possible.

Patients can develop cholinergic side effects secondary to the build up of ACh at muscarinic and nicotinic receptors. Muscarinic side effects include nausea, vomiting, abdominal cramping, diarrhea, increased oral and bronchial secretions, bradycardia, and rarely confusion or psychosis. In patients with significant side effects, pretreatment with anticholinergic medications is recommended (e.g., anaspaz, propanthine, glycopyrrolate, or diphenoxylate with atropine) 30 minutes prior to their pyridostigmine dosing.

Very rarely, excessive pyridostigmine may result in a cholinergic crisis in which the build up of ACh at the

nicotinic AChR "desensitizes" or blocks receptors leading to increased weakness. This type of crisis needs to be distinguished from the "myasthenic crisis" due to the underlying disease.[710] These two types of crises may be distinguished by performing an edrophonium test on the patient as described above. If IV edrophonium results in clinical worsening, the increased weakness in the patient is most likely the result of overdosing the anticholinesterase medication. If weakness improves following edrophonium, the weakness is due to the underlying MG.

Pyridostigmine is typically delivered orally but exists in a parenteral preparation as well. It should be noted that the IV dose is 1/30th to 1/60th that of the oral preparation. Neostigmine can be used in lieu of pyridostigmine but the latter is typically preferred, as it is longer acting and may have better activity on bulbar muscles. Physostigmine should not be used as a treatment for MG, as, unlike the other two agents, it crosses the blood–brain barrier and leads to unwanted CNS cholinergic effects.

Patients with MuSK antibody MG are frequently insensitive to the beneficial effects of anticholinesterases.[88,90] These patients commonly respond to the other immunomodulating drugs described in subsequent paragraphs that have been traditionally used in patients who are anti-AChR seropositive and negative.[73,85,88,90]

Corticosteroids

The most commonly used immunosuppressive agents are corticosteroids. Various trials have demonstrated the efficacy of corticosteroids in the treatment of MG.[129,711–717] Corticosteroid treatment results in marked improvement (45%) or remission (30%) in the majority of patients with myasthenia. Prednisone, at least initially, is the drug of choice for the majority of patients with moderate to severe generalized MG. Patients with diabetes or significant osteopenia represent two groups where alternative first-line treatments may be considered. There are two treatment strategies generally employed when using prednisone in patient with MG: (1) aggressive high-dose daily steroids at the onset of treatment approach and (2) "a start low and go slow approach." A more rapid improvement is likely to occur from a high-dose regimen. Prednisone is initiated at a dose of 1.5 mg/kg/d (up to 100 mg) for 2–4 weeks. Typically, the patient is transitioned to an alternate-day regimen. This can be done by maintaining the high dose on odd days and going immediately to zero on the even days. Alternatively, weaning can be accomplished by lowering the dose on the alternate day, e.g., 100 mg on odd days and 80 mg on the even. Higher doses are maintained until strength has normalized or the improvement plateaus. Subsequently, prednisone is tapered slowly, e.g., by reducing 5 mg every 2–3 weeks until 20 mg qod is reached. Past 20 mg qod, tapering generally progresses more slowly, with incremental drops of 1–2.5 mg being recommended. It is usually at these lower doses that patients may relapse. Most patients will require some amount of immunosuppressive medication. The goal is to find the lowest dose necessary to maintain their strength. Understandable fears regarding the adverse effects of long-term corticosteroids may lead the inexperienced clinician to wean steroids too rapidly, a frequent observation made in experienced neuromuscular clinics. The addition of other immunosuppressive agents may have a prednisone sparing effect and allow for lower doses of the corticosteroid. It is an entirely reasonable and often effective strategy to begin corticosteroids and another immunomodulating agent simultaneously. As the second-line drugs typically have significantly slower onsets of action, the strategy is to get the patient under control with corticosteroids and then maintain that control with a second-line agent with a more delayed onset effect, as the steroids are being weaned over the ensuing months.

Importantly, as many as 30% of patients experience a varying degree of initial worsening (within the first 1–3 weeks) lasting about 1 week after they are started on high doses of steroids.[129,707,718] Significant weakness is estimated to occur in <10% of patients. Nevertheless, it is prudent to hospitalize patients for the 1 week after initiating treatment with high-dose corticosteroids. The mechanism of the exacerbation of myasthenic symptoms is not clear. It would appear to be related to NMT as opposed to nerve or muscle as it corresponds with worsening of the decremental response to repetitive stimulation.[719] It has been hypothesized that corticosteroids have mild neuromuscular blocking properties that precede the beneficial effects of immunomodulation. It is possible that the worsening may have a mechanism similar to weakness in patients with acute quadriplegic myopathy who most frequently develop generalized weakness in the setting of high-dose corticosteroid combined with neuromuscular blocking agents. The AChR antibodies in myasthenics in combination with corticosteroids may have the same synergistic role that corticosteroids have with nondepolarizing neuromuscular blocking agents in critical illness myopathy.

In view of the transient myasthenic worsening associated with corticosteroid introduction, some have advocated the "start low and go slow approach."[18] Patients are started at a dose of 15–20 mg/d and the dose is slowly increased by 5 mg every 2–4 days or so until definite improvement is noted. Alternatively, based on results of the recent mycophenolate trials, patients may be maintained on and experience a beneficial effect without escalating the prednisone dose past 20 mg/day. Unfortunately, improvement takes much longer with this approach and is therefore unsatisfactory in patients with severe weakness. This approach may be preferable in patients with

mild generalized disease not controlled with pyridostigmine or patients with ocular myasthenia that require immunosuppression.

There are a multitude of potential serious side effects associated with the chronic administration of corticosteroids. The risk of infection, diabetes mellitus, hypertension, glaucoma, osteoporosis, steroid myopathy, and aseptic necrosis of the joints are notable examples. The majority of these are dose and duration dependent. It is prudent to obtain a chest X-ray, purified protein derivative (PPD) skin test, and a detailed history regarding exposure to tuberculosis, strongyloidosis, or other organisms that might proliferate in an immunosuppressed patient. Patients with prior history of tuberculosis or those with a positive PPD may need to be treated prophylactically with isoniazid. In addition, measurement of bone density with dual-energy X-ray absorptiometry (DEXA) at baseline and every 6–12 months while patients are receiving corticosteroids is recommended. A bone density <2.5 standard deviations below normal is considered positive for osteoporosis. Calcium supplementation (1 g/d) and vitamin D (400–800 IU/d) are started prophylactically for steroid-induced osteoporosis. Postmenopausal women should be treated with a bisphosphonate, which has been demonstrated to be effective in the prevention and treatment of osteoporosis.[720,721] Efficacy in preventing osteoporosis has been reported with these agents in postmenopausal women with and without concurrent estrogen therapy, in premenopausal women, and in men who were receiving corticosteroids.[721] Some authorities advocate alendronate (5 mg orally per day) as prophylaxis for osteoporosis on any patient placed on corticosteroids,[721] although the long-term side effects of bisphosphonates are not known, especially in men and young premenopausal women. If dual-energy X-ray absorptiometry scans demonstrate osteoporosis at baseline or during follow-up studies, the initiation of alendronate 10 mg/d is recommended. If there is mild bone loss not yet diagnostic for osteoporosis, we consider starting alendronate 5 mg/d. Alendronate can cause severe esophagitis, and absorption is impaired if taken with meals. Therefore, patients must be instructed to remain upright and not to eat for at least 30 minutes after taking this medicine.

Prophylactic treatment with histamine-H_2 receptor blockers is not required in the majority of patients and is used only in those who become symptomatic. Patients are instructed to start a low-sodium, low-carbohydrate, high-protein diet to prevent excessive weight gain. In addition, patients are also given physical therapy and encouraged to slowly begin an aerobic exercise program. It is hypothesized that both osteopenia and steroid myopathy are enhanced by immobility. Blood pressure is monitored along with periodic eye examinations for cataracts and glaucoma. Fasting blood glucose and serum potassium levels are periodically checked. Potassium supplementation may be required, if the patient becomes hypokalemic.

High-dose, long-term steroids and lack of physical activity can cause type 2 muscle fiber atrophy with proximal muscle weakness. Distinction from myasthenic weakness is important and may be difficult. Patients who become weaker during prednisone taper, particularly in cranial and upper extremity muscles, and have worsening of their decremental response on repetitive stimulation or increasing jitter and blocking on SFEMG are more likely experiencing a flare of MG. In contrast, patients with continued high doses of corticosteroids, normal repetitive stimulation and SFEMG, and other evidence of steroid toxicity (i.e., Cushingoid appearance), and increasing leg weakness probably have type 2 muscle fiber atrophy and could benefit from physical therapy and steroid dose reduction.

Azathioprine

Azathioprine is a probably the most frequently used second-line immunomodulating agent used in the treatment of patients with MG. Several trials have demonstrated the efficacy of azathioprine alone or in combination with prednisone.[712,716,722–724] Improvement is noted in 70–90% of patients with myasthenia treated with azathioprine, including some patients who are steroid resistant.[707] Patients treated with azathioprine may also be maintained on lower doses of prednisone (i.e., a steroid-sparing effect).

As described above, azathioprine may be used initially in addition to prednisone in an attempt to limit long-term corticosteroid exposure. In adults, azathioprine is commonly initiated at a dose of 50 mg/d in adults and gradually increased over 1–2 months to a total dose of 2–3 mg/kg/d. A systemic reaction characterized by fever, abdominal pain, nausea, vomiting, and anorexia occurs in 12% of patients requiring discontinuation of the drug. This reaction generally occurs within the first few weeks of therapy and resolves within a few days of discontinuing the azathioprine. Rechallenge with azathioprine may be successful but usually results in the recurrence of the systemic reaction. If patients tolerate azathioprine initially, they usually do so on a long-term basis. Other uncommon but major complications of azathioprine are bone marrow suppression, hepatic toxicity, pancreatitis, teratogenicity, oncogenicity, and risk of infection. Prior to beginning azathioprine, patient should be screened for thiopurine methyltransferase (TPMT) deficiency. Patients who are heterozygous for a mutation in TPMT may be able to tolerate azathioprine at lower dosages but those who are homozygous for TPMT mutations should not receive drug as they cannot metabolize it and may have severe bone marrow toxicity. Allopurinol should be avoided, because it interferes with

azathioprine metabolism, increasing levels, and increasing the risk of bone marrow and liver toxicity. One practical limitation of azathioprine is its delayed onset of action of 6 months or more. For this reason, it is rarely used as the sole initial agent.

Complete blood count (CBC) and liver function tests are monitored every 2 weeks until the patient is on a stable dose of azathioprine. An elevated mean corpuscular volume is an anticipated effect of azathioprine therapy and is used by some clinicians as an indicator of a biological response. If the white blood count falls below $4000/mm^3$, the dose should be decreased. Azathioprine is held if the white blood count declines to $2500/mm^3$ or the absolute neutrophil count falls to $1000/mm^3$. Leukopenia can develop as early as 1 week or as late as 2 years after initiating azathioprine. As in most drugs with potential hepatotoxic effects, azathioprine should be discontinued if transaminases increase more than two to three times the baseline values. Liver toxicity generally develops within the first several months of treatment. Leukopenia generally reverses in 1 month and hepatotoxicity can take several months to resolve. Patients can occasionally be successfully rechallenged with azathioprine after bone marrow and liver abnormalities resolve.

Cyclosporine

Cyclosporine primarily inhibits T-cell-dependent immune responses and has been demonstrated to be effective in the treatment of patients with MG.[725–729] Most patients notice improvement within 2–3 months of treatment initiation. Mean time to maximum improvement is approximately 7 months.[725] Cyclosporine also appears to have a steroid-sparing effect. As many as 95% of patients are able to discontinue or decrease their corticosteroid dose.[725] Renal toxicity occurs in approximately a quarter of patients. The need to monitor creatinine and trough cyclosporine levels frequently has limited the enthusiasm of some clinicians for its use. Patients receiving the calcineurin inhibitors cyclosporine or tacrolimus may also develop a calcineurin inhibition syndrome that includes prominent and at times debilitating tremor requiring dose reduction. Cyclosporine is used primarily in patients who are refractory to prednisone and azathioprine. There is a general perception that brand name drugs, e.g., Neoral® or Sandimmune®, are preferable to their generic counterparts. Initially a total dose of 3.0–4.0 mg/kg/d in two divided doses is used and gradually increased to a maximum dose of 6.0 mg/kg/d as necessary. The cyclosporine dose is initially being titrated to maintain trough serum cyclosporine levels of 100–200 ng/mL. Blood pressure, electrolytes and renal function, and trough cyclosporine levels need to be monitored on a monthly basis. The dose is lowered as necessary to keep the trough <150 ng/mL and the creatinine level stable. Any upward trend of creatinine levels should promote a dose reduction. After patients achieve maximum improvement, the dose is reduced over several months to the minimum dose necessary to maintain the therapeutic response. Patients need to be informed of the numerous drugs that can aggravate renal toxicity.

Mycophenylate

Mycophenylate mofetil is a relatively new immunomodulating agent that inhibits the proliferation of T and B lymphocytes by selectively blocking purine synthesis in lymphocytes. Mycophenylate has been used in transplant patients to prevent rejection. It has been studied in several small open-label trials in patients with MG with reported beneficial effect.[730–733] Enthusiasm generated by these reports and the apparent relative safety of this drug have been tempered by two recent controlled trials. Both compared prednisone plus placebo to prednisone plus mycophenolate. There was no significant difference between the quantitative MG score of the two groups of 80 and 176 patients, respectively.[734]

Patients taking mycophenolate mofetil have been reported to be able to lower their doses of other immunomodulating agents without loss of effect but only a few patients have improved using it as the sole treatment. Improvement has been noted as early as 2 weeks and often within the first 3 months after starting the medication. The benefit can be delayed for up to 12 months. The typical dose is 1–2 g/d in two doses. Higher doses may be used, but blood counts need to be monitored for hematologic abnormalities, which may occur at higher doses. Mycophenylate is excreted through the kidneys; therefore, the dose should be decreased (no more than 1 g/d total dose) in patients with renal insufficiency. A benefit of mycophenylate compared to other immunosuppressive agents is the lack of renal or liver toxicity with the drug. The major side effect is diarrhea. Starting slowly and increasing the dose slowly may diminish the risk and severity of this troublesome side effect. Less common side effects include abdominal discomfort, nausea, peripheral edema, fever, and leukopenia. Measurement of drug levels is not done routinely.

Mycophenolic acid or mycophenolate sodium (Myfortic®) is an alternative preparation that comes in 180 and 360 mg enteric-coated tablets. As a result, it has the potential for less gastrointestinal side effects. Unlike mycophenolate mofetil, it is not available for parenteral use. The daily dose is 720–1440 mg/d in two divided doses.

Tacrolimus and Sirolimus

As in cyclosporine, these are two immunomodulating drugs developed for and used by the organ transplant community. There has been limited experience with tacrolimus and essentially no published experiences with sirolimus in MG.[132,735–743] Tacrolimus has

similar toxicities to cyclosporine but has been reported to benefit some who have failed to respond or become refractory to the effects of cyclosporine. Sirolimus has a different toxicity profile than cyclosporine or tacrolimus, particularly in reference to renal function. The authors' limited and anecdotal experience suggests potential benefit in the setting of declining renal function in patients with severe disease refractory to other agents.

Methotrexate

This agent has not been used as frequently for MG as it has been for autoimmune myopathies (e.g., inflammatory myositis). Our experience suggests that methotrexate can be effective. Its earlier onset of action provides an advantage over azathioprine. It may be initiated orally at 7.5 mg/week given in three divided doses 12 hours apart. The dose is gradually increased by 2.5 mg each week up to 25 mg/week as necessary. The major side effects of methotrexate are alopecia, stomatitis, interstitial lung disease, teratogenicity, oncogenicity, risk of infection, and pulmonary fibrosis, along with bone marrow, renal, and liver toxicity. Doses over 50 mg/week, rarely required or used for MG, require leukovorin rescue. All patients are concomitantly treated with folate.

Cyclophosphamide

There have been a few reports describing the use of cyclophosphamide in the treatment of all forms of acquired MG, including patients with MuSK antibodies.[744–747] Because of significant side effects (i.e., gastrointestinal upset, bone marrow toxicity, alopecia, hemorrhagic cystitis, teratogenicity, sterilization, and increased risk of infections and secondary malignancies), most clinicians avoid cyclophosphamide for MG if at all possible. Cyclophosphamide may be considered in patients with severe generalized MG refractory to other modes of immunotherapy.

There are a few general principles that apply to the use of long-term immunomodulatory treatment for MG or any other immune-mediated neuromuscular disease. Most of these agents undoubtedly increase the risk of skin cancers. Limitation of sun exposure and the liberal use of sun block are encouraged. When these agents are used in transplant recipients, *Pneumocystis carinii* prophylaxis is often recommended. The role of *P. carinii* prophylaxis in patients with neuromuscular disease treated with immunomodulating therapy is less well defined but should be considered, particularly in individuals receiving multiple agents. Finally, the natural history of MG is not predictable in most patients. It is reasonable, after a year or more of drug-induced remission, to consider a gradual wean from immunomodulating agents with the hope that a protracted remission has been obtained.

IV immunoglobulin

The administration of IVIG may result in clinical improvement in some patients with MG.[95,98,748–754] Some studies have found that IVIG is equivalent to PEX in the treatment of patients,[751] while other studies have suggested that PEX is more efficacious.[754,755] A similar benefit of PEX over IVIG has been suggested to exist in the anti-MuSK population of patients with MG. [37,73,85,86,88,94,132,735] IVIG has not been compared to standard immunosuppressive agents (e.g., corticosteroids, azathioprine, and cyclosporine) in a double-blind prospective fashion. Of the two, the authors prefer PEX as opposed to IVIG for the treatment of myasthenic crisis. IVIG is reserved for patients with generalized myasthenia in crises who are refractory to PEX or corticosteroids or as an agent to bolster patient strength in anticipation of thymectomy. As the lifestyle burden imposed by the duration of IVIG infusions is significant, chronic IVIG use is often restricted to those whose disease has failed to respond adequately to corticosteroids, azathioprine, mycophenylate, or cyclosporine. In these situations, IVIG (2 g/kg) in two to five divided doses is given over an equal number of days. Repeat infusions are given at monthly intervals for at least 3 months. Treatment is subsequently individualized to identify the smallest dose at the longest intervals that provides the desired effect. Some patient may need treatment (0.4–2 g/kg) every week, while others may go several months between IVIG courses. All patients should have an IgA level checked prior to treatment, because those with low IgA levels may be at risk of anaphylaxis. Patients should also have renal functions checked, especially those with diabetes mellitus, because of a risk of IVIG-induced renal failure. Flu-like symptoms, headaches, myalgias, fever, chills, nausea, and vomiting, are common and occur in as many as half the patients receiving IVIG. These symptoms can be reduced by premedication with low-dose corticosteroids, acetaminophens, and/or antihistamines and by lowering the infusion rate. Rash, aseptic meningitis, and stroke may also complicate IVIG infusions.

Rituximab

Rituximab is a monoclonal antibody directed against CD-20 lymphocytes developed for the treatment of B-cell lymphomas. There are case reports suggesting a beneficial response of rituximab in patients with both AChR and MuSK MG.[756,757]

Plasma exchange

PEX has widely accepted efficacy in the treatment of MG.[32,89,751,754,755,758–761] It is used primarily in patients in myasthenic crisis or in those with moderate weakness prior to thymectomy in order to maximize their perioperative strength. Its utility as a chronic treatment is hampered by the same cost and time considerations as IVIG. In addition, there is the risk and discomfort

associated with the potential need for recurrent central venous access and large volume transfer including sepsis, pneumothorax, thrombophlebitis, and cardiovascular instability. The typical course involves 2–3 L individual exchanges of plasma every other day until strength is significantly improved. Improvement is noticeable after two to four exchanges, again probably correlating with AChR regrowth. PEX lowers the serum concentration of AChR antibodies, but it must be repeated at relatively regular intervals due to its limited duration of effect. Within a week following PEX, the autoantibodies begin to rebound. Patients receiving PEX are commonly on immunomodulating agents as well. The timing of oral dosing and exchanges should be adjusted so as to not negate drug effect.

Thymectomy

As previously emphasized, a large number of patients with autoimmune MG have thymic abnormalities. Removal of this structure is a time-honored treatment of unproven benefit in MG.[309,318,319,517,697] Thymectomy is universally recommended in patients with thymoma in the hopes of preventing the morbidity and mortality of local spread and potentially of metastatic spread. Any benefit pertaining to myasthenic control is a secondary consideration. The role of thymectomy in patients with MG without thymoma is less clear and is the subject of a Practice Guideline by the American Academy of Neurology.[706] This evidence-based review of 21 published level II studies (nonrandomized observational studies with concurrent controls) regarding thymectomy in patients with MG without thymoma found that patients undergoing thymectomy were 1.7 times as likely to improve, 1.6 times as likely to become asymptomatic, and twice as likely to attain medication-free remission.[706] The relative rate of improvement was greater for patients with more severe disease. Unfortunately, the degree and onset of improvement postoperatively are not predictable and are often delayed for years in any given patient. In addition, currently available studies do not clarify whether improvements noted in surgical groups are based more on selection bias than thymus removal. The aggressiveness of concurrent medical therapy is another confounding variable in these existing uncontrolled trials. The American Academy of Neurology (AAN) position is that thymectomy should be considered as an option to increase the probability of improvement or remission in patients with nonthymomatous MG.[706] They also recommended that a prospective, randomized controlled trial contrasting standardized medical treatment with thymectomy be performed.

Decision making regarding thymectomy is rendered even more difficult in anti-MuSK MG. Although there is limited evidence, reported experiences to date would not support its efficacy in this population.[74,79,85,88]

The operative techniques in the reviewed trials illuminate another area of uncertainty regarding thymectomy, i.e., which surgical approach to use. The reviewed studies used transternal, transcervical, or unidentified approaches.[706] Some authorities recommend an aggressive transcervical–transternal approach in order to remove accessory thymic tissue in the neck or in of the multiple intrathoracic and cervical regions that thymus tissue may reside.[692] The few controlled trials comparing outcomes in patients with myasthenia undergoing different surgical techniques have yielded inconsistent results.[706] Complications of thymectomy include exacerbation of myasthenic weakness with respiratory failure in 6%, infection in 11%, and nerve injury (recurrent laryngeal, phrenic, and brachial plexus) in 2%, while mortality rates of thymectomy is <1%.[706,762] Newer, less invasive surgical techniques such as video-assisted thoracic surgery may have lower complication rates.[763] Randomized controlled trials addressing the best surgical technique are needed.

If thymectomy is being considered, some surgeons will prefer to have the corticosteroids held until after the procedure due to concerns of increased infection rate and slower wound healing. The authors' collective experience would suggest that patients treated with high doses of corticosteroid prior to thymectomy have done well without significant postoperative complications.

CONGENITAL MYASTHENIC SYNDROMES

Identification of CMS is therapeutically important, as these are not immune-mediated disorders and use of immune-modulating therapies exposes the patient to risk without potential benefit. Therapies are largely supportive or directed at increasing cholinergic effects at the end plate by augmenting ACh release or delaying its degradation. Even this strategy has associated risk, as cholinesterase inhibitors may have no effect or may actually worsen patients with AChE, rapsyn deficiency, or the slow channel syndrome. Increased oropharyngeal secretions may be a particularly significant source of morbidity from these drugs in these young patients. Edrophonium and pyridostigmine may improve strength in patients with presynaptic defects such as choline acetyltransferase deficiency, primary AChR deficiency, and the fast channel syndrome.[185] In contrast, drugs that block open channels such as quinidine or fluoxetine may truncate the prolonged EPP duration and represent both a rational and an effective treatment in slow channel syndrome.[163,764] Ephedrine may have nonspecific beneficial effects in occasional patients with CMS including those with AChE deficiency. Patients with Dok-7 have variable including worsening responses to pyridostigmine. Many of these patients will respond

favorably to 3,4 diaminopyridine (DAP) and ephedrine. Carbonic anhydrase inhibitors may be effective in the rare patients of CMS associated with sodium channel mutations. Familial limb-girdle myasthenia is responsive to cholinesterase medications.

In view of its ability to enhance ACh release, 3,4 DAP has been tried in different CMS subtypes.[765,766] The drug works on potassium channels in the presynaptic nerve terminal to prolong depolarization, increase calcium entry, and facilitate ACh release. It was used to treat 31 patients with various forms of CMS including 10 with fast channel syndrome, 17 with primary AChR deficiency, and four other patients with CMS.[765] All patients improved after a single test dose of 3,4 DAP at a dose of 0.25 g/kg. A maintenance divided, daily dose of 1 mg/kg/d, provided the best and most sustained response in fast channel patients. Patients with primary AChR deficiency responded less frequently and less robustly, while the other patients with CMS failed to improve. Patients with slow channel syndrome worsened on the drug. Understandably, side effects may relate to enhanced neural activity in other systems including cholinergic, adrenergic, and CNS neurons, with seizure activity being the potential adverse effect of most concern.

Parents of children at risk of apneic episodes should obtain and familiarize themselves with the use of an apnea monitor and be instructed in the use of parenteral cholinesterase inhibitors and positive pressure bag and mask resuscitation. As with any chronic neuromuscular disease, noninvasive or invasive positive pressure ventilation, spinal instrumentation, and percutaneous enteral feeding tubes are therapeutic options for patients in whom the respective needs arise.

LAMBERT–EATON MYASTHENIC SYNDROME

If a tumor is identified in a patient with LEMS it should be removed if respectable, assuming that the patient's overall medical condition warrants it. Following tumor resection and appropriate chemotherapeutic and radiation therapy intervention, a number of patients recover quite well from the muscle symptoms and demonstrate improvements in their electrophysiologic studies.[346,767–769] Their CMAP amplitudes at rest increase and their decremental and incremental responses diminish. Additionally, the degree of jitter and blocking improve with SFEMG. In patients without definable tumor, careful observation and serial evaluations are necessary to ensure the earliest possible identification of tumor appearance.

In both patients with and without tumor, a number of therapeutic medications can be given to assist with the symptoms of weakness and fatigue.[197,212,567] In most cases, the medication must be given on a long-term basis and is directed at both increasing the safety factor for NMJ transmission and suppressing the autoimmune response. Anticholinesterase medication can be tried in LEMS in an attempt to increase the amount of ACh in the NMJ.[194,329,330,332,334,337,338,346,770] Anywhere from a 50% to 100% CMAP amplitude increase can be seen. The response is variable and often modest in comparison to MG.

The amount of ACh released per neural stimulation can be augmented by administering guanidine. This is believed to prolong the nerve terminal action potential, allowing more calcium to enter, thus facilitating an increase in quantal content.[332,334,346] Although this medication may be symptomatically effective, there are a number of unfortunate side effects such as bone marrow, renal, and hepatic toxicity as well as gastrointestinal dysfunction that limit its use.

The aminopyridines block voltage-dependent potassium conductance, thereby prolonging nerve terminal depolarization and facilitating ACh release. 4-DAP can be effective in improving muscle strength. Its use is limited by the increased incidence of CNS side affects including seizures and agitated confusion.[608,771,772] 3,4 DAP is a related medication with limited CNS side effects. Several studies purport clinical and electrophysiological improvement in LEMS with 3,4 DAP.[335,344,346,726,727,770,773,774] A prospective, randomized placebo-controlled trial of 3,4 DAP in 26 patients with LEMS (paraneoplastic and nonparaneoplastic) revealed improvement in strength and summated CMAP amplitudes.[726,727] The starting dose was 20 mg three times daily and was gradually adjusted to achieve a maximal benefit. The medication is generally well tolerated, with a few patients experiencing perioral and acral paresthesias. It is recommended that doses should not exceed 80 mg/d, as higher doses may result in seizures.[726,727] 3,4 DAP is not as yet FDA approved, and its availability is limited in the United States. It is available on a compassionate-use basis for patients with LEMS from Jacobus Pharmaceutical Company, Inc, Princeton, NJ, pending approval from the FDA. Information regarding the application process to receive 3,4 DAP can be obtained by faxing the drug company at (609)-799-1176.

An alternative pharmacologic approach is attempted immunosuppression with corticosteroids or other agents described in the MG section.[209,212,346,775,776] These drugs must be given over a long time period, and although of benefit, relapses do occur with their withdrawal. Dosing is similar to that described in the MG section. One theoretical concern is that suppressing the patient's immune system may have a deleterious effect on the patient's immune response to their underlying neoplasm. One hypothesis as to why LEMS often precedes tumor detection is that the same immune response that produces LEMS has the beneficial effect of suppressing

tumor growth. Whether this theoretical risk of immunosuppression in LEMS is a legitimate concern is unknown.

Unlike MG, there is no role for thymectomy in the treatment of LEMS. Plasmapheresis may be helpful in patient with LEMS, but the effect wears off after a few weeks and must be repeated.[346,776–780] Both clinical and electrical improvement in CMAP amplitudes at rest, following exercise, or in response to high rates of repetitive stimulation may be seen following plasmapheresis.[777,778] The peak response is observed by about 2 weeks after the treatment, with a diminution in effectiveness by the end of 3–4 weeks. As in MG, plasmapheresis is a temporizing measure and patients will need the addition of an immunosuppressive agent if a response is to be sustained.

IVIG has been noted to be beneficial in small, uncontrolled series of patients with LEMS.[346,781] Dosing is similar to that outline for MG. Prospective, double-blind, controlled trials are necessary to better assess the efficacy of this treatment.

BOTULISM

Intensive care is the foundation of care for the patient with botulism. It is undoubtedly the major reason why contemporary mortality rates are less than reported historically. Monitoring ventilation and the prompt application of positive pressure ventilation are the most important aspects of surveillance and intervention. As with any paralyzing illness, attention to positioning for purposes of comfort, minimizing aspiration risk, improving ventilation, and avoidance of skin break and compression neuropathies are crucial. Secretion clearance and the avoidance of malnutrition and deep vein thrombosis are equally important. Constipation adds to both the discomfort and the morbidity of the disease. Psychological support and a clear understanding of the disease course should be explained to the patients and their families.

Antitoxin should be considered if administered within 24 hours of symptom onset, while the toxin is still (at least partially) circulating.[580,585,588] It is not generally recommended for infantile cases. Once the toxin enters the nerve terminal, the risk of allergic reaction to this equine-derived biological undoubtedly exceeds any potential benefit. The antitoxin, which is available typically from governmental agencies, targets only the exotoxins of the A, B, and E strains of *C. botulinum*. A single vial, diluted 10::1 with normal saline, should be administered as a slow IV drip. There is no benefit to doubling or repeating the dose. Human botulinum immune globulin has a limited role and is approved only for the treatment of infantile botulism. It has been shown to reduce the length of hospitalization as well as for the need for mechanical ventilation.[782]

Guanidine and several aminopyridine derivatives (4-aminopyridine and 3,4 DAP) have the ability to increase the amount of ACh from nerve terminal damaged by BTX in vitro, but human trials have resulted in mixed results as well as disturbing side effects.[236] Trying to extricate unbound toxin from the GI tract in infantile and foodborne botulism either by lavage or by catharsis is controversial and not routinely used. Potential future options for patients affected by botulinum intoxication is the administration of drugs that antagonize the effects of the toxin.[585,783]

With wound botulism, the wound should be debrided. Antibiotics generally have no role in most forms of botulism. If antibiotics are to be used in patients with wound botulism, they should follow the administration of the antitoxin as organism lysis may lead to significant toxin release. Consideration should also be given to avoid antibiotics such as the aminoglycosides with neuromuscular blocking properties. Recovery is usually satisfactory in all patients, provided they are cared for in a hospital setting from the first manifestations of the disease. In the elderly, associated complications can lead to unavoidable death. There are long-term sequelae of fatigue and some mild reduction in respiratory capacity in selected patients.

Historically, a diagnosis of botulism was associated with an estimated 60% mortality rate. Currently, the mortality rate of foodborne and infantile botulism approximates 5%,[784,785] whereas that from wound botulism is typically higher and estimated at about 15%.[402] Patients often complain of marked fatigue, exercise intolerance, general weakness, dry mouth, and shortness of breath, which may persist for over 1 year and seldom allow them to return to full-time work for months.[607] The return of normal strength seems to precede resolution of these other less objective symptoms.

TICK PARALYSIS

Tick removal and hospitalization with careful observation for potential ventilatory failure are the most important aspects of the management of the patient with tick paralysis.[240–242] Tick removal is of course dependent on its detection. A careful search should take place in anyone in whom a diagnosis of Guillain–Barré syndrome is being entertained.[255] High-yield areas include the inferior hairline on the neck or under significant folds of hair about the parietal scalp region. Additional places for ticks to lodge are in the skin fold areas of the axilla, inguinal region about the external genitalia, and under the breasts. Close inspection of the external and internal ear canal is important, as ticks may occasionally be found posterior to the auricle or in the external auditory canal. The index of suspicion should be escalated during summer months in patients with exposure to woody or high grassy areas.

The best manner to remove a tick is a subject with substantial folklore. It is inappropriate to douse the tick with gasoline, lighter fluid, petroleum jelly, or any other type of substance.[243,254] Ticks will not pull back voluntarily when exposed to these substances and can survive with little in the way of oxygen for extended periods. Burning the tick is also ill advised, as this may do more harm to the patient than the tick. It is simply best to use a pair of tweezers or forceps and firmly grasp the tick as close to the patient's skin as possible, i.e., near it mouth parts. A firm steady pull should then be applied. Close inspection of the tick typically reveals a white substance about its mouth, which is a sticky substance secreted by the tick to help maintain its attachment to the victim. If tweezers are unavailable, the hands may be used in a similar fashion but only after gloves are worn. The body of the tick should never be pierced as more toxin may be released. It is unlikely that the tick's head and body will separate if removal is attempted in the above manner. The wound site should then be cleaned thoroughly with a medicinal disinfectant or gentle soap and water.

Upon removal of the tick, the patient usually demonstrates an almost miraculous functional recovery in a matter of hours. Within 24–48 hours of tick removal most patients are well enough to be discharged from the hospital provided the tick is removed prior to profound functional loss. An exception is the Australian variety of the tick.[241,617] This is a particularly virulent form of paralysis and may continue to progress to respiratory failure even after the tick is removed. An antitoxin derived from polyclonal dog antiserum is available for the Australian form of the disease. However, the antiserum treatment is expensive and only effective if given in the early stages of paralysis. Serum sickness is a distinct risk associated with its use.

In cases of prolonged paralysis, supportive care identical to that outlined for the care of the patient with botulism should be provided.

▶ SUMMARY

DNMT should be considered in any patient with signs and symptoms of painless weakness, even of apparently isolated muscles. In particular, involvement of oculobulbar muscles and fatigability should alert the clinician to consider a DNMT. The absence of muscle atrophy and the tendency for the symptoms to vary over time are two significant clues to discriminate DNMT from the motor neuron and muscle diseases. We are fortunate to understand the pathogenesis of these disorders more than we do for the majority of neuromuscular diseases. As a consequence, the opportunity for effective treatment options frequently exist with the attendant satisfaction that follows.

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CHAPTER 24

Muscular Dystrophies

The muscular dystrophies are a group of hereditary, progressive muscle diseases in which there are necrosis of muscle tissue and replacement by connective and fatty tissue. Before discussing specific types of the muscular dystrophies, it is important to have an understanding of the relevant muscle proteins that are affected in the various dystrophies. The different forms of muscular dystrophies result from mutations affecting proteins localizable to the sarcolemma, myonuclei, basement membrane and extracellular matrix surrounding muscle fibers, and sarcomere as well as nonstructural enzymatic proteins.

▶ DYSTROPHIN–GLYCOPROTEIN COMPLEX AND RELATED PROTEINS (Figs. 24–1 and 24–2)

DYSTROPHIN

The identification and characterization of dystrophin as abnormal gene product in Duchenne and Becker muscular dystrophies (DMD and BMD) were the major discoveries that began our better understanding of the muscular dystrophies.[1–3] Dystrophin is located on the cytoplasmic face of skeletal and cardiac muscle membrane and constitutes approximately 5% of sarcolemmal cytoskeletal protein. Dystrophin is a rod-shaped molecule composed of four domains.[3] The amino-terminal domain binds to the cytoskeletal filamentous actin. The second domain bears similarity to spectrin and provides structural integrity to red blood cells. The third domain is a cysteine-rich region, and the fourth domain is the carboxy terminal. The cysteine-rich domain and the first half of the carboxy-terminal domain of dystrophin are important in linking dystrophin to β-dystroglycan and the glycoproteins that span the sarcolemma.

Dystrophin is also present in the brain where it localizes subcellularly to the postsynaptic density, a disk-shaped structure beneath the postsynaptic membrane in chemical synapses. The postsynaptic density may play an important role in synaptic function by stabilizing the synaptic structure, anchoring postsynaptic receptors, and transducing extracellular matrix–cell signals.

DYSTROPHIN-ASSOCIATED PROTEINS/GLYCOPROTEINS

Dystrophin is tightly associated with a large oligomeric complex of sarcolemmal proteins forming the dystrophin–glycoprotein complex (Fig. 24–1).[4–6] Mutations in the various genes, which encode for the different proteins of the dystrophin–glycoprotein complex, are now known to be responsible for many forms of muscular dystrophy (Table 24–1). In addition to dystrophin, the dystrophin–glycoprotein complex is composed of an entirely cytoplasmic group of proteins referred to as the syntrophin complex, the dystroglycan complex, and the sarcoglycan complex (Fig. 24–1). The syntrophin complex binds to the carboxy terminus of dystrophin and is composed of three distinct 59-kD dystrophin associated proteins (DAPs), which are encoded by separate genes. α-Syntrophin is expressed only in muscle, and the gene has been localized to chromosome 20q11.2. β1- and β2-syntrophin are more widely expressed, and their genes have been localized to chromosomes 8q23–24 and 16q22–23, respectively. Dystrobrevin is encoded on chromosome 2p22–23 and is a cytoplasmic protein, which binds to the syntrophin complex and to the C terminus of dystrophin. The dystroglycan complex is composed of α- and β-dystroglycan. β-Dystroglycan spans the sarcolemmal membrane and has a cytoplasmic tail that binds to dystrophin while the extracellular tail binds α-dystroglycan. α-Dystroglycan, which is entirely extracellular, also binds to α-laminin (merosin), a basal lamina protein. Of note, a gene located on chromosome 3p21 encodes for both the α- and the β-dystroglycan. Importantly, α-dystroglycan undergoes N-linked and extensive O-linked glycosylation, which appears to be important for normal binding to merosin and perhaps other extracellular matrix proteins.[7]

The sarcoglycan complex includes four membrane-spanning proteins: (1) α-sarcoglycan (previously known as adhalin), (2) β-sarcoglycan, (3) γ-sarcoglycan, and (4) δ-sarcoglycan. In addition, there is a 25-kD transmembrane protein, sarcospan, which colocalizes with the sarcoglycan complex. The sarcoglycan complex associates with the cysteine-rich domain and/or the first half of the carboxy terminal of dystrophin directly or indirectly via the dystroglycan complex. The exact relationship between the sarcoglycan complex and the dystrophin–dystroglycan complex is still unclear. Mutations in the various sarcoglycan genes are responsive for limb-girdle muscular dystrophies (LGMDs) 2C, 2D, 2D, and 2F.

MEROSIN/LAMININ

The basal lamina surrounding each muscle fiber is closely adherent to the sarcolemma and is composed

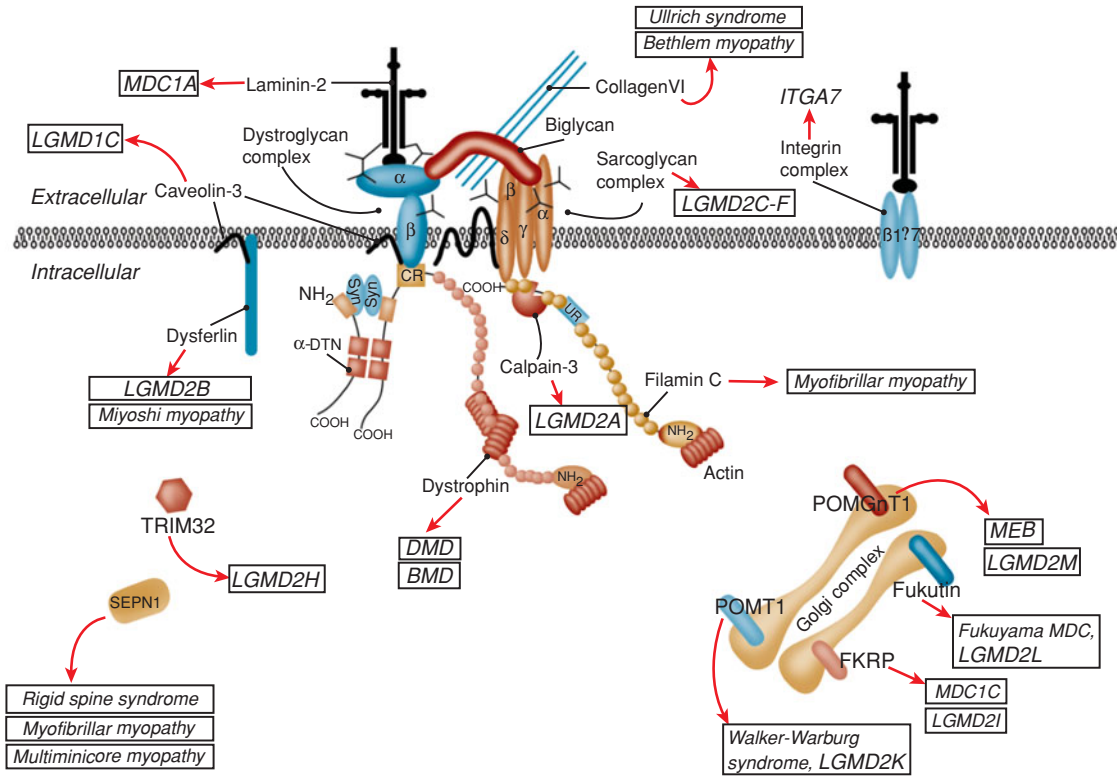


Figure 24–1. Sarcolemmal membrane and enzymatic proteins. This schematic shows the location of various sarcolemmal and enzymatic proteins associated with muscular dystrophies. The diseases these molecules cause when mutated are shown in boxes. Dystrophin, via its interaction with the dystroglycan complex, connects the actin cytoskeleton to the extracellular matrix. Intracellularly, it interacts with dystrobrevin (α-DTN) and syntrophins (Syn) (shown in blue). Extracellularly, the sarcoglycan complex (orange) interacts with biglycan, which connects this complex to the dystroglycan complex and the extracellular matrix collagen. Intracellularly, δ- and γ-sarcoglycans interact with filamin C. The four proteins shown in the Golgi complex have been demonstrated to affect the glycosylation state of the α-dystroglycan and mediate its binding to the extracellular matrix. Fukutin and FKRP have been shown to localize to the medial Golgi. The localization of POMT1, POMGnT1, and LARGE is unknown and believed to be in the Golgi complex as they are involved in the glycosylation process. LGMD, limb girdle muscular dystrophy; DMD, Duchenne muscular dystrophy; BMD, Becker muscular dystrophy; MDC, muscular dystrophy congenital; MEB, muscle-eye-brain disease; SEPN1, selenoprotein N1. (Modified with permission from Dalkilic I, Kunkel LM. Muscular dystrophies: Genes to pathogenesis. Curr Opin Genet Dev 2003;13(3):231–238.)

of type I and IV collagen, heparan sulfate, proteoglycan, entactin, fibronectin, and laminin. Laminin is a large flexible heterotrimer composed of three different but homologous α, β, and γ chains, held together by disulfide bonds. There are five different α chains, three β chains, and two γ chains that have been characterized. The major isoform of laminin heavy chains in muscle is laminin-2, which is composed of α2, β1, and γ1 chains. Muscle also contains laminin-4, composed of α2, β2, and γ1 subunits. Merosin is the collective name for laminins that share a common α2 chain. Alpha-dystroglycan binds specifically to laminin-2 but not to the other extracellular components (Fig. 24–1). Ligands for the sarcoglycan complex are unknown, but it has been postulated that the complex is directly or indirectly linked to laminin-4.[8]

Merosin is also expressed in the endoneurial basement membrane surrounding the myelin sheath of peripheral nerves.[9] Likewise, α- and β-dystroglycan are found in peripheral nerves. Expression of α- and β-dystroglycan is restricted to the outer membrane of Schwann cells and is not present in the inner membrane or on compact myelin. Transmembrane β-dystroglycan anchors extracellular α-dystroglycan to the outer membrane of Schwann cells and myelin. As in muscle, merosin serves as a ligand in the Schwann cell dystroglycan complex by binding to α-dystroglycan. This complex appears to have a role in peripheral myelinogenesis. Mutations involving the merosin gene not only result in a form of congenital muscular dystrophy (MDC), but they also are associated with mild

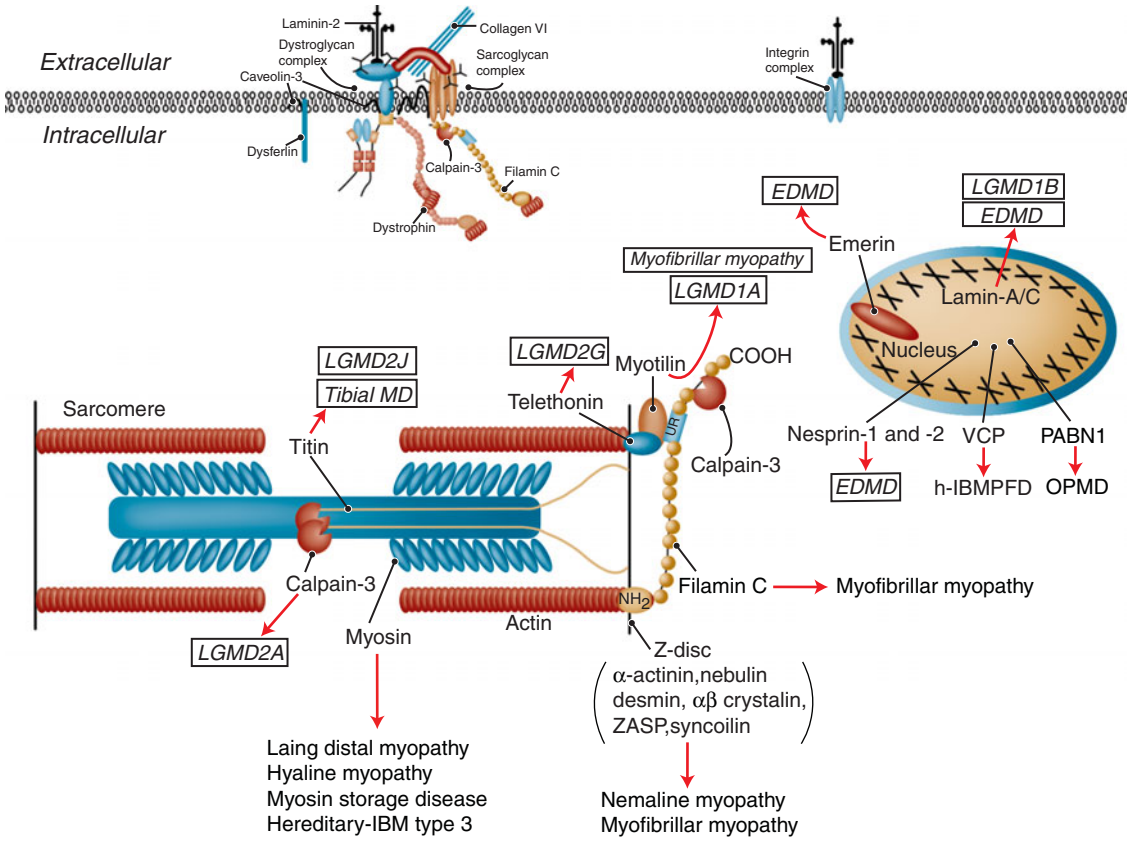


Figure 24–2. Sarcomeric and nuclear proteins involved in the muscular dystrophies. The schematic for the sarcomere and the nucleus showing the localization of the proteins involved in muscular dystrophies. The diseases these give rise to are shown in boxes. (Modified with permission from Dalkilic I, Kunkel LM. Muscular dystrophies: Genes to pathogenesis. Curr Opin Genet Dev 2003;13(3):231–238.)

dysmyelination in the central and peripheral nervous systems.

INTEGRINS

Integrins are transmembrane, heterodimeric (α/β) receptors, which play key roles in establishing linkages between the extracellular matrix and the cytoskeleton as well as in transducing extracellular matrix–cell signals.[10] Integrins are important in cell adhesion, migration, differentiation, proliferation, and cytoskeletal organization. The major integrin expressed throughout the sarcolemma in mature muscle fibers is α7β1D. Studies have demonstrated that α7β1D integrin binds to merosin in skeletal muscle, which appears to be as important as the linkage of α-dystroglycan to merosin in providing structural stability (Fig. 24–1). Mutations of the α7 subunit lead to abnormal binding of merosin to integrin and are causative of some forms of MDC.

UTROPHIN (DYSTROPHIN-RELATED PROTEIN)

Utrophin is an autosomal homolog of dystrophin. It is ubiquitously expressed but is localized exclusively at the neuromuscular junction in normal skeletal muscle. Utrophin associates with DAPs, suggesting that the utrophin–glycoprotein complex plays a role in the formation and integrity of the neuromuscular junction. Upregulation of utrophin is evident in the dystrophinopathies, perhaps as a compensatory mechanism.

▶ OTHER SARCOLEMMAL PROTEINS

DYSFERLIN

Dysferlin is another cytoskeletal protein present in skeletal and cardiac muscle. It is located predominantly on the subsarcolemmal surface of the muscle membrane, but it

▶ TABLE 24–1. GENETIC CLASSIFICATION OF THE MUSCULAR DYSTROPHIES

Disease	Inheritance	Chromosome	Affected Protein
X-linked dystrophies			
Duchenne/Becker	XR	Xp21	Dystrophin
Emery–Dreifuss (EDMD1)	XR	Xq28	Emerin
Limb-girdle dystrophies (LGMDs)			
LGMD 1A	AD	5q22.3–31.3	Myotilin
LGMD 1B	AD	1q11–21	Lamin A/C
LGMD 1C	AD	3p25	Caveolin-3
LGMD 1D	AD	6q23	?
LGMD 1E	AD	7q	?
LGMD 1F	AD	7q31.1–32.2	?
LGMD 2A	AR	15q15.1–21.1	Calpain-3
LGMD 2B*	AR	2p13	Dysferlin
LGMD 2C	AR	13q12	γ-Sarcoglycan
LGMD 2D	AR	17q12–21.3	α-Sarcoglycan
LGMD 2E	AR	4q12	β-Sarcoglycan
LGMD 2F	AR	5q33–34	δ-Sarcoglycan
LGMD 2G	AR	17q11–12	Telethonin
LGMD 2H**	AR	9q31–33	E3-ubiquitin-ligase (TRIM 32)
LGMD 2I	AR	19q13	Fukutin-related protein (FKRP)
LGMD 2J	AR	2q31	Titin
LGMD 2K	AR	9q31	POMT1
LGMD 2L	AR	9q31–33	Fukutin
LGMD 2M	AR	1p32	POMGnT1
Congenital muscular dystrophies (MDCs)			
MDC1A	AR	6q22–23	Laminin-α-2 chain (Merosin)
α-7 Integrin related MDC	AR	12q13	α-7 Integrin
	AR	19q13	FKRP
Fukuyama/LGMD 2L	AR	9q31–33	Fukutin
Walker–Warburg/LGMD 2K	AR	9q31	POMT1
Muscle–Eye–Brain disease	AR	1p32	POMGnT1
MDC1C	AR	22q12.3–q13.1	LARGE
Rigid spine syndrome	AR	1p35–36	Selenoprotein N1
Ullrich/Bethlem	AR/AD	21q22.3 and 2q37	Collagens 6A1, 6A2, and 6A3
Distal dystrophies/myopathies			
Welander	AD	2p13	?
Udd	AD	2q31	Titin
Markesbery–Griggs	AD	10q22.3–23.2	ZASP
Nonaka	AR	9p1-q1	GNE
Miyoshi*	AR	2p13	Dysferlin
Laing	AD	14q11	MyHC 7
Other dystrophies			
Facioscapulohumeral	AD	4q35	FRG1?
Scapuloperoneal dystrophy	AD	2q35	Desmin
	AD	12	?
Oculopharyngeal	AD	14q11.2–13	PABP2
Myotonic dystrophy-1	AD	19q13.3	DMPK
Myotonic dystrophy-2	AD	3q21	ZNF9
Myofibrillar myopathy	AD	5q22.3–31.3	Myotilin
	AD	10q22.3–23.2	ZASP
	AD	7q32.1	Filamin-c
	AD	11q21–23	αB-crystallin
	AD/AR	2q35	Desmin
	AR	1p36	Selenoprotein N1
Hereditary IBM (h-IBM)			
ARh-IBM	AR	9p1–q1	GNE
h-IBM with Paget disease, and FTD	AD	9p13–p12	Valosin containing protein (VCP)
h-IBM 3	AD	17p13.1	MyHC IIa

*LGMD 2B and Miyoshi distal dystrophy are the same condition.
**LGMD 2H and sarcotubular myopathy (discussed in Chapter 25) are allelic disorders
POMGnT1, O-mannose β-1,2-N-acetylglucosaminyl transferase; POMT1, O-mannosyltransferase gene; FRG1, FSHD region gene 1; GNE, UDP-N-acetylglucosamine 2-epimerase/n-acetylmannosamine kinase; ZASP, Z-band alternatively spliced PDZ motif-containing protein; H-IBM, hereditary inclusion body myopathy; FTD, frontotemporal dementia; MyHC, myosin heavy chain; EDMD, Emery Dreifuss muscular dystrophy; ?, unknown protein.

has a small transmembrane spanning tail (Fig. 24–1). The protein does not appear to be directly connected to the dystrophin–glycoprotein complex. The function of dysferlin is not entirely known. Dysferlin may have a role in membrane fusion and repair by regulating vesicle fusion with the membrane.[11,12] Additionally, dysferlin may assist in stabilizing the sarcolemmal membrane or in signal transduction.[13,14] Mutations affecting the dysferlin gene result in LGMD2B and Miyoshi type distal myopathy.

CAVEOLAE

Caveolae are 10–100-nm invaginations in the sarcolemma, derived by the oligomerization of approximately 14–16 caveolin-3 monomers that form a scaffolding complex of proteins and lipids (Fig. 24–1).[15,16] Caveolin-3 cofractionates with the dystrophin–glycoprotein complex but is thought to be part of a discrete complex. It does not directly bind to dystrophin or the sarcoglycans but does apparently interact with dysferlin. Caveolin-3 is necessary for the proper formation of T tubules and may assist in organization of signaling complexes, calcium channels (i.e., dihydropyridine and ryanodine receptors), and sodium channels. Mutations in the gene encoding for caveolin-3 are responsible for causing LGMD 1C, rippling muscle disease, a form of distal myopathy, and some cases of idiopathic hyper-CK-emia.[17,18]

▶ SARCOMERIC PROTEINS

In addition to the above sarcolemmal and related proteins, there are a number of important proteins that compose and support the sarcomere (Fig. 24–2). The major contractile myofibrillar proteins are the thick and thin filaments. The main component of the thick filaments is a polymer of myosin. A single thick filament is composed of nearly 300 myosin molecules. Each individual myosin molecule, in turn, consists of a single long "tail" attached to two "head" portions that project out from the tail. The head and its projecting part are referred to as a cross-bridge, which has two flexible hinges: one at the head/arm interface and the other at the arm/filament interface. The entire myosin filament is twisted about a central axis, allowing the cross-bridges to extend longitudinally and circumferentially 360°. The head or the myosin heavy chain (MyHC) includes ATP-binding sites that act as an ATPase as well as an actin-binding region. The energy liberated by this process is used to maintain the cross-bridge in the extended or "cocked" position. There are three major MyHC isoforms that are expressed in human skeletal muscle (type I, MyH7, expressed in type 1 fibers; IIa, MyH2, expressed in 2A fibers; and IIx, MyH1, expressed in 2B fibers).[19] Mutations in genes that encode for various MyHC isoforms cause various myopathies and cardiomyopathies.

The thin filament is composed of three subcomponents: actin, tropomyosin, and troponin. Polymerized globular or G-actin molecules form two helical strands of filamentous or F-actin. Each G-actin molecule contains one molecule of ADP. Two chains of a tropomyosin molecules wind loosely within the helical structure of the F-actin. The tropomyosin molecules overlie "active sites" on the actin molecules that link with the myosin heads forming the cross-bridges. The third major subcomponent of the thin filament, troponin, consists of three globular proteins: troponin I, T, and C. Troponin I binds strongly to actin, troponin T is attached to tropomyosin, while troponin C has a large affinity for calcium. The troponin complex attaches the tropomyosin molecules to the actin molecules, thereby forming the complete thin filament. The interaction between the myosin cross-bridges and actin filaments causes the muscle fiber to shorten or contract because the above-noted filaments slide past each other.

One end of the actin filaments is firmly anchored to the Z-disk and the other end projects out between myosin filaments. These Z-disks extend from myofibril to myofibril across the diameter of a muscle fiber. The region of muscle or myofibril between two Z-disks is called a sarcomere. The major protein of the Z-disk is α-actinin. Nebulin is a giant protein, which is attached to α-actinin at the Z-disk and spans the entire length of the thin filament. There are two nebulin molecules for every thin filament. Desmin is an intermediate-size filament that encircles the Z-disk and helps to link the Z-disk to the sarcolemma, myonuclei, and adjacent myofibers. The cytoplasmic heat-shock protein, αB-crystallin, interacts with desmin in the assembly and stabilization of the Z-disk. Syncoilin, together with plectin, may also link desmin filaments to the Z-disk.[20] Furthermore, ZASP (Z-band alternatively spliced PDZ motif-containing protein) binds to α-actinin and assists in cross-linking thin filaments of adjacent sarcomeres.[21]

Other filamentous proteins are also important in providing stability to the sarcomere (Fig. 24–2). The giant protein titin (also known as connectin) is attached to the Z-disk and spans from the M-line to the Z-line of the sarcomere. Titin serves to connect the myosin filaments to the Z-disk. Telethonin is another sarcomeric protein present in skeletal and cardiac muscle. It colocalizes with titin to the Z-disks and along the thick filaments. Telethonin is also linked with myotilin, which in turn interacts with α-actinin and actin. In addition, filamin-c binds actin and is also involved in the formation of the Z-disk. Filamin-c also binds γ- and δ-sarcoglycan at the sarcolemma and may also play a role involved in signaling pathways from the sarcolemma to the myofibril.[22]

The interaction of all these sarcomeric proteins and Z-disk is important in myofibrillogenesis. As will be discussed, mutations affecting the genes encoding for these various sarcomeric proteins are responsible for causing

different dystrophies, congenital myopathies, and inherited cardiomyopathies.

The myofibrils are surrounded by intracellular fluid called sarcoplasm. Within the sarcoplasm lie large numbers of mitochondria required for energy and other organelles. Within the sarcoplasma and surrounding the myofibrils there is an intricate series of channels called the sarcoplasmic reticulum. Longitudinal sarcoplasmic reticulum channels terminate along large terminal cisternae at either end of the sarcomere. T tubules closely associate with terminal cisternae. Two terminal cisternae are in close association with one T tubule forming a so-called triad. The T tubule conducts action potentials into the terminal cisternae and the depths of the muscle (see below). The action potentials open voltage-gated L-type calcium channels, called the dihydropyridine receptor, located on the sarcolemmal membrane. The dihydropyridine receptor receptor also serves as a voltage sensor for the calcium release channel, the ryanodine receptor, located on the sarcoplasmic reticulum. Mutations in these genes are responsible for hypokalemic periodic paralysis, malignant hyperthermia, and central core disease. In addition, there is a separate calcium reuptake channel located on the sarcoplasmic reticulum called sarcoplasmic reticulum calcium-ATPase (SERCA1). Mutations in the gene encoding for this protein (SERCA1) lead to Brody disease characterized by impaired relaxation of muscles.

▶ NUCLEAR PROTEINS

Emerin is a member of the nuclear lamina-associated protein (LAP) family and is located on the inner nuclear membranes of skeletal, cardiac, and smooth muscle fibers (Fig. 24–2).[23–26] The nuclear lamina is a multimeric matrix composed of a complex of intermediate-sized filaments (lamins A, B, and C), which associates with the nucleoplasmic surface of the inner nuclear membrane. Of note, lamins A and C are produced by alternative splicing of a single gene. Emerin is attached to the inner nuclear membrane through its carboxy-terminal tail, while the remainder of the protein projects into the nucleoplasm. The lamins bind to emerin, specific lamin receptors, and perhaps other LAPs located on the inner nuclear membrane. This complex of proteins is important in the organization and structural integrity of the nuclear membrane. In addition, LAPs, lamin receptors, and the lamins bind to chromatin and promote its attachment to the nuclear membrane. Abnormalities in these nuclear envelop proteins apparently disrupt the structure of the nuclear membrane, the organization of interphase chromatin, and perhaps also signal transduction between the nucleus and the sarcoplasm.[27,28] Mutations in the genes that code for emerin and lamin A/C are responsible for X-linked Emery–Dreifuss muscular dystrophy (EDMD) and autosomal-dominant EDMD/limb-girdle dystrophy 1B, respectively.

Valosin-containing protein (VCP) localizes to nuclei around nucleoli and is associated with a variety of cellular activities, including cell-cycle control, membrane fusion, and the ubiquitin–proteasome degradation pathway. Mutations in VCP gene cause hereditary inclusion body myopathy with Paget disease and frontotemporal dementia (h-IBMPFD). The gene that encodes for another nuclear protein, poly(A) binding protein nuclear (PABN1) is mutated in oculopharyngeal muscular dystrophy (OPMD).

▶ ENZYMATIC PROTEINS

Calpain-3 is a muscle-specific, calcium-dependent, nonlysosomal, proteolytic enzyme present in muscle. The pathophysiologic mechanism of how mutations involving this enzyme result in a dystrophic process is not completely understood. Calpain-3 exists in both the cytosol and the nuclei of skeletal muscle fibers (Figs. 24–1 and 24–2), where it may be directly involved in or may participate in the activation of other enzymes involved in muscle metabolism. Mutations in the calpain-3 gene are responsible for LGMD 2A.

Tripartite motif-containing protein 32 (TRIM 32), also known as E3-ubiquitine ligase, may function by tagging proteins (e.g., ubiquination) for degradation by proteosomes (Fig. 24–1). Mutations in TRIM 32 cause LGMD 2H.[29]

Fukutin is a glycosyltransferase and its deficiency is associated with abnormal glycosylation of alpha-dystroglycan and results in Fukuyama congenital muscular dystrophy and LGMD2L (Figs. 24–1 and 24–2). Mutations in a protein of similar function, fukutin-related protein (FKRP), are found in some patients with MDC with normal merosin (MDC 1C) and in LGMD 2I.[30–32] Interestingly, impaired glycoslylation of alpha-dystroglycan is felt to be responsible for other forms of MDC (muscle–eye–brain disease [MEB] and Walker–Warburg syndrome [WWS]).[33] MEB is caused by mutations in *O*-mannose-β-1,2-*N*-acetylglucosaminyl transferase (POMGnT1), which also causes LGMD 2M. WWS may result from mutations in *O*-mannosyltransferase (POMT1) that also causes LGMD 2K. Mutations in the human LARGE gene, which is an enzyme is required for glycoslylation of alpha-dystroglycan, are responsible for another rare form of MDC with mental retardation. Thus, it appears that normal glycoslylation of alpha-dystroglycan is important for muscle function but also for normal development of the central nervous system, which is affected in these forms of MDC. In addition, UDP-*N*-acetylglucosamine 2-epimerase/*n*-acetylmannosamine kinase (GNE), which is involved in the posttranslational glycosylation of proteins, is mutated in some forms of autosomal-recessive inclusion body myopathy (also known as the Nonaka type of distal myopathy).

▶ MUSCULAR DYSTROPHIES

The muscular dystrophies traditionally have been classified according to their pattern of weakness (e.g., limb girdle, facioscapulohumeral, and scapuloperoneal) and mode of inheritance (Table 24–1). Advances in genetics have led to the classification of muscular dystrophies based on the responsible gene defect.

▶ THE DYSTROPHINOPATHIES: DUCHENNE AND BMD

DUCHENNE MUSCULAR DYSTROPHY

Clinical Features

The best known of the muscular dystrophies is Duchenne muscular dystrophy (DMD). DMD is an X-linked recessive disorder, but approximately one-third of patients with DMD are a result of spontaneous mutations. The incidence is roughly 1 per 3500 male births, with a prevalence approaching 1 per 18,000 males.[36]

The natural history of children with DMD is well known.[37,38] Most male children appear quite normal at birth and achieve the anticipated milestones of sitting and standing with little or only slight delay. However, some affected boys are hypotonic and weak at birth. Careful inspection of neck flexors in infants and toddlers suspected of having the disease usually reveal some degree of weakness. A wide-base, waddling gait is noted by about 2–6 years of age. The affected child has difficulty running and jumping. There is a tendency for the child to walk on the toes. Calf hypertrophy may also be appreciated (Fig. 24–3). The progressive leg weakness leads to increasing falls between the ages of 2 and 6 years. Children also have difficulty arising from the floor and employ the characteristic Gower sign to enable them rise to a standing position. Weakness is characteristically worse proximally than distally and more so in the lower compared to upper limbs. Usually by 8 years of age, affected children have difficulty climbing stairs and need to pull themselves up the stairs using the handrails. Between 6 and 12 years of age, weakness progresses to the point that the upper limb and torso muscles are profoundly affected. Ambulation becomes progressively more difficult, and affected children are confined to a wheelchair by 12 years of age. This in turn leads to the development of kyphoscoliosis and worsening of contractures. The biceps brachii, triceps, and quadriceps reflexes diminish and are absent in 50% of children by the age of 10 years. An interesting finding is the persistent ability to obtain an ankle jerk in at least a third of patients, even in end stages of the disease. Contractures about the hip and ankles also significantly impair posture.

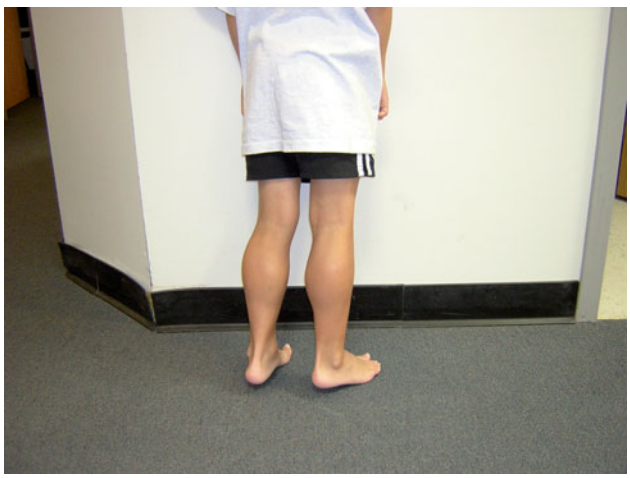


Figure 24–3. Duchenne muscular dystrophy. Enlarged calf muscles (pseudohypertrophy) and tight head cords resulting in toe walk are seen in this affected boy.

Respiratory function gradually declines and leads to death in most patients by the early twenties. In addition to skeletal muscle, cardiac muscle is also involved. Most patients are asymptomatic early in the course; however, dysrhythmias and congestive heart failure can occur late in the disease. Approximately 90% of patients have electrocardiogram (EKG) abnormalities, most commonly sinus tachycardia, tall right precordial R waves, and deep narrow Q waves in the left precordial leads.[39–41] Echocardiogram reveals dilation and/or hypokinesis of ventricular walls. Unfortunately, most patients with DMD die in their late teens or early twenties from ventilatory or cardiac failure. Smooth muscle is also affected, and patients can develop gastroparesis and intestinal pseudo-obstruction.

The central nervous system is also involved in DMD. The average IQ of the affected children is approximately one standard deviation below the normal mean.[42] The mechanism by which the central nervous system is affected is unclear, but, as noted above, dystrophin is expressed at some synapses in the brain.

Laboratory Features

The serum creatine kinase (CK) levels are markedly elevated (50–100 times normal or greater) at birth and peak at around 3 years of age. Subsequently, serum CK levels decline approximately 20% per year as a result of decreasing muscle bulk, although the CK levels never normalize.

Electrodiagnostic testing in dystrophinopathies is of limited value, particularly when there is a family history of the disorder. Diagnosis requires genetic testing for identifiable mutations in the dystrophin gene and, if that is unrewarding, a muscle biopsy. Electrodiagnostic testing may be helpful in sporadic cases and in BMD in which CK levels can be only mildly elevated and the differential diagnosis is much broader. Needle electromyography (EMG) demonstrates increased insertional and

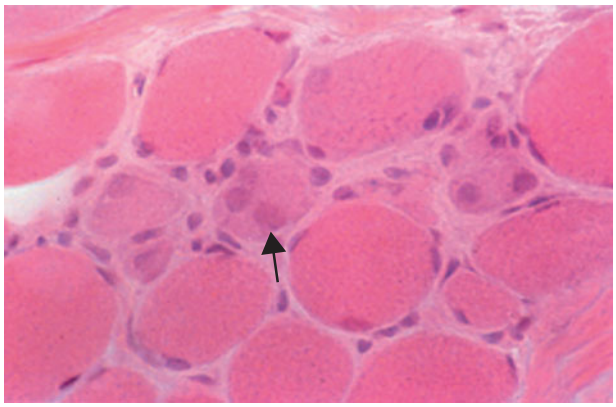


Figure 24–4. Duchenne muscular dystrophy. Muscle biopsy in a patient with DMD demonstrates mild variability in fiber size with small regenerating fibers that have enlarged nuclei. Hematoxylin and eosin (H&E).

spontaneous activity in the form of fibrillation potentials and positive sharp waves. However, as muscle tissue is progressively replaced with both adipose cells and connective tissue, insertional activity diminishes. The mean amplitudes of nonpolyphasic motor unit action potentials (MUAPs) are reduced, but large-amplitude polyphasic potentials can also be seen. Both short- and long-duration MUAPs can be demonstrated in individual muscles, reflecting the chronicity of the myopathic process. An early recruitment pattern of MUAPs is evident at low force thresholds.

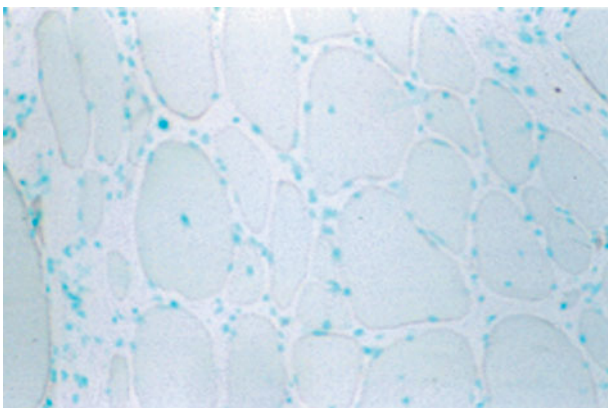
Histopathology

Muscle biopsies reveal scattered necrotic and regenerating muscle fibers, variability in muscle fiber size, increased endomysial and perimysial connective tissue, scattered hypertrophic and hypercontracted fibers in addition to small, rounded, regenerating fibers (Fig. 24–4). Fiber splitting and central nuclei can also be seen but occur less often than in other muscular dystrophies. The process of degeneration and regeneration continues until the limited regenerative capacity of the satellite cells is exceeded, at which time the necrotic muscle tissue is replaced with fat and connective tissue.

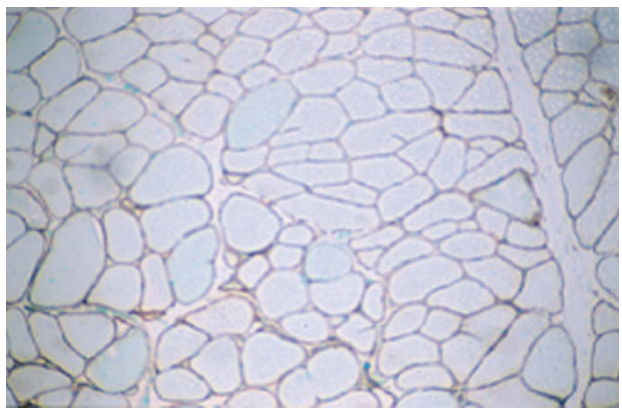
Endomysial inflammatory cells consisting of cytotoxic T lymphocytes (two-thirds) and macrophages (one-third) are present to a variable degree and phagocytize necrotic fibers.[43] Rarely, non-necrotic fibers expressing major histocompatibility antigen are invaded by CD8+ cytotoxic T cells.

Immunohistochemistry demonstrates reduced or absent dystrophin on the sarcolemma (Fig. 24–5). About 60% of patients with DMD will have some faint staining of the muscle membrane using antibodies directed against the amino terminal or rod domain of dystrophin. However, less than 1% of muscle fibers have sarcolemmal staining, with antibodies directed against the carboxy terminal of dystrophin. The few dystrophin-positive muscle fibers are known as revertants. They arise secondary to spontaneous subsequent mutations that restore the "reading frame" and allows transcription of dystrophin, albeit of abnormal size and shape. On the other hand, utrophin, which is normally restricted to the neuromuscular junction, is overexpressed in DMD and is present throughout the sarcolemma.

Immunoblot or Western blot of muscle tissue assesses both the quantity and the size of the dystrophin present. With use of carboxy-terminal antibodies, Western blot reveals 0–3% of the normal amount of dystrophin present in muscle tissue, and the size of the remaining dystrophin is usually diminished.[2] With amino-terminal or rod-domain antibodies, approximately 50% of patients with DMD have some detectable truncated dystrophin. Immunohistochemical analysis in dystrophinopathies may also demonstrate a reduction of dystroglycan, dystrobrevin, and all the sarcoglycan proteins, including sarcospan.



A



B

Figure 24–5. Immunoperoxidase staining using dystrophin (Dys 2) antibodies demonstrates absence of sarcolemmal staining on muscle fibers in DMD (A) and normal staining in a control biopsy (B).

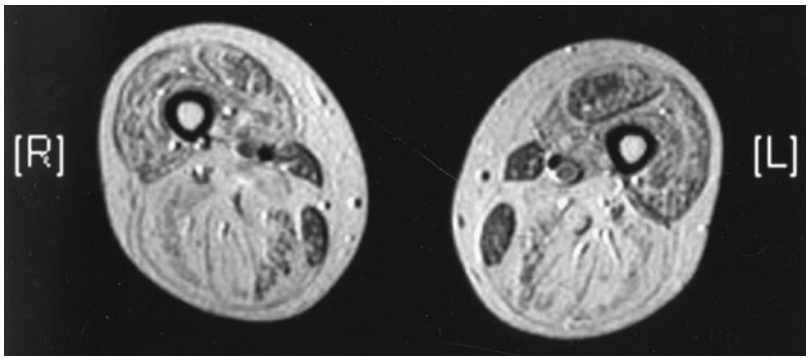


Figure 24–6. Becker muscular dystrophy. Skeletal muscle MRI (T1 weighted) of the thigh in a patient with BMD demonstrates the bright and feathery appearance of fat and connective tissue replacing muscle in the thighs.

BECKER MUSCULAR DYSTROPHY

Clinical Features

BMD represents a milder form of dystrophinopathy. BMD can be distinguished from DMD clinically by its slower rate of progression and by dystrophin analysis. The incidence of BMD is approximately 5 per 100,000.[36,44] Approximately 10% of cases are the result of spontaneous mutations. Clinical features that help with diagnosis of possible BMD include (1) a family history compatible with X-linked recessive inheritance, (2) ambulation maintained past the age of 15 years, (3) a limb-girdle pattern of muscle weakness, and (4) calf hypertrophy (pseudohypertrophy).[45] Some patients exhibit preferential involvement of the quadriceps muscle (quadriceps myopathy).[46]

A wide spectrum of clinical phenotypes and variability can be seen even within families.[47] Most patients develop difficulty in walking; however, by definition, they remain ambulatory past the age of 15 years. Approximately 50% of affected individuals lose the ability to ambulate independently by the fourth decade. Some patients manifesting with only myalgias,[48] myoglobinuria,[49] cardiomyopathy,[50,51] and asymptomatic hyper-CK-emia have been demonstrated to have mild forms of dystrophinopathy. Cardiac abnormalities are similar to those described for DMD.[52] Mental abilities have not been investigated as thoroughly as in DMD, but some series have demonstrated a borderline or mildly impaired IQ in patients with BMD.[45,47] The life expectancy is reduced.[45]

Laboratory Features

Serum CK levels are elevated, often 20–200 times normal. Patients with only exertional myalgias may have only slightly elevated serum CK levels. EMG is abnormal in weak muscles as discussed in DMD section. Skeletal muscle magnetic resonance imaging (MRI) scans can demonstrate fatty replacement of affected muscle groups (Fig. 24–6).

Histopathology

The histological features are similar to those observed for DMD but are less severe (Fig. 24–7).[53] BMD may be distinguished histologically from DMD with immune staining, which demonstrates the presence of dystrophin using carboxy-terminal antibodies on muscle membranes in most cases of BMD. In contrast, immunostaining with antibodies directed against the carboxy terminal of dystrophin is usually negative in DMD. However, the degree and intensity of the dystrophin staining are usually not normal in BMD. The staining pattern may be uniformly reduced or can vary between and within

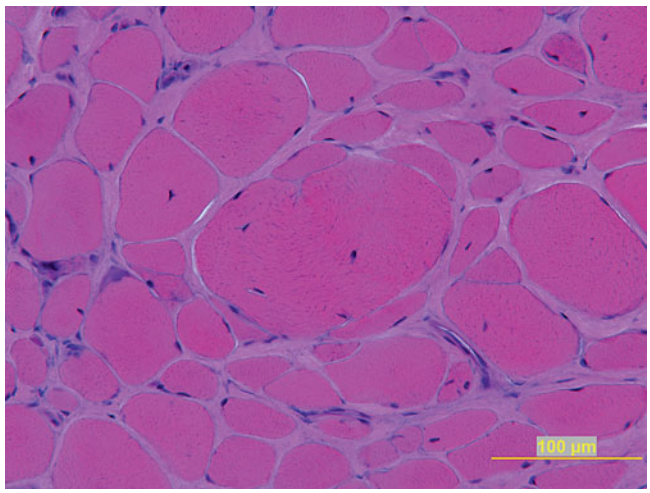


Figure 24–7. Becker muscular dystrophy. Muscke biopsy demonstrates increased endomysial connective tissue, marked variability in muscle fiber size, slightly increased internalized nuclei, and splitting of muscle fibers. H&E.

fibers. Western blot analysis of muscle tissue typically reveals an abnormal quantity and/or size of the dystrophin protein.[2,54]

OUTLIERS

This older term was used for children who have a clinical phenotype in between that of DMD and BMD. These children continue to ambulate after the age of 12 years but use a wheelchair by the age of 15 years. In early childhood, they may be distinguished from children with the more severe DMD clinical phenotype by the presence of antigravity neck flexion strength. Children with DMD cannot lift their heads fully against gravity when lying supine (Medical Research Council grade less than 3) unlike outliers and BMD children who typically can. Immunologic studies on muscle tissue usually reveal the presence of some dystrophin, although often reduced in amount and/or size.

FEMALE CARRIERS

The daughters of men with BMD (males with DMD are usually infertile) and the mothers of affected children who also have a family history of DMD or BMD are obligate carriers of the mutated dystrophin gene. Mothers and sisters of isolated patients with DMD or BMD are at risk of being carriers. One of the most important aspects of caring for patients and families with dystrophinopathies is to determine the carrier status of "at-risk" females for the purpose of genetic counseling. There is a 50% chance that males born to carrier females will inherit the disease and 50% of the daughters born will become carriers themselves. Women carriers are usually asymptomatic, but a few develop muscle weakness.[55] These cases are usually explained by the Lyon hypothesis: skewed inactivation of the normal X-chromosome and dystrophin gene results in increased transcription of the mutated dystrophin gene. Females with translocations at the chromosomal Xp21 site or Turner syndrome (XO genotype) may also develop dystrophinopathies.

Manifesting carriers typically have a mild limb-girdle phenotype similar to BMD. Prior to the advances in molecular genetics, these women were often diagnosed with LGMD, particularly when there was no family history of DMD or BMD. Rarely, females can manifest severe weakness as seen in DMD.

Laboratory and histologic features of manifesting carriers are similar to those discussed for DMD and BMD. Immunostaining for dystrophin demonstrates an absent, decreased, or mosaic pattern of staining in many female carriers; however, staining can be normal.[55–58] Thus, immunostaining and Western blot analysis are not very sensitive in identifying carrier status of asymptomatic females.

Serum CK levels are an insensitive measure of carrier status.[59,60] CK levels can be elevated early in life; however, a normal serum CK does not exclude a carrier status. Elevated serum CK levels are identified in less than 50% of obligate carriers. The most reliable method of detecting carrier status is with genetic testing. This is accomplished first by assessing if affected male relatives have an identifiable mutation in the dystrophin gene. The detection of such a mutation makes carrier detection of at-risk female relatives much easier and also allows for subsequent prenatal detection in at-risk fetuses. If a mutation is demonstrated in an affected male relative, at-risk females can be screened for the same mutation. However, it should be noted that the carrier status of a mother of a sporadic DMD case must be interpreted cautiously because of the potential for germline mosaicism.[61] In a germline mosaic, the mutation involves only a percentage of the germ cells (i.e., oocytes) but are not present in the leukocytes in which DNA analysis is performed. In these rare cases, an affected child may have an identifiable mutation on DNA analysis, but the mother could have no demonstrable mutation in the leukocytes and she might still be a carrier. The recurrence rate in germline carriers is unknown and dependent on the number of mutated oocytes but has been estimated to be as high as 14%.[61] Prenatal diagnosis can be made with DNA analysis of chorionic villi or amniotic fluid cells when there is an identifiable mutation in the family.

MOLECULAR GENETICS AND PATHOGENESIS OF THE DYSTROPHINOPATHIES

Dystrophin is a structural protein, which is intimately bound to the sarcolemma and provides structural integrity to the muscle membrane (Fig. 24–1).[6] Abnormal quantity or quality of dystrophin results in the muscle losing its ability to maintain its integrity during contraction, leading to membrane tears and subsequent muscle fiber necrosis.

The dystrophin gene, located on chromosome Xp21, is composed of approximately 2.4 megabases of genomic DNA and includes 79 exons, which code for a 14-kb transcript.[1,3] The large size of the gene probably accounts for the high spontaneous mutation rate responsible for one-third of new cases. Large deletions, several kilobases to over 1 million base pairs, can be demonstrated in approximately two-thirds of patients with dystrophinopathy. Approximately 5–10% of DMD cases are caused by point mutations, resulting in premature stop codons.[62] Duplications are evident in another 5% of cases. Mutations occur primarily in the center (80%) and near the amino terminal (20%) of the gene.[62] Mutations that disrupts the translational reading frame of the gene lead to near total loss of dystrophin and

DMD, while in-frame mutations result in the translation of semifunctional dystrophin of abnormal size and/or amount and in outlier or BMD clinical phenotypes.[2] Although there are exceptions to the "reading-frame rule," 92% of phenotypic differences are explained by in-frame and out-of-frame mutations.[62] The clinical severity does not appear to correlate with the location of mutations in DMD. It appears that the quality or remaining functional capability of the mutated dystrophin protein is more important than the actual quantity. The reduction in the various sarcoglycans, which is also evident on immunohistochemical studies of DMD and BMD, suggests that normal dystrophin is important for the integrity of the sarcoglycan complex.

TREATMENT OF THE DYSTROPHINOPATHIES

Corticosteroids

Prednisone (0.75 mg/kg/d) has been shown to increase strength and function (peaking at 3 months) and slow the rate of deterioration in children with DMD.[63–68] The beneficial effects are noted as early as 10 days and are sustained for at least 3 years. These apparent clinical benefits are accompanied by an increase in muscle mass and decline in the rate of muscle catabolism.[66] The mechanism is not felt to be related to the immunosuppressive action of prednisone on inflammatory infiltrates in the muscle but rather by altering muscle metabolism, particularly protein synthesis and/or breakdown. Lower doses of prednisone (<0.75 mg/kg/d) are not as effective in DMD. There have been no large, double-blinded, placebo-controlled studies assessing the efficacy of steroids in BMD, although small series suggest a possible benefit.[69]

Unfortunately, high-dose prednisone is associated with significant side effects including weight gain, stunted growth, Cushingoid appearance, excessive hair growth, irritability, and hyperactivity. In addition, prednisone is also associated with an increased risk of infections, cataract formation, hypertension, glucose intolerance, osteoporosis, and osteonecrosis. Twice-weekly oral prednisone given on a weekend (5 mg/kg/dose) appeared to be beneficial compared to historical controls in a small open-label study of 20 boys with DMD,[70] and a large randomized, blinded study comparing this dosing regimen to daily prednisone would be valuable. An analog of prednisone, deflazacort (not FDA approved), has been studied in a few clinical trials.[68,71,72] These studies suggest that deflazacort at doses of 0.9 and 1.2 mg/kg/d may be as effective as prednisone 0.75 mg/kg/d and associated with fewer side effects.

A randomized, double-blind, placebo-controlled trial of oxandrolone (0.1 mg/kg/d) for 6 months in 51 boys with DMD demonstrated no statistically significant improvement in manual muscle strength.[73] Modest improvement in strength has been reported in a small number of patients with DMD and BMD treated with short courses of creatine monohydrate (5–10 gm/day).[74,75] Creatine supplementation may increase the muscle supply of phosphocreatine and increase the ATP resynthesis.

Gene Therapy

Two potential strategies for replacing the defective dystrophin protein are somatic gene therapy via myoblast or stem cell transplantation and direct gene replacement using modified viral vectors. Controlled trials of human myoblast transfer in DMD have not resulted in any significant clinical improvement.[76] Stem cell therapies are currently being evaluated in animal models and may proceed to human trials in the near future.

Direct gene replacement therapy involves the introduction of artificially engineered dystrophin gene constructs into plasmid or viral vectors. Gene therapy trials are ongoing, but many potential problems including increasing the yield of transfected muscle fibers need to be worked out before it is a realistic treatment option. Studies are also ongoing of various compounds that have the ability to allow RNA transcriptase to read through stop codon mutations.

Supportive Therapy

Patients are best managed using a multidisciplinary approach. Ideally, neuromuscular clinics should involve neurologists, physiatrists, physical therapists, occupational therapists, speech therapists, respiratory therapists, dietitians, psychologists, and genetic counselors, in order to assess all the needs of individual patients. Physical therapy is a key component in the treatment of patients with muscular dystrophy. Because contractures develop early in the disease, particularly at the heal cords, iliotibial bands, and the hips, appropriate stretching exercises must be started early in the disease. Long leg braces may aid ambulation.

Scoliosis is a universal complication of DMD, particularly once the child is nonambulatory. Scoliosis results in patient pain, aesthetic damage, and perhaps ventilatory compromise. We consider spinal fusion in children with 35° scoliosis or more and who are in significant discomfort. Ideally, forced vital capacity should be greater than 35% to minimize the risk of surgery. Quality of life seems to be improved following spinal stabilization; however, scoliosis surgery does not appear to increase respiratory function.

DMD, GLYCEROL KINASE DEFICIENCY, AND ADRENAL HYPOPLASIA CONGENITA

DMD and glycerol kinase deficiency (GKD) can occur together as part of a contiguous gene syndrome at chromosome Xp21.[77–79] The gene order for the contiguous

loci is Xpter—AHC–GKD–DMD—centromere, and thus patients may also have adrenal hypoplasia congenita (AHC) depending on the extent of the mutation. Microdeletions can span these contiguous genes, producing a clinical phenotype that is different from that seen in patients who have mutations only within the individual DMD, GK, or AHC genes. Most children with combined DMD and GKD exhibit severe psychomotor delay. In addition to muscular weakness due to DMD, children who are affected often experience episodic nausea, vomiting, and stupor from GKD. Further, mutations involving the DAX1 gene responsible for AHC can result in life-threatening adrenal insufficiency manifested by addisonian hyperpigmentation of the skin, hypogonadotropic hypogonadism/cryptorchidism, hyperkalemia, hyponatremia, and hypoglycemia. Glycerol kinase is responsible for the first step in glycerol metabolism:

glycerol + ATP ⇔ glycerol 3-phosphate + ADP.

The enzyme is important in glycolysis, gluconeogenesis, and triglyceride metabolism. GKD results in glyceroluria and hyperglycerolemia. GKD should be considered in a young child with elevated serum triglyceride levels because the standard serum triglyceride test actually measures free glycerol. The neurological side effects of GKD are responsive to a fat-restricted diet and avoiding prolonged fasting.

AHC is caused by mutations in the dosage-sensitive sex reversal AHC, X-chromosome, gene 1, or DAX1. The DAX1 protein is a member of the nuclear hormone receptor superfamily and functions to regulate the transcription of genes involved in the normal development of the adrenal glands. Decreased serum levels of gonadotropins and a subnormal increase in serum cortisol in response to exogenous administration of adrenocorticotropic hormone are found. Treatment of adrenal insufficiency is replacement of glucocorticoids, mineralocorticoids, and testosterone.

Mutations involving the 3′ (carboxy terminal) portion of the dystrophin gene usually span into the GK locus. Thus, patients with dystrophinopathies who have 3′ mutations should be evaluated for the contiguous gene syndrome. Most patients have DMD; BMD can also occur. Diagnosis of X-chromosomal microdeletions can be made with Southern blotting, DNA amplification through PCR, or fluorescent in situ hybridization analysis. Further, fluorescent in situ hybridization provides a rapid and accurate evaluation for these microdeletions and can also be used for carrier detection and prenatal diagnosis.

LIMB-GIRDLE MUSCULAR DYSTROPHY

The LGMDs are a heterogeneous group of disorders that clinically resemble the dystrophinopathies, except for the equal occurrence in males and females (Table 24–1).[4,6,80–82] The prevalence rate of LGMD ranges from 8 to 70 per million. These disorders are inherited in an autosomal-recessive or autosomal-dominant fashion. Autosomal-dominant LGMDs are classified as type 1 (e.g., LGMD 1), while recessive forms are termed type 2 (e.g., LGMD 2). Further alphabetical subclassification has been applied to these disorders, as they have become genotypically distinct (e.g., LGMD 2A, LGMD 2B, etc.—see Table 24–1). For the most part, the clinical, laboratory, and histopathological features of the LGMDs are nonspecific, with a few exceptions to be discussed.

▶ AUTOSOMAL-DOMINANT LGMD (Table 24–1)

LGMD 1A

Clinical Features

Gilchrist and colleagues described the original family (144 patients over seven generations) with this autosomal-dominant inherited LGMD.[83] Other patients have subsequently been reported.[84,85] Progressive weakness may begin in early or late adult life. There is often an early predilection for the scapular–humeral–pelvic muscles. However, distal leg and occasionally arm weakness can be weaker than proximal muscles in some patients.[20] Affected muscle groups are typically atrophic, and early contractures of the elbows and heal cords develop early. Patients can also have an associated cardiomyopathy. Unlike the dystrophinopathies and other LGMDs (e.g., the sarcoglycanopathies), calf hypertrophy is rare.

Laboratory Features

Serum CK levels are normal or elevated up to nine times normal. Muscle biopsies are notable for the frequent occurrence of rimmed vacuoles and occasional nemaline rod-like inclusions.[84,85] Muscle biopsies can demonstrate features of myofibrillar myopathy (MFM) on routine light microscopy, immunohistochemistry, and electron microscopy (EM).[20]

Molecular Genetics and Pathogenesis

LGMD 1A is caused by mutations in the gene that encodes for myotilin located on chromosome 5q22.3–31.3.[20,86] Spontaneous mutations are common, so a lack of a family history should not exclude the diagnosis. Myotilin is a sarcomeric protein that colocalizes with α-actinin at the Z-disk. Some of the clinical, laboratory, and histologic features are similar to those described in autosomal-dominant hereditary inclusion body myopathy (h-IBM) and myofibrillar myopathy (MFM). In fact, recently some patients with MFM have been found to

have mutations in the myotilin gene (discussed in more detail in the section on MFM).[20]

LGMD 1B

Clinical Features

LGMD 1B can present with weakness in the hip and shoulder girdle or have a predilection for the humeral–peroneal muscle. In addition, this dystrophy is frequently associated with cardiac conduction defects, and some patients manifest only with a cardiopathy.[87,88] The cardiopathy and associated arrhythmias can result in sudden death and often requiring pacemaker insertion. This clinical phenotype can resemble that seen in the more common X-linked EDMD. In fact, LGMD 1B had been termed autosomal-dominant EDMD until the two disorders were found to be allelic.[27,89]

Laboratory Features

Serum CK levels may be normal or elevated up to 25 times normal.

Histopathology

Muscle biopsies demonstrate variation in fiber size, increased endomysial connective tissue, normal dystrophin, sarcoglycan, and emerin staining. Occasionally, rimmed vacuoles are evident on muscles biopsy.[87,88] Emerin and lamin A/C expressions on the nuclear membrane are typically normal with immunohistochemistry. On EM, myonuclei exhibit the loss of peripheral heterochromatin or its detachment from the nuclear envelop, altered interchromatic texture, and fewer nuclear pores compared to normal.[26]

MOLECULAR GENETICS AND PATHOGENESIS

LGMD 1B is caused by mutations in lamin A/C on chromosome 1q11–21.[27,28,89] The pathogenic role of lamin A/C is discussed in more detail in the EDMD section.

LGMD 1C

Clinical Features

This autosomal-dominant LGMD is caused by mutations in the caveolin-3 gene and is associated with a heterogeneous phenotype. Affected individuals may present in childhood or adult life with proximal weakness or exertional myalgias.[16] Calf hypertrophy may be evident. The rate of progression is variable. Other patients manifest with rippling muscle disease, distal weakness (anterior tibial or gastrocnemius), or asymptomatic hyperCK-emia.[15,17,18] Spontaneous mutations are not uncommon, so a lack of a family history does not exclude the diagnosis.[15]

Laboratory Features

Serum CK is elevated threefold to 25-fold.

Histopathology

Muscle biopsies demonstrated nonspecific myopathic features with normal dystrophin, sarcoglycan, and merosin staining. Reduced caveolin-3 staining may be appreciated along the sarcolemma. EM reveals a decreased density of caveolae on the muscle membrane as well.

Molecular Genetics and Pathogenesis

LGMD 1C is caused by mutations in the caveolin-3 gene located on chromosome 3p25.[15,16] Caveolin-3 is located on the sarcolemma (Fig. 24–1). It cofractionates with the dystrophin–glycoprotein complex but is thought to be part of a discrete complex. Caveolins play a role in the formation of caveolae membranes, where they act as scaffolding proteins to organize and concentrate caveolin-interacting lipids and proteins.[16] Caveolin-3 might also function to facilitate organization of signaling complexes, and the sodium channels that later function might contribute to the pathogenesis of rippling muscle disease.

LGMD 1D

LGMD 1D rare dystrophy is associated with slowly progressive weakness often associated with cardiomyopathy beginning in early adult life. The disorder has been linked to chromosome 6q23, but the gene has not been identified.

LGMD 1E

LGMD 1E is associated with onset in late adult life. In addition to extremity weakness, dysphagia is common. There is typically no cardiac involvement. The gene has not been found, but the myopathy is linked to Chromosome 7q.[90]

LGMD 1F

LGMD 1F has its onset from infancy to late adulthood. It has been linked to chromosome 7q32.1–32.2, but the gene is as yet unknown.[91]

▶ AUTOSOMAL-RECESSIVE LGMD

LGMD 2A

Clinical Features

This LGMD was first described by Fardeau and colleagues in inhabitants of Reunion Island in the Indian Ocean, but, subsequently, the dystrophy has been reported throughout the world.[4,92–96] It is the most common form of LGMD in people of eastern European, Spanish, and Italian ancestry as well as those from Brazil. The onset of weakness ranges from early childhood to mid-adult life. There is an early predilection for the pelvic-girdle muscles and posterior thigh (gluteus maximus, thigh adductors, hamstrings, and, to a lesser degree, the gluteus medius and psoas), followed 2–5 years later by periscapular and humeral muscle weakness and atrophy (latissimus dorsi, serratus anterior, rhomboids, pectoralis major, and the biceps brachii). The deltoid and brachioradialis are less severely affected, while the distal leg, supra- and infraspinati, triceps, brachialis, and forearm muscles are relatively spared. Only mild weakness of neck muscles can be detected. Facial muscles are usually unaffected. Ocular and velopharyngeal muscles are not involved. There is often slight scoliosis from truncal weakness. Abdominal muscles are more affected than paraspinal spinal muscles. Early contractures at the elbows and calves are typically present such that patients may mimic EDMD. Unlike patients with dystrophinopathies, sarcoglycanopathies, and LGMD 2I, calf hypertrophy is rare. Muscle stretch reflexes are absent or diminished. Progression is steady but variable between different affected kinships. However, there can be variability of phenotypic expression within families.[95] For the most part, the earlier onset of symptoms and signs correlates with a faster evolution of the disease process. Approximately 50% of patients are nonambulatory by the age of 20 years, but some are able to walk late in life. Ventilatory function is only moderately affected. Cardiac function is normal and there is no intellectual impairment. Life expectancy is close to normal.

Laboratory Features

Serum CK levels are usually increased up to 20 times normal early in the disease but decrease close to the normal range later when patients are wheelchair bound. Rare affected children have had peripheral eosinophilia. Skeletal muscle MRI scans demonstrate fat and connective tissue replacing normal muscle fibers. In the thigh, there is a predilection for the posterior thigh (Fig. 24–8).

Histopathology

Muscle biopsies demonstrate variation in fiber size—increased endomysial connective tissue. A lobulated appearance of muscle fibers on NADH staining is a frequent observation; however, this finding is not specific for calpainopathies. Interestingly, recently there was a report of six unrelated calpainopathy patients presenting as eosinophilic myositis in childhood.[97] We have also found mutations in calpain-3 gene in adults who were originally misdiagnosed as having eosinophilic myositis that was refractory to immunosuppressive treatment (Fig. 24–9).

Calpain-3 this is a cytosolic enzyme; immunostaining cannot be performed for diagnosis. Western blot analysis demonstrates reduced calpain-3 in most biopsies, but in 20% of cases the Western blot is normal. The mutation in the gene may not alter the size or amount of calpain-3 but may affect the enzyme activity. Unfortunately, there are no readily available test to assess enzyme activity at this time. In addition, definite diagnosis requires demonstration of a mutation in calpain-3 gene because secondary deficiency in calpain-3 can be seen in other dystrophies, most notably the dysferlinopathies and titinopathies.

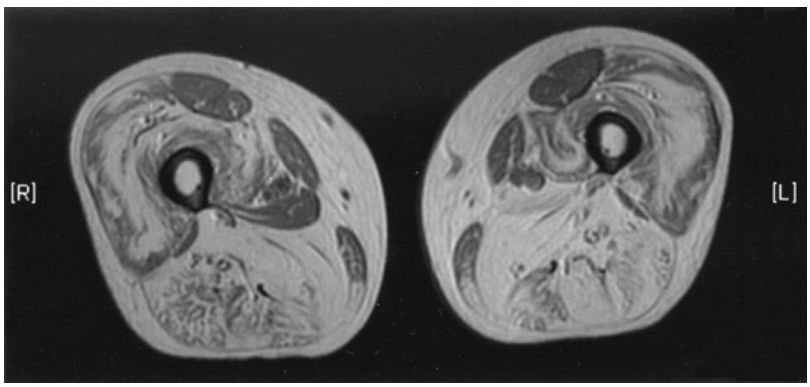


Figure 24–8. LGMD 2A. Skeletal muscle MRI scan (T1 weighted) of the thigh reveals fat and connective tissue (bright signal) replacing normal muscle fibers with a predilection for the posterior thigh muscles.

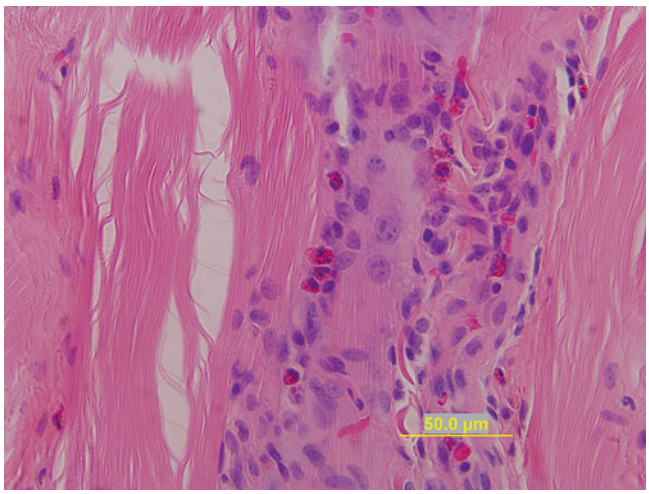


Figure 24–9. LGMD 2A. Muscle biopsy demonstrates eosinophilic infiltrate that can be mistaken for eosinophilic myositis. Paraffin section, H&E.

Molecular Genetics and Pathogenesis

LGMD 2A is caused by mutations in the calpain-3 gene.[96,98–101] Large series of patients with LGMD have shown that calpainopathies account for approximately 20–26% of dystrophies with normal dystrophin and sarcoglycans.[102,103] Of note, approximately 21–23% of patients in large series have had only one identifiable mutation. Over two-thirds of patients with calpainopathy manifest with a BMD-like phenotype, approximately 10% present with severe childhood-onset weakness similar to DMD, 3% have a distal myopathy, and 6% have asymptomatic hyper-CK-emia.[103] Prenatal diagnosis of LGMD 2A is possible through DNA analysis of fetal cells obtained by amniocentesis or chorionic villus sampling.

Calpain-3 is a muscle-specific, calcium-dependent, nonlysosomal, proteolytic enzyme. The mutation leads to an absence or a reduction in this enzyme, but how this results in the dystrophic process is not fully understood. Calpain-3 activates other enzymes involved in muscle metabolism.[100] Lack of calpain-3 might lead to the accumulation of toxic substances in muscle cells. Perhaps, calpain-3 plays a role in gene expression by regulating turnover or activity of transcription factors or their inhibitors.[100]

The reason for the peripheral eosinophilia and the eosinophilic infiltrate noted in biopsies of some affected individuals with LGMD 2A is not clear. Calpain-3 is highly expressed in T lymphocytes, and these cells secrete interleukin-5 and interleukin-3, cytokines that are required for the growth and differentiation of eosinophils. Perhaps, the mutation in the gene causes not only LGMD but also a perturbation of T-cell function leading to eosinophilia.[104]

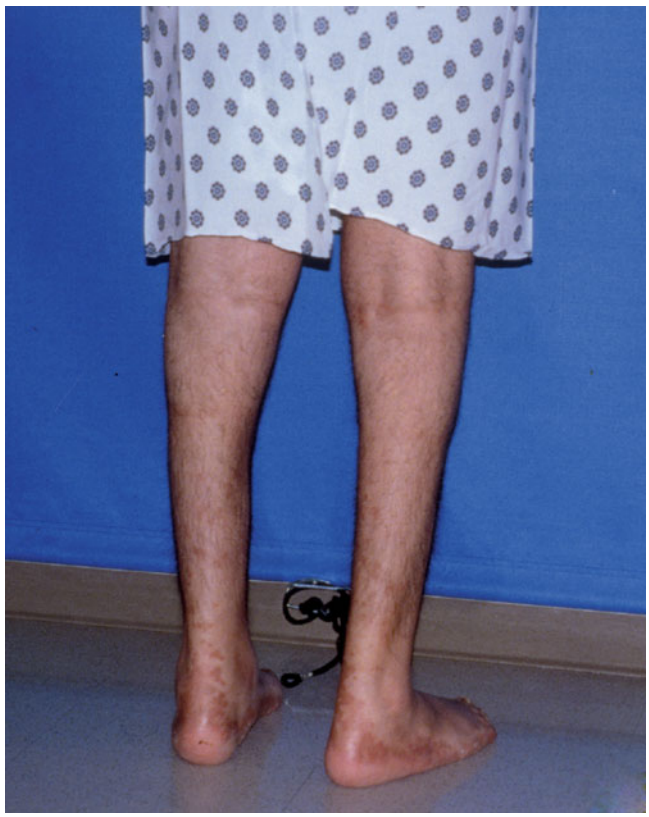


Figure 24–10. LGMD 2B/Miyoshi myopathy. Note the marked atrophy of the calves in a patient with Miyoshi myopathy.

LGMD 2B

Clinical Features

LGMD 2B usually presents in the late teens or early twenties, although onset as late as the age of 48 years has been reported.[105–110] The clinical phenotype is quite variable, with some patients having a "limb-girdle" pattern of weakness, others having early involvement of the posterior calf muscles (i.e., Miyoshi myopathy), and still others with anterior tibial weakness or combination of any of the above. Most patients manifest at least initially with a Miyoshi phenotype, with atrophy and weakness of the gastrocnemius and soleus muscles (Fig. 24–10). This is in contrast to many other forms of LGMD, which more typically have calf muscle hypertrophy or pseudohypertrophy. Not uncommonly, involvement of the calf muscles is asymmetric. A very uncommon presentation is early involvement of the paraspinal muscles leading to rigid spine syndrome or, on the opposite end of the spectrum, a lax spine with hyperlordosis or kyphosis.

On examination, patients will have difficulty standing on their tip toes. Over time, the hamstrings and gluteal muscles are affected and then the distal arms. Less commonly, affected individuals manifest with proximal hip-girdle weakness followed by shoulder-girdle weakness. Mild scapular winging may be evident at

any stage of the disease. Still other patients have early, prominent involvement of the anterior tibial muscles. In our experience, a good examination will often detect atrophy and weakness of the calf muscles in patients with the "limb-girdle" and the "anterior tibial" phenotypes. A helpful sign in dysferlinopathies is the early loss of the Achilles' tendon reflexes. Usually, this is the most preserved reflex in other forms of LGMD but is the earliest lost muscle stretch reflex in the dysferlinopathies. Of note, there is intra- and interfamilial variability in disease progression and pattern of muscle involvement. Interestingly, a recent report noted symptomatic carriers with a single mutation in the dysferlin gene suggesting some cases may be dominant in inheritance.

Progression is usually slow, although we have seen several patients with a rather abrupt onset and rapid progression to a nonambulatory state. The subacute rapid progression and the prominent inflammatory cell infiltrate seen on muscle biopsy (see histopathology) can lead to the misdiagnosis of polymyositis.

Laboratory Features

Serum CK levels are usually markedly elevated (usually 35–200 times normal). Because dysferlin is present on white blood cells, Western blot analysis on these cells for dysferlin represents a noninvasive method of confirming the diagnosis.[111]

Histopathology

Muscle biopsies demonstrate variation in fiber size, scattered necrotic and regenerating fibers, and—increased endomysial connective tissue. Immunostaining reveals absent or diminished sarcolemmal staining with dysferlin antibodies. In contrast, there may be increased cytoplasmic staining. The reduced sarcolemmal immunostaining can be secondary and seen in other types of LGMD[112]; therefore, Western blot needs to be performed on the muscle or white blood cells to confirm a primary deficiency. Not uncommonly, a prominent mononuclear inflammatory cell infiltrate is evident in the endomysium and surrounding blood vessels. This accounts for many cases of dysferlinopathy being misdiagnosed as polymyositis.[113] In contrast to polymyositis, the inflammatory cells do not typically appear to invade nonnecrotic fibers. Another immunohistological feature that is helpful is demonstrating deposition of membrane attack complex on the sarcolemma of non-necrotic muscle fibers (Fig. 24–11)—an early finding in dysferlinopathies and other dystrophies with inflammation that is not seen in primary inflammatory myopathies such as polymyositis, dermatomyositis, and inclusion body myositis (IBM). On electron microscopy, reduplication of the basal lamina, disruption in the sarcolemma, invaginations or papillary exophytic defects of the muscle membrane, and subsarcolemma vesicles may be appreciated.[114]

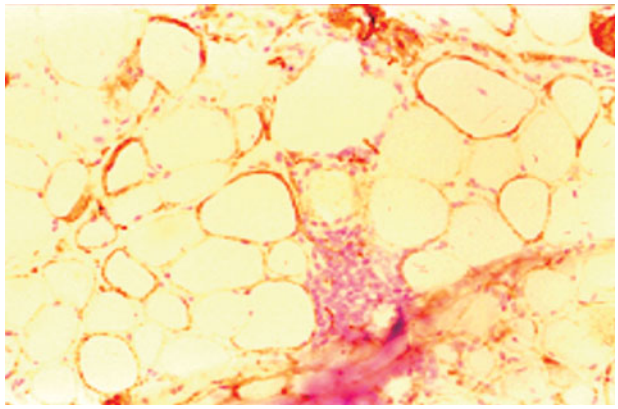


Figure 24–11. LGMD 2B/Miyoshi myopathy. Muscle biopsies often demonstrate endomysial inflammatory cell infiltrate that can lead to misdiagnosis as polymyositis. An early observation is the demonstration of membrane attack complex on the sarcolemma of non-necrotic muscle fibers in dysferlinopathies (also seen in FSHD) that is not appreciated in PM. Immunoperoxidase with anti-MAC antibodies. LGMD, limb-girdle muscular dystrophy; FSHD, facioscapulohumeral muscular dystrophy.

Molecular Genetics and Pathogenesis

Mutations within the dysferlin gene are the cause of Miyoshi myopathy, LGMD 2B, and some distal myopathies with anterior tibial weakness.[13,105,115]A study of 407 muscle biopsies from patients with unclassified myopathies (nondystrophinopathy and nonsarcoglycanopathy) demonstrated that 6.5% had abnormal dysferlin by Western blot and immunostaining.[103] Dysferlinopathy accounted for 1% of patients with an unknown LGMD and 60% of patients with a distal myopathy. The clinical phenotype of patients with dysferlinopathy broke down as follows: 80% manifest with distal weakness, 8% have LGMD phenotype, and 6% present with asymptomatic hyper-CK-emia.

Dysferlin shares amino acid sequence homology with *C. elegans* spermatogenesis factor FER-1, thus the origin of its name. Dysferlin is located predominantly on the subsarcolemmal surface of the muscle membrane, but it has small transmembrane spanning tail (Fig. 24–1). It does not appear to have a significant interaction with the dystrophin–glycoprotein complex, and immunostaining for dystrophin, dystroglycans, merosin, and the sarcoglycans is normal. Recent studies have suggested that at least one role of dysferlin is patching defects in skeletal membrane and mutations in the gene result in defective membrane repair.[12]

SARCOGLYCANOPATHIES (LGMD 2C, LGMD 2D, LGMD 2E, AND LGMD 2F)

Clinical Features

The sarcoglycanopathies account for approximately 10% of LGMD in the following frequencies: α-sarcoglycan

6.6%, β-sarcoglycan 3.1%, γ-sarcoglycan 1.5%, and δ-sarcoglycan <1%.[4,116,117] The clinical, laboratory, and histologic features of the sarcoglycanopathies are quite similar to the dystrophinopathies, with some children developing early onset of severe weakness resembling DMD and other patients having a later onset and slower progression similar to BMD. Proximal leg and arm muscles are affected early, and calf pseudohypertrophy can often be appreciated. Cardiomyopathy can also occur similar to the dystrophinopathies.[118]

Laboratory Features

Serum CK levels are markedly elevated. In contrast to the dystrophinopathies, there are no significant intellectual impairments or cardiac abnormalities in the sarcoglycanopathies.

Histopathology

Muscle biopsies demonstrate normal dystrophin; however, each of the sarcoglycans are absent or diminished on the sarcolemma, regardless of the primary sarcoglycan mutation.

Molecular Genetics and Pathogenesis

LGMDs 2C, 2D, 2E, and 2F are caused by mutations in the γ-, α-, β-, and δ-sarcoglycan genes, respectively.[6,102,116,117,119–125] The clinical phenotypes appear to correlate with the expression of the sarcoglycans. The proteins of the sarcoglycan complex appear to function as a unit. Mutations involving any of the sarcoglycans result in destabilization of the entire complex and reduced expression of the other proteins. As apparent with the dystrophinopathies, the clinical severity of the sarcoglycanopathies may correlate with the type of mutation (i.e., whether the reading frame is preserved) and subsequent level of functional protein expression.

CONGENITAL FIBROSIS OF THE EXTRAOCULAR MUSCLES

Mutations in the sarcospan gene located on chromosome 12p11.2 are associated with congenital fibrosis of the extraocular muscles, a rare form of muscular dystrophy.[126]

LGMD 2G

Clinical Features

This myopathy is associated with prominent early weakness of the quadriceps and anterior tibial muscle groups and has mean age of onset of muscle weakness of 12.5 years.[127,128] Cases resembling Miyoshi myopathy (LGMD 2B) with calf weakness have also been described.[129]

Laboratory Features

Serum CKs are elevated threefold to 17-fold.

Histopathology

Besides the usual dystrophic features, many muscle fibers had one or more rimmed vacuoles. Immunohistochemistry and Western blot analysis demonstrate a deficiency of telethonin.[128]

Molecular Genetics and Pathogenesis

LGMD 2G is caused by mutations in the telethonin gene located on chromosome 17q11–12.[128] Telethonin is a 19-kD sarcomeric protein that is expressed in skeletal and cardiac muscles, where it localizes to the central parts of the Z-disk.[130] It is a ligand for the giant sarcomeric protein, titin, which helps phosphorylate the C-terminal domain of telethonin in early differentiating myocytes. Telethonin may also overlap with myosin as well. It is amongst the most abundant proteins in muscle. The interaction of telethonin with titin appears to be important in myofibrillogenesis.[130,131]

LGMD 2H

Clinical Features

This genetically distinct LGMD was initially reported in families of Manitoba Hutterite origin.[29,132] Age of onset of weakness ranges from 8 to 27 years. The myopathy is slowly progressive, and most affected individuals are still ambulatory, without assistance in the fourth decade of life.

Laboratory Features

Serum CKs are elevated fivefold to 50-fold. There may be nonspecific EKG changes.

Histopathology

Muscle biopsies demonstrate typical dystrophic features. In addition, many fibers (mostly type 2) contain small vacuoles that immunostain for sarcoplasmic reticulum-associated ATPase. These vacuoles abut T-tubules and appear to be membrane bound and appeared on EM.

Molecular Genetics and Pathogenesis

LGMD 2H and sarcotubular myopathy (discussed in Chapter 25 with the Congenital Myopathies) are now known to be allelic disorders caused by mutations in the gene that encodes for E3-ubiquitine ligase (also known as TRIM 32) located on chromosome 9q31–q33 was recently reported.[29] TRIM 32 may function by ubiquinating proteins that need degradation by proteosomes. The mechanism by which this leads to muscle destruction is unclear, but one might speculate on the possible toxic accumulation of "aged" or otherwise abnormal proteins not cleared by proteasomes.

LGMD 2I

Clinical Features

LGMD 2I was initially described in a large consanguineous Tunisian family with 13 affected members.[133] However, it subsequently has been demonstrated worldwide and is the most common form of LGMD in England, the Netherlands, and northern Europe. The onset can range from infancy (MDC type 1C) to the fourth decade of life.[30,31] The pattern of weakness and course is variable. Some individuals have more hip-girdle involvement, while others are weaker in the proximal arms and neck flexors. Calves are often hypertrophic. Importantly, approximately one-half of patients develop a dilated cardiomyopathy and ventilatory muscle weakness.[134–136]

Laboratory Features

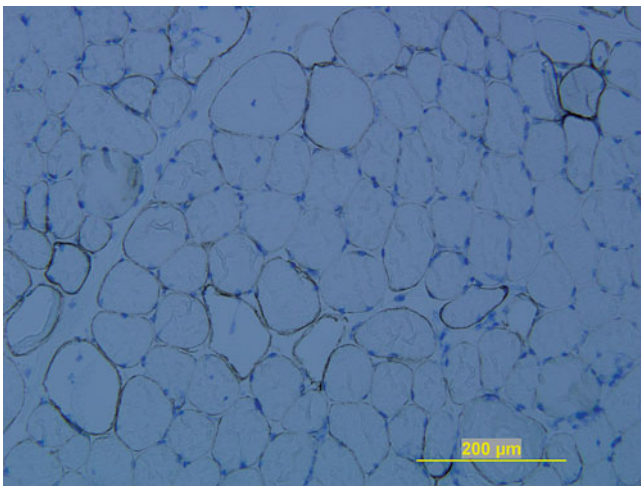
Serum CKs are elevated 10–30 times normal in some younger patients who are affected but may be normal in older individuals.

Histopathology

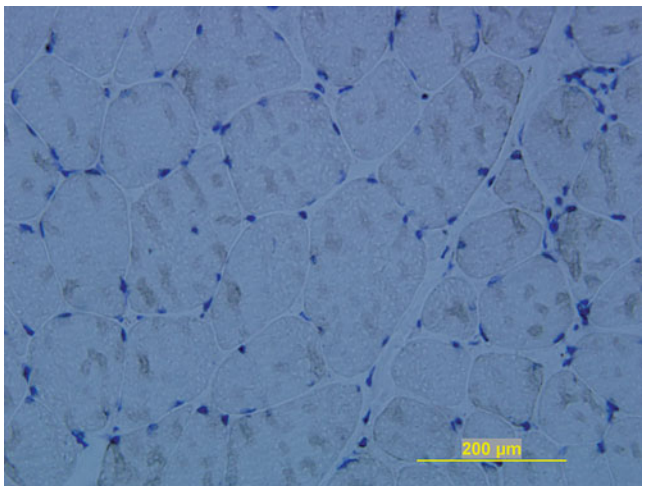
Nonspecific dystrophic features are evident on muscle biopsy. Of note, immunohistochemistry demonstrates normal dystrophin and sarcoglycan staining. However, α-dystroglycan and occasional merosin are reduced or absent on immunostaining (Fig. 24–12).

Molecular Genetics and Pathogenesis

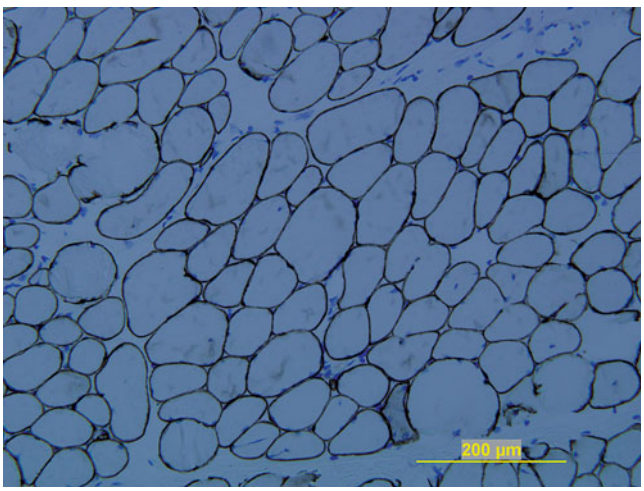
The LGMD 2I is caused by mutations in the gene that encodes for FKRP located on chromosome 19q13.3. Mutations in this gene are also responsible for MDC type 1C; FKRP is a glycosyltransferase and its deficiency is associated with abnormal glycosylation of alpha-dystroglycan, which apparently disrupts the dystrophin–glycoprotein complex. Abnormalities in glycosylation of α-dystroglycan is recurring theme in the MDCs, as this is also causative mechanism in Fukuyama disease, MEB, WWS, and LARGE-related CMD (MDC 1D). There is a correlation between a reduction in alpha-dystroglycan, the mutation, and the clinical phenotype in MDC 1C and LGMD 2I.[32]



A



B



C

Figure 24–12. LGMD 2I. Muscle biopsies demonstrate reduced or patchy merosin staining (A), absent alpha-dystroglycan staining (B), but normal dystrophin staining (C) around the sarcolemma. Immunoperoxidase.

FKRP localizes in rough endoplasmic reticulum, while fukutin localizes in the *cis*-Golgi compartment (ER).[137] Fukutin and FKRP appear to be involved at different steps in *O*-mannosylglycan synthesis of alpha-dystroglycan, and FKRP is most likely involved in the initial step in this synthesis. ER retention of mutant FKRP may play a role in the pathogenesis of these dystrophies and potentially explain why the allelic disorder LGMD 2I is milder, because the mutated protein is able to reach the Golgi apparatus.[138]

LGMD 2J

LGMD 2J is caused by mutations in the titin gene. Most patients with titinopathy manifest with autosomal-dominant inheritance of the tibial myopathy (Udd-type distal myopathy), which is discussed in greater detail in the "Distal Myopathy" section. Patients with LGMD 2J have heterozygous mutations in the titin gene and usually present in late adulthood with anterior tibial weakness. However, the clinical phenotype can be quite variable.[139] Some patients manifest in childhood with a limb-girdle pattern of weakness, some have involvement mainly of the upper limb (biceps, forearms, and hands), while others have atrophy and weakness of the posterior calves without anterior tibial involvement.

Homozygous mutations of the titin gene more commonly lead to a severe phenotype with limb-girdle weakness.[129,139] The variability of the clinical phenotype has led to the conclusion that no clinical phenotype can be excluded to be caused by a titin mutation.[139]

LGMD 2K

LGMD 2K is caused by mutations in the POMT1 gene which is more commonly associated with Walker-Warburg syndrome (discussed in Congenital Muscular Dystrophy section). However, rare patients have a milder LGMD phenotype.

LGMD 2L

LGMD 2L is caused by mutations in the fukutin gene that usually causes Fukuyama muscular dystrophy (discussed in Congenital Muscular Dystrophy section). However, mutations may rarely be associated with a more benign LGMD phenotype.

LGMD 2M

LGMD 2M is caused by mutations in the POMGnT1 gene that usually causes Muscle-Eye-Brain disease, but rarely can cause a more benign form of dystrophy.

TREATMENT OF LGMD

Treatment is largely supportive. Physical and occupational therapy are important to prevent contractures and improve function. Large therapeutic trials of corticosteroids (similar to those conducted for DMD) have not been performed in patients with LGMD, although some patients with LGMD reported benefit from such treatment.[140] Modest improvement in strength has been reported in a small number of patients with LGMD treated with short courses of creatine monohydrate (5–10 g/d).[75] Advances in molecular genetics may lead to better forms of treatment in the future.

▶ CONGENITAL MUSCULAR DYSTROPHY

The congenital muscular dystrophies or MDCs are a heterogeneous group of autosomal-recessive inherited disorders, characterized by perinatal onset of hypotonia and weakness, dystrophic appearing muscle biopsies, and the exclusion of other recognizable causes of myopathy of the newborn (Table 24–1). The abbreviation assigned by the Human Genome Organization is "MDC" for muscular dystrophy, congenital. The MDCs have been classified in the past according to clinical, ophthalmological, radiological, and pathological features. A more recent classification was proposed based on the location of the defective proteins and purported pathogeneses of the individual dystrophies.[141,142] The major categories of MDCs include (1) those associated with mutations in genes encoding structural proteins of the basal lamina, extracellular matrix, or sarcolemmal proteins that bind to the basal lamina; (2) those associated with impaired glycolylation of α-dystroglycan; and (3) that associated with selenoprotein 1 mutations.

▶ MDC ASSOCIATED WITH GENETIC DEFECTS OF STRUCTURAL PROTEINS OF THE BASAL LAMINA OR EXTRACELLULAR MATRIX

MDC 1A (ALSO KNOWN AS MDC WITH LAMININ α2 OR MEROSIN DEFICIENCY OR THE CLASSIC/OCCIDENTAL TYPE)

Approximately 30–40% of patients with MDC have absent or severely decreased merosin.[143–147] In addition, there are patients with partial merosin deficiency, analogous to the dystrophinopathies and sarcoglycanopathies.[145,146,148–153] However, some of these partial merosinopathies are now known to be secondary deficiencies related to glycosylation defects in α-dystroglycan.

Clinical Features

Children with MDC 1A usually present at birth with generalized weakness and hypotonia birth. There is a predilection for neck-, shoulder-, and hip-girdle muscles.[244] Calf hypertrophy may be appreciated early in the course. Contractures develop, but severe arthrogryposis is rare. Respiratory and feeding problems can be present but usually not severe enough to require ventilator support at birth.[141] Some children develop a cardiomyopathy. Limited extraocular movements can be observed in the later stages.

Merosin-negative MDC typically has more severe weakness and is associated with a poorer prognosis compared with merosin-positive cases.[144] Most children with MDC 1A never ambulate independently, although rare children are able to stand and occasionally walk with assistance. Individuals with only partial merosin deficiency have a milder course and can present in childhood with a DMD phenotype or in early adulthood with a phenotype similar to BMD or LGMD.[143–147,154]

Most children with MDC 1A have normal intelligence, despite abnormal white matter changes apparent on MRI. However, there is a high incidence of epilepsy (12–30%) as well as a few reported cases of occipital dysplasia in merosin-deficient CMD.[148,152] Epilepsy can also occur in patients with partial merosin deficiency. Rare patients with MDC 1A with epilepsy and occipital agyria also have mental retardation.

Laboratory Features

Serum CK levels are markedly elevated, usually over 2000 IU/L in the merosin-negative infants, while partial merosinopathies are associated with normal or mildly elevated serum CKs. Brain MRI often demonstrates diffuse white matter abnormalities in T2-weighted images suggestive of dysmyelination in most children after the age of 6 months (Fig. 24–13). Additionally, occipital polymicrogyria/agyria and hypoplasia of pons and/or cerebellum are evident in rare cases.[141] Patients with partial merosin deficiency may or may not have cerebral hypomyelination on MRI. Visual- and somatosensory-evoked potential may reveal delayed latencies in MDC 1A.[155] Slowing of nerve conduction velocities is also commonly appreciated.[147]

Histopathology

Muscle biopsies demonstrate variation in fiber size, increased endomysial connective tissue, and notably decreased or absent merosin (Fig. 24–14).

Molecular Genetics and Pathogenesis

MDC 1A is associated with mutations in α-2 subchain of merosin on chromosome 6q21–22. The gene codes for a 390-kD protein, which is synthesized as one chain but processed into two fragments. On immunoblot, these two fragments have molecular masses of approximately 80 kD (C terminal) and 300 kD (N terminal).[146]

Merosin is also present in the basal lamina of myelinated nerves. Abnormal expression of merosin may

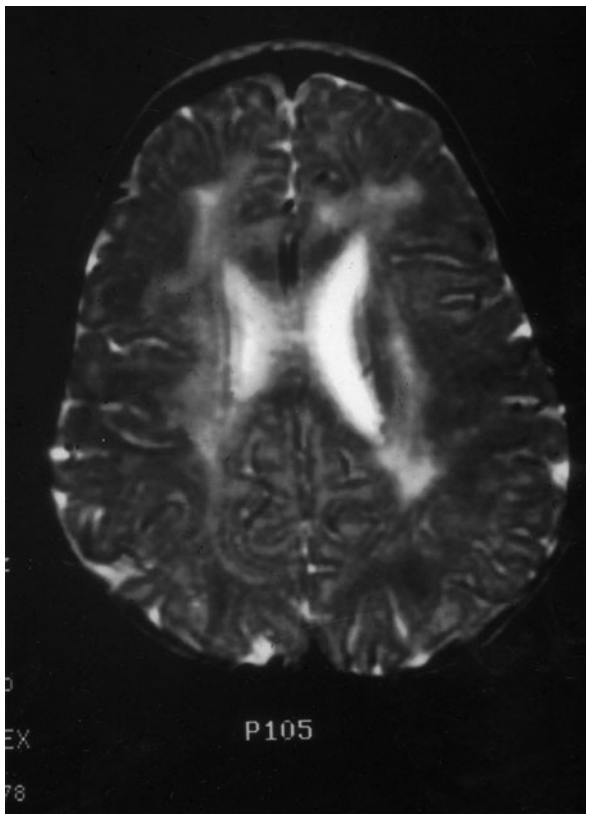


Figure 24–13. Congenital muscular dystrophy. T2-weighted MRI of brain of an infant with merosin-negative congenital muscular dystrophy reveals increased signal of the subcortical white matter consistent with hypomyelination.

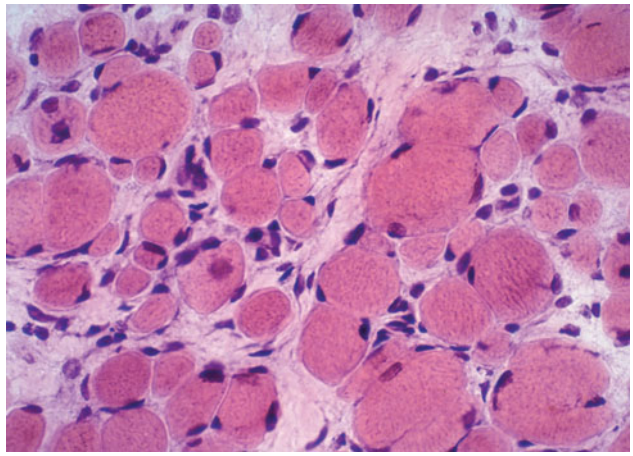


Figure 24–14. Congenital muscular dystrophy. Muscle biopsy demonstrates fiber size variability and increased endomysial and perimysial connective tissue consistent with a dystrophic process. H&E.

interfere with myelinogenesis and may account for the hypomyelination evident in the central and peripheral nervous system. Importantly, merosin is expressed in skin, and thus merosin-negative MCD can be diagnosed on skin biopsies.[150,156] Further, prenatal diagnosis of merosin-negative MCD can be made on chorionic villous sampling.[151,157]

Merosin binds to α-dystroglycan and α7β1D integrin (Fig. 24–1). As with primary dystrophinopathies and adhalinopathies, the merosinopathies may result in a disruption and loss of integrity of the dystrophin–glycoprotein complex. Mutations in the α-2 subchain of merosin result in a markedly diminished expression of α7β1D integrin, but a normal or only mildly decreased expression of components of the dystroglycan or sarcoglycan complexes on the sarcolemma. Of note, mutations involving the α7 subunit of integrin that binds to merosin also results in a form of MDC.[158]

MEROSIN-POSITIVE CLASSIC MDC

As noted in the previous discussion, merosin-positive forms of classic MDC are clinically more benign than merosin-negative MDC. These merosin-positive MDC cases are genetically heterogeneic. Some partial merosin deficiency cases (the so-called MDC 1B) map to genetic loci on chromosome 1q42. The exact gene for MDC 1B has not as yet been identified. Some cases of partial merosin deficiency or MDCs with normal merosin are due to mutations in glycosyltransferases, which cause secondary α-dystroglycanopathy (these are discussed in a separate section).

Mutations of the α7 subunit of integrin gene located on chromosome 12q13 have been demonstrated in three patients to date with merosin-positive MDC.[158] Children who are affected presented with congenital onset of generalized weakness and hypotonia and had delayed motor milestones. Mental retardation was evident in one child who had a normal MRI of the brain and EEG. Serum CK was only mildly elevated (less than five times normal). Muscle biopsies only showed mild variation of fiber size with normal merosin expression on immunohistochemistry.

▶ ULLRICH DISEASE

Clinical Features

Ullrich congenital muscular dystrophy (UCMD) is associated with weakness at birth or early infancy, contractures of the proximal joints, hyperextensibility of the distal joints, high-arched palate, and protuberant calcanei.[159] UCMD is allelic with the more benign Bethlem myopathy. UCMD was initially felt to be autosomal recessive while Bethlem myopathy was autosomal dominant, but UCMD can be autosomal dominant in inheritance.[160] UCMD is associated with congenital muscle weakness, delayed motor milestones, proximal joint contractures, scoliosis, and marked distal joint hyperextensibility. Intelligence is normal.

Laboratory Features

Serum CK is normal or mildly elevated.

Histopathology

Muscle biopsies reveal variation in muscle fiber size, scattered regenerating and degenerating fibers, and increased endomysial connective tissue. Immunohistochemistry reveals that collagen VI is present in the interstitium but absent from the sarcolemma.[159] EM demonstrates that collagen VI in the interstitium fails to anchor normally to the basal lamina surrounding muscle fibers.

Molecular Genetics and Pathogenesis

Collagen VI is composed of three chains, α1, α2, and α3, and is a ubiquitously expressed extracellular matrix protein. The three chains are encoded by the genes *COL6A1* and *COL6A2* on chromosome 21q22.3 and *COL6A3* on chromosome 2q37. UCMD and the less severe Bethlem myopathy are caused by mutations in these genes.[160] UCMD had been considered a recessive condition, and homozygous or compound heterozygous mutations have been defined in COL6A2 and COL6A3. In contrast, the milder disorder Bethlem myopathy has dominant inheritance and is caused by heterozygous mutations in COL6A1, COL6A2, and COL6A3.[160] Recent studies have demonstrated that UCMD can be inherited in a dominant fashion as well.[160] Collagen VI deficiency in muscle or cultured fibroblasts was complete in the severe cases and partial in the milder forms, which suggests a correlation between the degree of collagen VI deficiency and the clinical severity in UCMD.[161] Not all patients with Ullrich disease have mutations in collagen VI. However, the absence of collagen VI is seen even in these cases, suggesting a mutation involving other proteins that interact with collagen VI.

▶ MDC ASSOCIATED WITH IMPARIED GLYCOSLYLATION OF α-DYSTROGLYCAN

The primary sequence of α-dystroglycan predicts a molecular mass of 72 kD; however, the mass of α-dystroglycan in skeletal muscle is 156 kDa.[141] The increase in the size is due to posttranslational modification of α-dystroglycan. In this regard, *O*-linked glycosylation

of the protein makes the major contribution to the observed molecular weight. The glycosyltransferase *O*-mannosyltransferase 1 (*POMT1*) forms a complex with a second putative *O*-mannosyltransferase (POMT2) to catalyzes the first step in *O*-mannosyl glycylation.[141,142] Subsequently, the transfer of *N*-acetylglucosamine to *O*-mannose of glycoproteins is catalyzed by *O*-mannose β-1,2-*N*-acetylglucosaminyltransferase (POMGnT1). Fukutin, FKRP, and LARGE are other secretory enzymes involved in posttranslational glycoslylation of α-dystroglycan, although the exact reactions they catalyze are not known.[141,142] Glycosylation of α-dystroglycan is required for normal binding to merosin.[162] Not only is glycosylation of α-dystroglycan important for proper muscle function, but impaired glycosylation of α-dystroglycan leads to defects in neuronal migration and the abnormalities in the central nervous system seen with Fukuyama-type congenital muscular dystrophy (FCMD), WWS, MEB, MDC 1C, and MDC 1D.

Muscle biopsy findings are indistinguishable form other forms of MDC using routine stains. A striking inflammatory infiltrate is occasionally present, which has led to the erroneous diagnosis of a congenital inflammatory myopathy or polymyositis. Importantly, abnormal glycosylation of α-dystroglycan caused by mutations responsible for FCMD, MEB, WWS, and MDCs 1C and 1D can be appreciated by reduced immunostaining of the sarcolemmal membrane, with antibodies directed against α-dystroglycan and merosin.[163–166]

▶ FUKUYAMA CONGENITAL MUSCULAR DYSTROPHY

Clinical Features

FCMD was originally described in Japan, where it is the most common form of MDC.[141,142,167] The myopathy presents with generalized proximal greater than distal weakness and hypotonia in infants. Mothers of affected children in retrospect often note decreased fetal movements. There is an increased frequency of spontaneous abortions of affected fetuses. Pseudohypertrophy of the calves is recognized in approximately half the children. Muscle stretch reflexes are reduced. Some children are born with arthrogryposis and contractures are progressive.

In addition to the myopathy, FCMD is associated with severe structural abnormalities of the brain, including microcephaly, cortical dysplasia, lissencephaly, pachygyria, polymicrogyria, and hydrocephalus.[167,168] Intellectual function is markedly compromised. Approximately 50% of children who are affected have seizure. Both physical and mental developments are delayed, with the majority never being able to stand or ambulate independently. Most children die by the age of 10–12 years of age from respiratory failure.

Laboratory Features

The serum CK level is usually elevated 10–50 times normal values. Electroencephalography is often abnormal, demonstrating epileptiform activity and generalized slowing. MRI and CT scans of the brain reveal structural abnormalities and evidence of hypomyelination.

Molecular Genetics and Pathogenesis

FCMD is caused by mutations in the fukutin gene, which is located on chromosome 9q31.[167–170] Fukutin is a secretory enzyme that localizes to the *cis*-Golgi compartment and is thought to be involved in that has a role in posttranslational glycoslylation of α-dystroglycan.[137] In addition to the skeletal muscle involvement, the disruption of normal glycosylation of α-dystroglycan or other proteins leads to defects in neuronal migration and differentiation, which accounts for the many abnormalities seen within the central nervous system.

▶ WALKER–WARBURG SYNDROME

Clinical Features

WWS, or cerebro-ocular dysplasia, is the most severe α-dystroglycanopathy and is associated with a life expectancy of less than 3 years. WWS presents as severe generalized weakness hypotonia in infancy.[163–165] In addition, the infants are usually born blind secondary to ocular malformations, which include fixed pupils, hypoplasia of the optic nerves, micro-ophthalmia, corneal opacities, cataracts, shallow anterior chambers, ciliary body abnormalities, iridolental synechiae, and retinal dysplasia and detachment. As with FCMD and MEB, WWS is associated with migrational and developmental disturbances of neurons in the brain, which include lissencephaly, polymicrogyria, hydrocephalus, hypomyelination of the subcortical white matter, and hypoplasia of the brainstem and vermis. Seizures are common.

Laboratory Features

Serum CK levels are elevated. Brain MRI scans reveal structural abnormalities, which are alluded to in the above section. Electroencephalography is often abnormal, revealing slowing of the background and epileptiform activity.

Molecular Genetics and Pathogenesis

The mutations have been identified in genes that encode for four proteins (POMT1, POMT2, fukutin, and FKRP) in patients with WWS, but they account for only a minority of cases.[141,163–165,171] Mutations in the POMT1 gene on chromosome 9q31–33 account for the 20% of WWS.[141,164] The clinical phenotype of patients with

mutations in the POMT1 gene is also variable, with rare cases being reported with LGMD and mild mental retardation (LGMD 2K).[172] As noted previously, glycosylation of α-dystroglycan is required for normal binding to merosin.[162]

▶ MEB DISEASE

Clinical Features

MEB disease was initially described in Finnish patients by Santavouri and colleagues [164,165,173–175] but has been subsequently reported in other populations. As in WWS, brain and eye abnormalities accompany the muscle weakness; however, MEB is less severe. Although infants are weak and motor development is slow, most affected children eventually can sit and stand and some ambulate. There are severe cognitive impairments associated with structural abnormalities in the brain, which include pachygyria, polymicrogyria, abnormal midline structures, and hypoplasia of the vermis and pons. MEB is also associated with progressive myopia, glaucoma, and late cataracts.

Laboratory Features

Serum CK levels are elevated. MRI of the brain may demonstrate polymicrogyria, abnormal midline structures, hypoplastic vermis, and pons.[164,173–175]

Molecular Genetics and Pathogenesis

MEB is caused by mutations in the gene that encodes for *O*-mannose-β-1,2-*N*-acetylglucosaminyl transferase (*POMGnT1*) on chromosome 1p32–p34.[164,165,170] POMGnT1 catalyzes the transfer of *N*-acetylglucosamine to *O*-mannose of glycoproteins. Mutations in this gene has also been associated with a milder myopathy, LGMD 2M.

MDC 1C

Clinical Features

MDC 1C is allelic to LGMD 2I and is caused by mutations in the gene that encodes for FKRP. The FKRP-related myopathies are very common, especially among patients of Northern European, including English, ancestry, and give rise to the largest phenotypical spectrum of muscular dystrophies so far connected to mutations of a single gene.[141,142] The age of onset can range from infancy (e.g., congenital) to the fourth decade of life, with a pattern of weakness similar to MDC 1A. A phenotype reminiscent of WWS can also be seen in patients with FKRP mutations. Early involvement of cardiac and respiratory muscles is common.[134–136]

Laboratory Features

CK levels were always very elevated (10–75× normal). Echocardiogram may reveal features of a dilated cardiomyopathy. Pulmonary function tests may reveal reduced forced vital capacity and inspiratory pressures. MRI of the brain may reveal microcephaly, cerebellar cysts, and hypoplasia of the vermis, and also white matter abnormalities on MRI as other alpha-dystroglycanopathies.[176]

Molecular Genetics and Pathogenesis

MDC 1C is caused by mutations in the gene that encodes for FKRP located on chromosome 19q13.3. FKRP localizes in rough endoplasmic reticulum and appears to be involved in one of the initial steps in *O*-mannosylglycan synthesis of alpha-dystroglycan.[137] ER retention of mutant FKRP may play a role in the pathogenesis and potentially explain why the allelic disorder LGMD 2I is milder, because the mutated protein is able to reach the Golgi apparatus.[138] There is a correlation between a reduction in alpha-dystroglycan, the mutation, and the clinical phenotype in MDC 1C and LGMD 2I.[32] Patients with MDC 1C have a profound depletion of α-dystroglycan, those with a Duchenne-like phenotype have a moderate reduction in α-dystroglycan, and individuals with the milder form of LGMD 2I demonstrate a variable but subtle alteration in α-dystroglycan immunolabelling.

MDC 1D

Clinical Features

This is a very rare dystrophy, which, as in other secondary α-dystroglycanopathies, is associated with generalized weakness, mental retardation, and global developmental delay.[34,35] Motor milestones are delayed, but individuals who are affected may be able to ambulate. The patient had profound mental retardation. There was nystagmus on examination but no other ocular abnormalities.

Laboratory Features

Serum CK was mild to moderately elevated. Mild structural abnormalities have been appreciated on brain MRI.

Molecular Genetics and Pathogenesis

Mutations in the human LARGE gene (also is required for glycoslylation of alpha-dystroglycan) is responsible for this rare form of CMD.[34,35] This gene encodes for another putative glycosyltransferase.

▶ MDC ASSOCIATED WITH SELENOPROTEIN N1 MUTATIONS

RIGID SPINE SYNDROME

Clinical Features

The rigid spine syndrome or rigid spine muscular dystrophy (RSMD) is heterogeneic disorder. One subtype, RSMD1, manifests in infancy with hypotonia, proximal weakness, and delayed motor milestones.[126,177–182] Affected individuals develop progressive limitation of spine mobility often associated with scoliosis and contractures at the knees and elbows. Thus, these patients share many clinical features with EDMD and UCMD/Bethlem myopathy. Of note, some patients previously diagnosed with multi/minicore congenital myopathy have a rigid spine. Respiratory weakness can develop due to stiffness of the rib cage and involvement of the diaphragm. Many patients require noninvasive ventilator support.

Laboratory Features

Serum CK levels are normal to slightly elevated. Conduction defects may be evident on EKG. Pulmonary function tests reveal a reduced vital capacity in patients old enough to cooperate. Electromyography (EMG) demonstrate myopathic appearing MUAPs, while insertional activity is typically normal and abnormal spontaneous activity is sparse.

Histopathology

Muscle biopsies reveal nonspecific myopathic features including variability in fiber size, increased internal nuclei, type 1 fiber predominance, and moth-eaten fibers and lobulated fibers on NADH-TR stains. Some cases are associated with multiple minicores. Cytoplasmic bodies, Mallory bodies, increased desmin expression, and sarcoplasmic and intranuclear tubulofilamentous inclusions may also be present similar to myofibrillar myopathy.[181] Endomysial fibrosis is apparent, particularly in axial muscles (i.e., rectus abdominus and paraspinal muscles). Immunostains for dystrophin, sarcoglycans, and the dystroglycans are normal.

Molecular Genetics and Pathogenesis

Some cases of autosomal-recessive RSMD have been linked to mutations in the gene that encodes for selenoprotein N1 located on chromosome 1p35–36.[126,180,183] Mutations in this gene have also been shown in some patients with multi/minicore myopathy and MFM.[184] Selenoprotein N1 is an endoplasmic reticulum glycoprotein. The function of this protein is not known.

▶ TREATMENT OF MDC

Treatment of the MDCs is supportive. Corticosteroids have not been studied in a prospective, placebo-controlled, double-blind fashion as in DMD, but it is clear that corticosteroids have note been associated with any significant benefit even in those cases with associated significant inflammation on muscle biopsy. Antiepileptic medications are necessary for control of seizures. Physical therapy and range of motion exercise are important to reduce contractures. Ventilator support, invasive or noninvasive, may be beneficial in patients with ventilatory muscle involvement.

▶ OTHER REGIONAL FORMS OF MUSCULAR DYSTROPHY

FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY

Clinical Features

Facioscapulohumeral muscular dystrophy (FSHD) is an autosomal-dominant disorder, with an incidence of approximately 4 per million and a prevalence of roughly 50 per million.[185,186] There is a variable degree of penetrance of clinical findings within families, while around 30% of affected family members are unaware of their deficits. Thus, it is very important to examine family members of patients suspected of having FSHD.

Onset of weakness is usually appreciated between 3 and 44 years, although onset as late as 75 years has also been reported.[187–191] As the name suggests, FSHD is characterized by muscle weakness and wasting in a rather specific distribution. The muscles of facial expression, particularly the orbicularis oculi, zygomaticus, and orbicularis oris muscles, are affected early. Patients may be unable to fully close their eyes against resistance and may sleep with incomplete eyelid closure. On examination of forced eye closure, many individuals demonstrate prominent Bell phenomena (visible sclera with eye closure). Affected persons can have a horizontal smile and weak puckering of the lips. Facial weakness may be strikingly asymmetric, mimicking a seventh nerve palsy. The muscles of mastication and the external ocular muscles are typically spared.

The scapula-stabilizer muscles (serratus anterior, rhomboid, middle trapezius, and, to some degree, latissimus dorsi muscles) are also weak and atrophic early in the course. Weakness of these muscles lead to upward and lateral rotation of the shoulder blades with scapular winging and the appearance of a "trapezius hump," which often is mistaken for muscle hypertrophy (Fig. 24–15). Although the deltoids are relatively spared during the early course of the disease, the sternocostal head of the pectoralis major is often atrophic and weak.

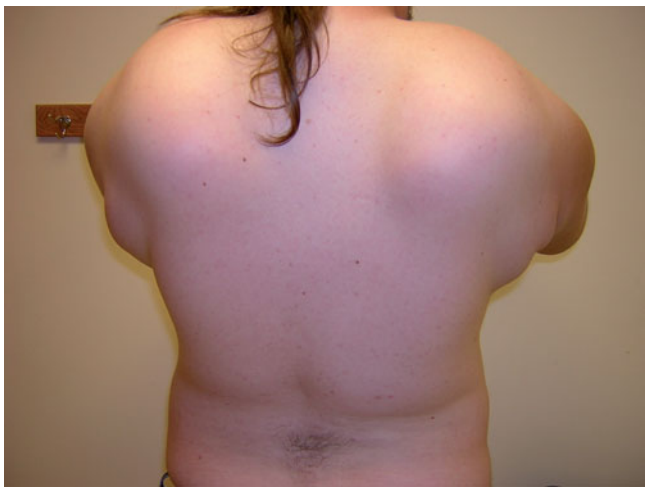


Figure 24–15. Facioscapulohumeral muscular dystrophy (FSHD). Characteristic appearance of a patient diagnosed with FSHD. On attempted forward flexion of the arms at the shoulders the scapulae elevates and laterally deviates off the posterior rib cage under the trapezius musculature, giving the false impression of very muscular individual. Palpation reveals the bone underlying the muscle tissue.

The clavicles are displaced more horizontally and may angle downward from the sternum to the upper arm. Combined with the internal rotation of the upper arms, the anterior axillary folds, which are normally vertical, become horizontally displaced. There are also significant weakness and atrophy of the biceps brachii and triceps, with relatively normal bulk of the forearm muscles producing the so-called "Popeye arms." Wrist extensors are weaker than wrist flexors. The characteristic facial and upper torso appearance led to the designation of "facioscapulohumeral" muscular dystrophy. Some patients with FSHD manifest only with scapular winging or a limb-girdle pattern of weakness, thus mimicking an LGMD.[192] Further, there can be striking asymmetric and sometimes unilateral involvement of the facial, scapular stabilizers, or humeral muscles.

The tibialis anterior is usually the earliest lower limb muscle to manifest weakness, and occasionally patients present with foot drop.[191] The gastrocnemius muscles are usually normal, although rare patients manifest with difficulty walking on their toes.[191] The muscle involvement may progress to the pelvic musculature, producing a hyperlordotic posture and a waddling gait. As in the face and arms, weakness in the legs is often asymmetric. Approximately 20% of patients with FSHD eventually will require wheelchairs.

Abdominal muscles may also be involved, producing a positive Beevor sign (the umbilicus may move up or down a few centimeters when the patient is supine and attempts to flex the head because of upper or lower abdominal muscle weakness). Sensation is intact to all modalities, and the reflexes are usually absent or diminished commensurate with the degree of muscle wasting.

Some patients with FSHD appear to experience a late exacerbation of muscle weakness. They may only have mild weakness for years and then suddenly have a marked increase of weakness in the typical distribution over the course of several years. Affected individuals usually have a normal life span; however, severe progressive respiratory muscle weakness has been reported in approximately 1% of large series of patients with FSHD.[193] Severe extremity weakness, wheelchair dependency, and kyphoscoliosis appear to be risk factors for respiratory failure. Further, rare patents develop cardiac involvement manifesting as conduction defects, supraventricular, or ventricular arrhythmias that may require pacemaker implantation.[194]

Infantile-onset FSHD is associated with severe weakness presenting in the first 2 years of life.[185,195] A wheelchair is required to maintain mobility by the time the patient is 9 or 10 years of age. Another form of FSHD involves a combination of facioscapulohumeral weakness, profound sensorineural hearing loss, and retinal telangiectasias (Coats' disease). Some infants present with profound facial diplegia mimicking Mobius syndrome.[196]

Laboratory Features

Serum CK levels normal or moderately elevated.

Histopathology

The muscle biopsy demonstrates variation in muscle fiber size with atrophic and hypertrophic fibers, scattered necrotic and regenerating fibers, increased internalized nuclei, and increased endomysial connective tissue.[195] Prominent mononuclear inflammatory infiltrate may be appreciated in the endomysium, which can lead to confusion with polymyositis (Fig. 24–16).[197] Immunostaining with antibodies directed against membrane attack complex may demonstrate deposition on the sarcolemma of non-necrotic muscle fibers.[198]

Molecular Genetics and Pathogenesis

The pathogenesis of FSHD is unknown. FSHD is an autosomal-dominant disorder linked to the telomeric region of chromosome 4q35 (Fig. 24–17).[185,186,199] However, approximately 3% of kinships do not map to this area, suggesting genetic heterogeneity.[200,201] An *Eco*RI polymorphism in this region is present on chromosome 4q35 in the majority of patients with FSHD.[185,186] This *Eco*RI polymorphism is variable in size but is reduced compared to normal (FSHD 10–30 kB; normal 50–300 kB). Within this *Eco*RI polymorphism lies a tandem array of 11–100 *Kpn*I units, each 3.3 Kb in size, which is

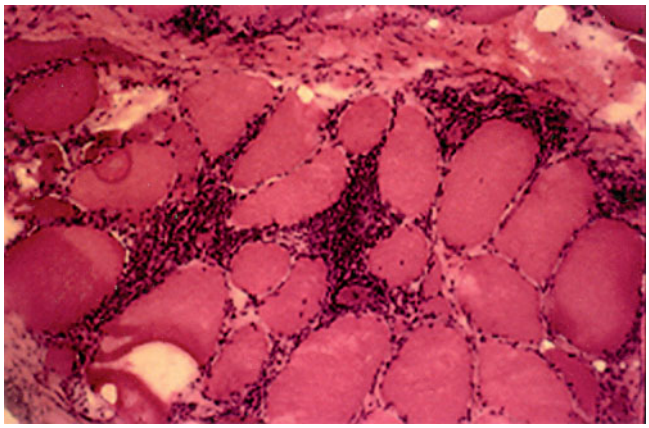


Figure 24–16. Facioscapulohumeral muscular dystrophy. Muscle biopsy demonstrates prominent inflammation (H&E). Physicians need to be aware that such prominent inflammation can be present in muscular dystrophies and can occasionally be misdiagnosed as an inflammatory myopathy (e.g., polymyositis). The inflammatory cells present in the dystrophic muscle usually do not invade non-necrotic muscle fibers, in contrast to the invasion of non-necrotic muscle fibers seen in polymyositis and inclusion body myositis.

termed D4Z4.[186] Most patients with autosomal-dominant FSHD carry one array of one to 10 units. It is this decrease in the number of these KpnI units or 3.3 kB repeats that result in the decreased size of the FSHD-associated polymorphism.

Another interesting observation is the allelic variation of chromosome 4qter, designated 4qA and 4qB, which differ by a few insertion/deletion events in the region distal to D4Z4.[186] The 4qA allele contains a block of beta-satellite DNA directly distal to D4Z4 on 4qA, which is not present on the 4qB allele. Although occurring in similar frequency in the normal population, FSHD-causing mutations are associated exclusively in the 4qA type of allele. Similar reductions in D4Z4 in 4qB alleles are nonpathogenic or have a highly reduced penetrance.

There is an inverse correlation between the size of the D4Z4 repeat unit and the severity of the disease.[202,203] Patients carrying one to three units are usually severely affected and often represent isolated (de novo mutations) cases, whereas patients carrying four to 10 units typically have an affected parent.[185]Anticipation phenomena may occur in some families, although the size of the mutation appears stable and there can be extreme variability in phenotype even within families.[203]

The mutation in FSHD is unlike other described genetic disorders, in which anticipation is associated with an increased size of a polymorphic trinucleotide repeat mutation. FSHD may result from the inappropriate overexpression of certain genes, rather than the absence or underexpression of genes, as in most dystrophies. The D4Z4 region normally contains a multiprotein complex that includes a transcriptional repressor whose deletion leads to inappropriate overexpression in FSHD skeletal muscle of 4q35 genes located upstream of D4Z4.[204] Amongst the genes that are overexpressed are *FRG1* (FSHD Region Gene 1), *FRG2* (FSHD Region Gene 2), or *ANT1* (adenine nucleotide translocator 1). Gabellini and colleagues made transgenic mice selectively overexpressing, in skeletal muscle, the 4q35 genes *FRG1*, *FRG2*, or *ANT1*.[205] They demonstrated that *FRG1* transgenic mice develop a muscular dystrophy, while *FRG2* and *ANT1* transgenic mice appeared normal. *FRG1* encodes a nuclear protein that localizes in nucleoli, speckles, and Cajal bodies and may be involved in premessenger RNA splicing. In this regard, in muscles of FRG1 transgenic mice and patients with FSHD, specific pre-mRNAs undergo aberrant alternative splicing. Their results suggest that FSHD results from inappropriate overexpression of *FRG1* in skeletal muscle, which leads to abnormal alternative splicing of specific pre-mRNAs.[205] However, not all studies have confirmed increase of *FRG1* in *FSHD*. Further, the degree of overexpression of *FRG1* required to produce a myopathy in these transgenic mice was much greater than seen in humans with FSHD.

Diagnosis

The diagnosis of FSHD is usually apparent on clinical grounds. Genetic testing is particularly useful for confirmation in patients without family history or unusual clinical phenotypes as well as for genetic counseling, genetic testing is very useful. As noted previously, over 95% of patients have deletions in D4Z4 region. False positives may result from rare, nonpathogenic contractions on 4qB or complex 4q–10q rearrangements and false negatives from deletions that extend to involve the p13E–11 probe.[186]

Treatment

A small open-label pilot study of prednisone 1.5 mg/kg/d for 12 weeks resulted in no significant improvement in strength or muscle mass.[190] An open-label trial of albuterol in 15 patients with FSHD for 3 months demonstrated increased lean body mass and muscle strength.[206] However, a subsequent larger, longer, double-blinded, placebo-controlled study of albuterol revealed no clear benefit.[207] Modest improvement in strength has been reported in a small number of patients with FSHD treated with short courses of creatine monohydrate (5–10 g/d).

Surgery to fix the scapula to the thorax, thereby increasing range of motion, is beneficial in some patients.[208,209] However, they need to have sufficient strength of the deltoid muscles in order to benefit from the procedure. Ankle–foot orthotics are useful in patients with foot drop secondary to tibialis anterior and peroneal muscle weakness.

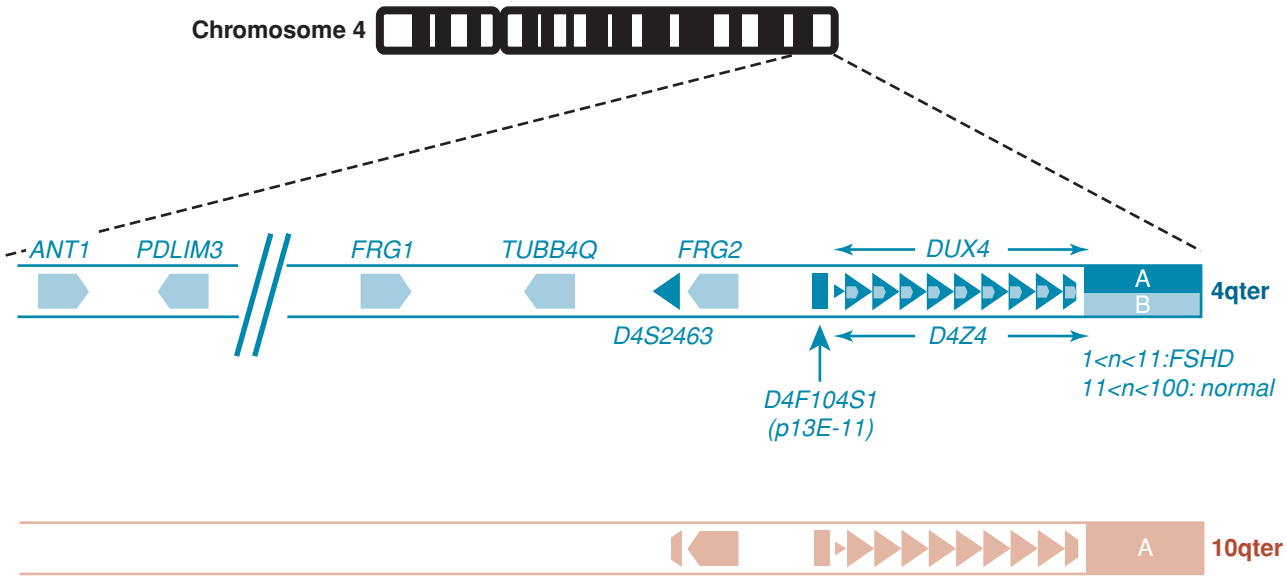


Figure 24–17. Schematic representation of the facioscapulohumeral muscular dystrophy (FSHD) locus. The polymorphic D4Z4 repeat array (arrowheads) in the subtelomere of chromosome 4 (blue) can vary between 11 and 100 units in the healthy population. One inversed copy of D4Z4 (D4S2463) is located 37 Kb proximally. Just preceding the D4Z4 repeat unit, probe p13E-11 (D4F104S1), used in the DNA diagnosis of FSHD, is situated. Within each unit, a putative open reading frame designated DUX4 (block arrow) is located, but expression of this gene has never been established. In a proximal direction, several additional genes have been identified (block arrows) including *FRG2*, *TUBB4Q* (a pseudogene), and *FRG1*. At a much larger distance, several other genes have been evaluated for their involvement in FSHD. Most notably, these include *ANT1* and *PDLIM3*. Distal to D4Z4, two allelic variants of 4qter have been identified: 4qA (dark blue) and 4qB (light blue). Both variants are almost equally common in the population and vary by a few insertion and deletion events. FSHD alleles are exclusively linked with the 4qA variant. The subtelomere of chromosome 10q is similarly organized as 4q due to an ancient duplication of the 4q subtelomere. The homology between 4qter and 10qter extends from the telomere to 40 kb proximally to D4Z4 within an incomplete inverted copy of D4Z4. In contrast to 4qter, there is no B variant of the 10q subtelomere. (With permission from Tawil R, Van Der Maarel SM. Facioscapulohumeral muscular dystrophy. Muscle Nerve 2006;34(1):1–15.)

SCAPULOPERONEAL MUSCULAR DYSTROPHY

Clinical Features

Patients with scapuloperoneal muscular dystrophy manifest with foot drop followed by scapular weakness within the first two decades of life.[210–215] Weakness is often asymmetric, and patients sometimes are misdiagnosed as having a peroneal neuropathy. A few patients may demonstrate a compensatory hypertrophy of the extensor digitorum brevis, perhaps because of attempting to dorsiflex the foot with this muscle. Ankle contractures are prominent features of the disease secondary to the weak anterior compartment muscles. The weak scapular muscles result in an appearance of the shoulder-girdle similar to that seen in FSHD. However, unlike FSHD, the humeral musculature is usually relatively spared. On the other hand, the peroneal muscles are more severely affected in scapuloperoneal muscular dystrophy compared to FSHD. Rarely, some patients may manifest mild weakness of the facial muscles, creating a diagnostic confusion with FSHD. However, facial muscle weakness is usually much less prominent than that seen in FSHD. Muscle weakness is slowly progressive.

Laboratory Features

The serum CK levels can be normal or moderately abnormal. The motor and sensory nerve conductions are normal aside from a reduced CMAP in the more severely affected muscles.[211,212,214,216] Needle electromyography may demonstrate sparse fibrillation potentials and myopathic units.

Histopathology

Muscle biopsies reveal nonspecific myopathic features including fiber size variation with atrophic and hypertrophic fibers, split fibers, necrotic and regenerating fibers, and increased endomysial connective tissue.[214,216,217] Some biopsies demonstrate inclusions typical of MFM.[215]

Molecular Genetics and Pathogenesis

Scapuloperoneal muscular dystrophy is an autosomal-dominant disorder. There is no linkage to chromosome

4q35 in scapuloperoneal muscular dystrophy; therefore, the disorder is not allelic to FSHD.[217] The kinship originally described by Kaeser[212] has been found to be caused by mutations in the desmin gene on chromosome 2q35 and is thus a form of MFM (discussed later). Another family with scapuloperoneal syndrome and cardiomyopathy has been linked to chromosome 12.[215]

Treatment

There are no reported studies regarding medical therapy in scapuloperoneal muscular dystrophy. Hopefully, studies being performed on patients with DMD and FSHD will apply to those with scapuloperoneal muscular dystrophy. Ankle–foot orthoses are beneficial in patients with ankle dorsiflexor weakness. Surgery to stabilize the scapula may improve arm function in some patients.

X-LINKED EDMD

Clinical Features

EDMD is characterized by (1) early contractures of the Achilles' tendons, elbows, and posterior cervical muscles; (2) slowly progressive muscle atrophy and weakness, with a predominantly humeroperoneal distribution in early stages; and (3) cardiomyopathy with conduction defects.[49,218–220] Prominent contractures are evident in early childhood or in the teenage years, with an inability to fully extend the elbows secondary to elbow flexion contractures (Fig. 24–18). Patients may toe walk due to early heal cord contractures. There is reduced mobility of the spine such that EDMD is in the differential diagnosis of the so-called "rigid spine syndrome."[221] Patients have difficulty flexing their neck and trunk. Importantly, the contractures of the Achilles' tendons, elbows, and paraspinal muscles are evident before there is any significant weakness, which helps distinguish EDMD from other the types of dystrophies associated with contractures.

Patients with EDMD usually appear normal at birth. Some children develop mild weakness. The characteristic pattern of muscle involvement helps distinguish EDMD from most other forms of dystrophy. There is an early predilection for weakness and atrophy affecting the humeroperoneal muscles (i.e., biceps brachii, triceps, anterior tibial, and peroneal muscles). Pes cavus deformities of the feet are common. Weakness is slowly progressive, and eventually the shoulder- and pelvic-girdle muscles can become involved. Most affected individuals are able to ambulate into the third decade. Unlike many of the LGMDs, which it may be confused with, there is no calf hypertrophy. Muscle stretch reflexes are diminished or absent early in the disease.

Importantly, EDMD is associated with potentially lethal cardiac arrhythmias by the end of the second or beginning of the third decade. Conduction defects range from first-degree A-V block to complete heart block. Syncope and sudden cardiac death can occur. Although female carriers do not manifest muscle weakness or contractures, they may develop the cardiopathy.

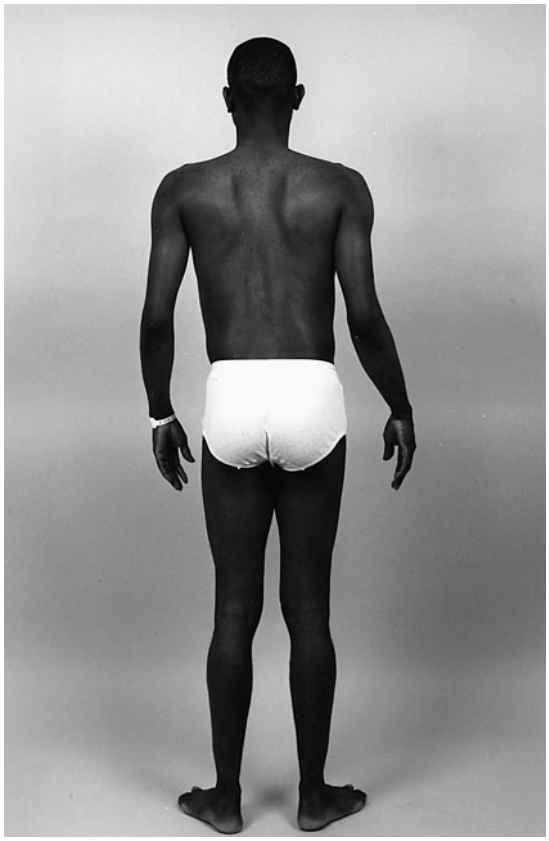


Figure 24–18. Emery–Dreifuss muscular dystrophy (EDMD). Posterior view of a patient with EDMD demonstrate atrophy of the triceps musculature, left more than right, and early contractures of the elbows (patient is unable to straighten the arms down at the side). There is also mild scapular winging.

Laboratory Features

The serum CK levels may be normal or moderately elevated. EKG frequently reveal sinus bradycardia, prolongation of the PR interval, or more severe degrees of conduction block. Motor and sensory nerve conduction studies are typically normal in these patients. EMG reveals myopathic MUAPs.

Histopathology

The muscle biopsy findings can be quite varied, depending on the degree of weakness of the biopsied muscle.[222] There is usually muscle fiber size variation with type 1 fiber atrophy. There can be a predominance of either type 1 or type 2 muscle fibers. Muscle fiber splitting, increased central nuclei, and endomysial fibrosis may be seen. Immunohistochemistry reveals the absence of emerin as well as abnormal lamin A/C and lamin B2 on the nuclear membrane.[24,25] Ultrastructural

studies demonstrate the focal absence of peripheral heterochromatin in areas between the nuclear pores, irregular and uniform thickening of the nuclear lamina, and compaction of heterochromatin in areas of irregular thickening of the nuclear lamina and areas where the peripheral heterochromatin does not adhere to the nuclear lamina.[25] Diagnosis can be confirmed by immunostaining muscle or skin tissue for emerin or by immunoblot analysis of leukocytes.

Molecular Genetics and Pathogenesis

EDMD is caused by mutations in a gene (*STA*) located on chromosome Xq28, which encodes for emerin (Table 24–1).[223] Emerin is located on the inner nuclear membranes of skeletal, cardiac, and smooth muscle fibers as well as skin cells.[23,24] Its carboxy-terminal tail anchors the protein to the inner nuclear membrane, while the remainder of the protein projects into the nucleoplasm. Emerin is a member of the nuclear LAP family.[23–25] The nuclear lamina is composed of intermediate-sized filaments (e.g., lamins A, B, and C) associated with the nucleoplasmic surface of the inner nuclear membrane. These lamins bind to various LAPs, including LAP1, LAP2, and lamin B receptor, which are located on the inner nuclear membrane. LAP2, lamin B receptor, and the lamins also bind to chromatin and thereby promote its attachment to the nuclear membrane. Mutations in emerin conceivably lead to disorganization of the nuclear lamina and heterochromatin that is apparent on EM and immunohistochemistry.[25]

Treatment

We obtain yearly electrocardiograms on all our patients (as well as on possible female carriers) and obtain 24-hour Holters and cardiology consultations on those with significant abnormalities (e.g., atrioventricular block) or cardiac symptoms. Affected individuals may require pacemakers, and some authorities have even recommended prophylactic pacemakers.[222] Physical therapy is aimed at minimizing contractures.

AUTOSOMAL-DOMINANT EDMD2/LGMD 1B

The clinical, laboratory, and histopathological features of this LGMD 1B are identical to those described above for typical X-linked EDMD1, except for autosomal-dominant inheritance and equal frequency of affected females.[27,28,89] Thus, as noted previously, autosomal-dominant EDMD2 and LGMD 1B are allelic disorders caused by mutations in the lamin A/C gene (*LMNA*) located on chromosome 1q11–23.[27,80,89,224] Mutations in the rod domain of *LMNA* cause hereditary dilated cardiopathy and conduction defects with or without an underlying skeletal muscle involvement.[27,28,89,225] De novo mutations are responsible for 76% of cases; therefore, mutations in *LMNA* should be considered in all familial and sporadic cases of EDMD and familial dilated cardiopathy.[27] Marked variability in the clinical phenotype can be seen within and between families with specific mutations in the *LMNA* gene.

Lamins A and C are produced by alternative splicing of the lamin A/C RNA transcript. As discussed in the Pathogenesis discussion regarding X-linked EDMD, these lamins are important in the organization and integrity of the nuclear membrane. Muscle biopsies demonstrate variation in fiber size, increased endomysial connective tissue, normal emerin expression, and usually normal lamin A/C expression. EM reveals nuclear alterations similar to X-linked EDMD in 10% of muscle fibers.[23,26] There are loss of peripheral heterochromatin or detachment from the nuclear envelop, alterations in interchromatin texture, and fewer nuclear pores compared to normal.

AUTOSOMAL-RECESSIVE EDMD3

Clinical Features

This is a rare autosomal-recessive muscular dystrophy, with contractures and severe rigidity of the spine reported in five unrelated children (three boys and two girls).[226] Onset was in the first 2 years of life, and the children were unable to walk by the age of 8 years. However, they had no cardiac abnormalities.

Laboratory Features

Serum CK was moderately elevated.[226]

Histopathology

Muscle biopsies revealed nonspecific dystrophic changes with normal expression of emerin, dystrophin, the sarcoglycans, and laminins α2, α5, β1, γ1 chains.[226]

Molecular Genetics and Pathogenesis

Autosomal recessive EDMD is also caused by mutations in LMNA.

OTHER EDMD

In over 60% patients with EDMD do not have mutations in the genes encoding emerin or lamin A/C (Zhang et al., 2007). Recently, mutations were identified in genes that encode for nesprin-1 and -2, in several sporadic cases and autosomal dominant families with EDMD-like phenotypes (Zhang et al., 2007). Nesprin-1 and -2 (*n*uclear *e*nvelope *sp*ectrin *r*epeat proteins) are spectrin-repeat containing proteins that are anchored in the outer and

inner nuclear membranes. Nesprin-1 and 2 are transcribed from two genes, *SYNE1* on chromosome 6q24 and *SYNE2* on chromosome 14q23. Nesprin-1 and -2 bind actin and both emerin and lamins A/C, thereby linking the nuclear lamina with the actin cytoskeleton.

BETHLEM MYOPATHY

Clinical Features

This disorder is an allelic and mild variant of UCMD discussed previously, and the clinical features are very similar to EDMD.[227–234] Bethlem myopathy is an autosomal dominant disorder. Onset is usually at birth or early childhood. Decreased fetal movements may be noted in utero, and neonates may demonstrate generalized hypotonia. Motor milestones are often delayed but are reached. However, weakness may not be evident until early adulthood. Variability in the age of onset and in clinical severity may even be seen within affected family members. There is proximal greater than distal muscle weakness, with the legs being more severely affected than the arms. Extensor muscles are weaker than flexor muscles. There can be mild neck and trunk involvement, but cranial muscles are spared. Muscle strength can be asymmetric. Calf hypertrophy may be seen. As in EDMD, contractures at the elbows and ankles are evident early in the course before any significant weakness manifests. Eventually, contractures develop in the wrists and fingers. Some patients manifest with only proximal hip- and shoulder-girdle weakness without evidence of contractures, thus resembling an LGMD. Muscle stretch reflexes may be normal or reduced.

Until recently, it was thought that the heart was spared in Bethlem myopathy—a feature that might help distinguish it from EDMD. However, a recent study of patients with Bethlem myopathy revealed that eight of 74 had abnormal EKG, four of 24 had abnormal Holter, and six of 51 had abnormal echocardiogram.[233] Abnormalities include atrial fibrillation, accelerated atrial rhythm, intraventricular conduction delay, right bundle branch, and pathological Q waves in lead V1, V6 and AVL and V6, and atrial dilatation. Thus, it appears that detailed cardiac investigations in Bethlem myopathy do reveal abnormalities in 10% of cases. However, the relationship of these cardiac abnormalities to Bethlem myopathy still remains to be established.

Ventilatory muscles appear to be involved in Bethlem myopathy and seems to be related to more severe weakness.[233] Pulmonary investigations performed in 56 patients revealed reduced vital capacity below 50% in five patients and 11 patients had vital capacities between 50% and 70%.[233] Two patients were on respiratory support. Others have also reported progressive respiratory insufficiency due to diaphragm muscle involvement.[230]

Laboratory Features

Serum CK is normal or mildly elevated. Cardiac studies (e.g., EKG, Holter monitor, and echocardiogram) may be abnormal as discussed in the previous section. Motor and sensory nerve conduction studies are normal. Insertional and spontaneous activity is usually normal on EMG, although a mixture of small-amplitude, short-duration polyphasic MUAPs with large-amplitude, long-duration MUAPs can be seen.[229,230]

Histopathology

Muscle biopsies demonstrate nonspecific myopathic features. There is variability in fiber size, increased splitting and central nuclei, and mild endomysial fibrosis. Lobulated type 1 fibers and moth-eaten fibers may be apparent on NADH-TR stains.

Molecular Genetics and Pathogenesis

Bethlem myopathy has been linked to dominant heterozygous mutations of the genes (COL6A1, COL6A2, and COL6A3) encoding for the α1 and α2 subunits of collagen VI located on chromosome 21q and α3 subunit of collagen VI located on 2q37.[160,232,235] Collagen VI bridges the extracellular matrix with the sarcolemma. Interestingly, compound heterozygous mutations have been defined in the COL6A2 and COL6A3 genes in the more severe UCMD (see the section on "Congenital Muscular Dystrophies").[160] Collagen VI deficiency in muscle or cultured fibroblasts was complete in the severe cases and partial in the milder ones, which suggests a correlation between the degree of collagen VI deficiency and the clinical severity in UCMD.[161]

Treatment

Physical therapy is indicated to prevent progressive contractures that can impair mobility and function.

BENT SPINE/DROPPED HEAD SYNDROME

Clinical Features

Neck extensor weakness can be an early and prominent manifestation of several disorders, in particular myasthenia gravis and amyotrophic lateral sclerosis.[236] However, there are a number of patients with weakness that remains restricted to the cervical and, sometimes, also to the thoracic and paraspinal muscles.[236–239] Onset of neck extensor weakness usually begins after 60 years of age leading to progressive head drop. Involvement of the thoracic paraspinal muscles leads to severe kyphosis or the bent spine posture upon standing. When patients are supine, their posture is normal, in contrast to

patients with fixed contractures of the spine. Weakness may remain clinically isolated to the neck extensors even for several years, although there may be subclinical (radiographic or electromyographic) evidence of disease in the upper thoracic paraspinal muscles. In addition, mild shoulder girdle may also develop. A family history of bent spine syndrome has been described in two distinct kinships.[238] Both cases involved a mother and a daughter (in one case two daughters were affected).

Laboratory Features

Serum CK is usually normal or only mildly elevated. Monoclonal gammopathy may be seen in cases of sporadic late-onset nemaline myopathy, which can occasionally present with a neck extensor myopathy.[240] CT and MRI of the low cervical and upper thoracic spine reveal atrophy and fatty or edematous changes in the paraspinal muscles (see Chapter 2, Figure 2-22A and B). Motor and sensory nerve conduction studies are normal. EMG reveals fibrillation potentials and positive sharp waves in cervical and thoracic paraspinals.[236,238] Short-duration, small-amplitude MUAPs with early recruitment are seen in the cervical and thoracic paraspinal muscles. EMG of the arms and legs is typically normal.

Histopathology

Muscle biopsies of the cervical paraspinal muscles demonstrate nonspecific myopathic features including fiber size variability in fiber size with atrophic and hypertrophic muscle fibers, increased internalized nuclei, fiber splitting, moth-eaten fibers, fibers with rimmed vacuoles, and increased endomysial connective tissue. Rare cases with endomysial inflammation have been reported.[241,242] Biopsies of proximal limb muscles may be normal or may demonstrate similar, but less prominent, abnormalities. Ragged red fibers and cytochrome C oxidase (COX)-negative fibers suggestive of mitochondrial dysfunction are not uncommon but may be age related. Late-onset nemaline myopathy can occasionally present initially as a head drop.[240]

Pathogenesis

Isolated neck extensor myopathy may just represent a "forme fruste" of the bent spine syndrome. The pathogenesis is unknown. In some cases, the myopathy may be the result of a monophasic inflammatory process restricted to the paraspinal muscles.[237] We suspect that in most cases this disorder represents a regional form of muscular dystrophy that predominantly affects the paraspinal muscles. Rarely, dysferlinopathies can present with a paraspinal myopathy that may potentially explain some cases of bent spine syndrome. Myotonic dystrophies may also rarely manifest initially with head drop.

Treatment

Immunosuppressive therapy and pyridostigmine are not typically beneficial. However, improvement with corticosteroid and azathioprine[237,241] or intravenous immunoglobulin[242] has been reported in rare patients. Cervical collars may help stabilize the head drop.

OCULOPHARYNGEAL MUSCULAR DYSTROPHY

Clinical Features

Oculopharyngeal muscular dystrophy (OPMD) is an autosomal-dominant disorder, which usually presents in the fourth to sixth decade of life with increasing ptosis.[243,244] The ptosis is almost always bilateral but can be asymmetric. The extraocular muscles are involved in approximately 50% of patients, yet double vision is uncommon. The pupils are spared. Approximately one-fourth of patients manifest initially with dysphagia, which is slowly progressive and lead to severe weight loss and aspiration.[244] Facial and masticatory muscles may be slightly weak in some patients. The gag reflex is impaired. Laryngeal involvement can also develop, resulting in dysphonia.

Some patients develop slight weakness of the neck and proximal limbs. Distal muscles may also occur, particularly in the distal oculopharyngeal dystrophy variant (see below). Sensation is normal, but muscle stretch reflexes can be reduced or absent. Life span is not altered.

Laboratory Features

Serum CK levels are normal or only mildly elevated. Swallowing studies demonstrate impaired pharyngeal and esophageal motility.

Histopathology

The muscles most severely affected are the extraocular and pharyngeal muscles, although minor abnormalities may be detectable in the limb muscles in advanced cases. Muscle biopsies reveal variation in fiber size, degenerating and regenerating fibers, increased internal nuclei, and an increase in adipose and endomysial connective tissue.[243,244] Rimmed vacuoles similar to those found in inclusion body myositis/myopathy and some of the distal myopathies are often, although not universally, observed. On EM, intranuclear inclusions are evident in up to 9% of muscle nuclei.[245] These tubulofilamentous inclusions have an outer diameter of approximately 8.5 nm and an inner diameter of 3 nm, are up to 0.25 μm in length, and are often arranged in tangles or palisades.[245] In addition, 15–18-nm tubulofilaments may be evident in the cytoplasm, as seen in inclusion body myositis, hereditary inclusion body myopathy, and some of the distal

myopathies. OPMD can be distinguished from various mitochondrial myopathies, which can also cause ptosis and ophthalmoparesis, by the lack of ragged red fibers. However, there have been a few cases of OPMD with abnormal mitochondrial structure and quantity on EM, although these findings, for the most part, are suspected to be age related. Further, muscle biopsies of pharyngeal muscles (taken at time of cricopharyngeal myotomy-anecdotal observations) reveal more severe abnormalities along with frequent rimmed vacuoles, ragged red fibers, and nemaline rods. Sural nerve biopsy in a few patients revealed a mild reduction in myelinated and unmyelinated nerve fibers; however, this could a confounding variable related to the patients' advanced ages.

Molecular Genetics and Pathogenesis

OPMD is caused by expansions of a short GCG repeat within the poly(A) binding protein nuclear (PABN1) gene on chromosome 14q11.1 (Table 24–1).[243–246] Normally, there are six GCG repeats encoding for a polyalanine tract at the N terminus of the protein, but approximately 2% of the population has polymorphism with seven GCG repeats (GCG).[7] In OPMD, there is an expansion to eight to 13 repeats (GCG).[8–13] These expansions are meitotically stable, explaining the lack of anticipation phenomena form one generation to the next. Patients who are homozygous for (GCG) expansions may manifest at an earlier age and have more severe weakness. Also, patients who are heterozygous for $(GCG)^{8–13}$ and the $(GCG)^{7}$ polymorphism are also more severely affected. Interestingly, a late-onset, autosomal-recessive form of OPMD can develop in patients who are homozygous for the $(GCG)^{7}$ polymorphism. The PABPN1 $(GCG)^{7}$ allele was the first example of a polymorphism that could act as a modifier of a dominant phenotype or as a recessive mutation.

PABPN1 is found mostly in dimeric and oligomeric forms with the nuclei (Fig. 24–2).[247,248] PABPN1 is involved in polyadenylation of mRNA and is adjoined to the polyadenylated mRNA complex for transport through the nuclei pores into the cytoplasm. In the cytoplasm, the PABPN1 detaches from the mRNA. The mRNA is translated into protein and the PABPN1 is actively transported back into the nuclei. The expansion of the GCG repeats probably results in abnormal folding of the polyalanine domains of PABPN1. The misfolded proteins are ubiquinated but are resistant to nuclear proteosomal degradation. The mutated PABPN1 oligomers then accumulate as the 8.5-nm intranuclear tubulofilamentous inclusions apparent on EM.[246–248] The more severe clinical phenotypes are associated with a large number of myonuclei containing intranuclear inclusions.[245] The aggregation of mutated PAPBN1 may lead to disruption of various nuclear or cytoplasmic processes leading to cell death.

Treatment

Noninvasive therapies include the use of eyelid crutches on glasses or even taping the eyelids. Ptosis surgery can also be performed if patients have sufficient orbicularis oculi strength to allow complete closure of the eyelids postoperatively. There is the risk of corneal abrasions and keratitis if the eyelids cannot close completely. Cricopharyngeal myotomy may be beneficial in patients with dysphagia. Patients with severe dysphagia resulting in aspiration or significant weight loss require percutaneous endogastric tube placement.

VARIANTS OF OPMD

There are a few genetically distinct variants of OPMD. Infantile or early childhood onset of ptosis, ophthalmoparesis, and severe generalized weakness with respiratory failure has been reported.[244] Another variant of OPMD is oculopharyngodistal myopathy. Most of the reports of oculopharyngodistal myopathy have come from Japan,[249,250] although the myopathy occurs in other ethnic groups.[251,252] Weakness develops earlier than classic OPMD, with onset in the first decade of life in some cases. We have seen a patient with distal OPMD and chronic intestinal pseudo-obstruction.[251]

The laboratory, histologic, and electrodiagnostic features of these variants are, for the most part, indistinguishable from OPMD. Intranuclear inclusions similar to OPMD may be found. Whether or not these variants have mutations in the PABPN1 gene remains to be determined. Mutations in the PABPN1 gene were not identified in one family with atypical OPMD (early onset in second–third decade, elevated serum CK, and profound ophthalmoplegia).[244]

DISTAL MYOPATHY/MUSCULAR DYSTROPHY

Although distal weakness is often presumed to be neuropathic in etiology, a variety of neuromuscular disorders, including myopathies, are associated with distal extremity weakness (Table 24–1).[253,254] The distal myopathies are characterized clinically by progressive atrophy and weakness of distal arm or leg muscles and histologically by nonspecific myopathic features on muscle biopsy. We consider the distal myopathies to be forms of muscular dystrophy. Advances in the molecular genetics of these disorders support this notion, as some types of distal myopathy have been found to be allelic with specific types of LGMD (tibial myopathy and LGMD 2J caused by titin mutations and Miyoshi myopathy and LGMD 2B caused by dysferlin mutations). Furthermore, there is a clear overlap of some distal myopathies with some forms of hereditary inclusion body myopathy and myofibrillar myopathy. The distal myopathies can be subdivided,

based on the clinical features, age of onset, CK levels, muscle histology, and mode of inheritance.

WELANDER DISTAL MYOPATHY

Clinical Features

Welander originally described the features of this autosomal dominant myopathy in a report of 249 cases from 72 Scandinavian families.[255] Onset of weakness usually begins in the fifth decade of life, with rare cases beginning before the age of 30 years (mean age of onset 47 years, range 20–77 years). Weakness is usually first noted in the wrist and finger extensors and slowly progresses to involve the affecting the distal lower limbs—ankle dorsiflexors more than the plantar flexors.[255–257] However, in approximately 10% of cases, weakness is initially appreciated in the legs or there is simultaneous involvement of the distal arms and legs. Although the extensor muscle groups are more severely affected, the flexor groups are involved in over 40% of cases. Rarely, proximal muscles become weak. Sensation is usually normal. Muscle stretch reflexes are initially preserved, but the brachioradialis and Achilles' reflexes diminish or disappear over time.

Laboratory Features

Serum CK levels are usually normal or only minimally abnormal.[57] Motor and sensory nerve conduction studies are usually normal for age. Diminished temperature and vibratory perception quantitative sensory testing has been demonstrated in some patients.[256–258] Needle EMG evaluation demonstrates early recruitment of small-amplitude, short-duration MUAPs.[256–258] Quantitative EMG further suggests a myopathic process.[256]

Histopathology

Muscle biopsies demonstrate variability in fiber size, increased central nuclei, split fibers, and increased endomysial connective tissue and adipose cells in longstanding disease.[256–261] Furthermore, rimmed vacuoles typical of IBM, h-IBM, and OPMD are seen in scattered muscle fibers. EM also reveals 15–18-nm cytoplasmic and nuclear filaments similar to those observed in IBM, h-IBM, and OPMD. In addition, disruption of myofibrils and accumulation of Z-disk-derived material similar to that found in MFM can also be demonstrated. Nerve biopsies may reveal a moderate reduction of mainly small-diameter, myelinated fibers.[258]

Molecular Genetics and Pathogenesis

The pathogenesis of Welander distal myopathy is unknown. It has been linked to chromosome 2p13; the gene has not been identified.

UDD DISTAL MYOPATHY

Clinical Features

This autosomal dominant distal myopathy usually presents after the age of 35 years, with weakness of the anterior compartment of the lower legs resulting in unilateral or bilateral foot drop.[139,262–269] The disorder is slowly progressive, beginning in the toe extensors and gradually involving anterior tibial muscles. Occasionally, the proximal legs and distal upper limbs (predominately the hand intrinsics and wrist extensors) are affected. Rarely, the arms are affected more than the legs, posterior calves are involved with sparing of the anterior tibial muscles, or patients have a limb-girdle distribution of weakness.[139] Facial muscles are usually spared, although bulbar weakness has been reported. Sensation is normal. Achilles' tendon reflexes are usually reduced.

Laboratory Features

Serum CK is normal or only slightly elevated.[139,262–269] Motor and sensory nerve conduction studies are normal. EMG of affected muscles reveals fibrillation potentials and positive sharp waves as well as small-amplitude, brief-duration MUAPs that recruit early.[262,266,268]

Histopathology

Muscle biopsies reveal nonspecific myopathic features similar to that seen in Welander myopathy.[262,266,268]

Molecular Genetics and Pathogenesis

Mutations in the gene that encode for titin on chromosome 2q31–33 have been identified.[139,270] The disorder is allelic to LGMD 2J. Why dominant mutations in the titin gene typically lead to a late onset distal myopathy while recessive mutations usually result in early onset LGMD 2J is not clear. A confounding factor is the variability of clinical phenotype sometimes seen even within families. The giant protein titin (also known as connectin) is attached to the Z-disk and spans from the M- to the Z-line of the sarcomere. Titin serves to connect the myosin filaments to the Z-disk and probably plays an important role in myofibrillogenesis.

MARKESBERY-GRIGGS DISTAL MYOPATHY

This is another late-onset, autosomal-dominant distal myopathy, typically beginning in the anterior compartment of the legs.[271] Some patients develop proximal leg and distal arm weakness (wrist and finger extensors) as well. Cardiomyopathy is very common. Serum CK is usually mildly elevated, and EMG reveals an irritative myopathy. Muscle biopsies demonstrate rimmed vacuoles and features of myofibrillar myopathy (MFM). Because

some of the clinical and laboratory features are similar to Udd distal myopathy, they were once thought to be allelic disorders. However, mutations have recently been identified in the gene that encodes ZASP as opposed to titin. Thus, Markesbery-Griggs distal myopathy is better characterized as one of the MFMs or ZASPopathy mutations and is discussed in greater detail in that section.

NONAKA DISTAL MYOPATHY (AUTOSOMAL-RECESSIVE INCLUSION BODY MYOPATHY)

Clinical Features

This autosomal-recessive myopathy was initially reported in Japan,[272–275] but it occurs worldwide, allelic to autosomal-recessive inclusion body myopathy.[276–279] Patients usually develop weakness of the anterior compartment of the distal lower limb, leading to foot drop in the second or third decade of life. The posterior compartment of the legs and distal upper limb muscles are also affected early, but to a lesser degree. The proximal arm and leg muscles as well as the neck flexors may become weak over time. The quadriceps may become affected but usually remain relatively spared compared to other muscle groups as are ocular and bulbar muscles. Sensation is normal. Muscle stretch reflexes can be normal or absent.

Laboratory Features

Serum CK is normal or only mildly elevated. Motor and sensory nerve conduction studies are usually normal. Electromyography reveals positive sharp waves and early recruitment of small-amplitude, brief-duration MUAPs in weak muscles.

Histopathology

Muscle biopsies demonstrate rimmed vacuoles with muscle fibers as well as other nonspecific myopathic features, as described in the other forms of distal myopathy.[272–279] Because of the frequent rimmed vacuoles, the biopsy can be erroneously interpreted as sporadic inclusion body myositis (s-IBM). However, inflammation cell infiltrate is usually absent. EM demonstrates 15–18-nm intranuclear and cytoplasmic tubulofilaments similar to that found in sporadic IBM.

Molecular Genetics and Pathogenesis

Nonaka myopathy and autosomal-recessive hereditary inclusion body myopathy (h-IBM) are allelic disorders caused by mutations in the gene that encodes for UDP-*N*-acetylglucosamine 2-epimerase/*n*-acetylmannosamine kinase (GNE) on chromosome 9p1–q1.[276,278,280] GNE may be involved in the posttranslational glycosylation of proteins to form glycoproteins.

MIYOSHI DISTAL MYOPATHY

This myopathy is associated with early adult onset of calf atrophy and weakness and markedly elevated serum CKs. It is caused by mutations in the dysferlin gene and is discussed in greater detail in the section on LGMD 2B.

LAING DISTAL MYOPATHY

Clinical Features

Laing and colleagues described an Australian family (nine affected members over four generations) with weakness beginning in the anterior compartment of the distal lower limbs and neck flexors between the ages of 4 and 25 years.[281] Subsequently, the finger extensors become involved and to a lesser extent the shoulder and hip girdle. Finger flexors and hand intrinsic muscles are spared.

Laboratory Features

Serum CK is normal or slightly elevated. Motor and sensory nerve conduction studies are normal. EMG reveals occasional fibrillation potentials and positive sharp waves and small-amplitude, short-duration, polyphasic MUAPs in distal more than proximal muscles.

Histopathology

Muscle biopsies demonstrated nonspecific myopathic features. Rimmed vacuoles are not seen. Large deposits of myosin heavy chain (MyHC) in the subsarcolemmal region of type 1 muscle fibers lead some authorities to prefer the term myosin storage myopathy to this group of disorders.[19]

Molecular Genetics and Pathogenesis

The disorder has been linked to mutations in the slow/beta cardiac MyHC 1 gene or *MYH7*, located on chromosome 14q.[282] MyHC is the major myosin isoform expressed in type 1 muscle fibers. Of note, mutations have also been identified in the *MYH7* in hyaline body myopathy (discussed in Chapter 25).[283] Mutations in *MYH7* are a common cause of familial hypertrophic cardiomyopathy, although patients with skeletal myopathy usually do not have much symptomatic skeletal muscle involvement and vice versa.[19]

▶ OTHER DISTAL MYOPATHIES

DISTAL MYOPATHY WITH VOCAL CORD PARALYSIS AND PHARYNGEAL WEAKNESS

Clinical Features

A large kinship with autosomal-dominant inheritance of distal limb weakness, vocal cord paralysis, and pharyngeal weakness has been described.[284] Weakness usually began in the anterior tibial muscles the fourth–sixth decade. Weakness was asymmetric in some. Vocal cord and pharyngeal involvement developed after the limb weakness manifested.

Laboratory Features

Serum CK levels were normal to moderately elevated. Motor and sensory nerve conduction studies are usually normal but may reveal mild slowing of conduction velocities. Needle electromyography revealed mixed neurogenic and myopathic features.

Histopathology

Muscle biopsies demonstrated nonspecific myopathic features along with rimmed vacuoles. EM did not reveal filamentous inclusions.

Molecular Genetics and Pathogenesis

The myopathy localized in this family to chromosome 5q31.[284] Of note, this is where the gene that encodes for myotilin is located and this kinship could be LGMD 1A.

▶ TREATMENT OF THE DISTAL MYOPATHIES

There is no medical treatment currently available for the distal myopathies. Braces for the lower limb weakness and other orthotic devices may be of benefit in improving gait and functional abilities.

▶ OTHER MUSCULAR DYSTROPHIES

MYOFIBRILLAR MYOPATHY

MFM is a clinically and genetically heterogeneous group of disorders, characterized by the pathologic finding of myofibrillar disruption on EM and excessive desmin accumulation in muscle fibers.[20,21,151,285–296] Because desmin is not the only protein that accumulates, the term "myofibrillar myopathy" was suggested to be a more accurate description of the spectrum of the histologic abnormalities.[293] This myopathy has been reported as desmin storage myopathy, desmin myopathy, familial desminopathy, spheroid body myopathy, cytoplasmic body myopathy, Mallory body myopathy, familial cardiomyopathy with subsarcolemmal vermiform deposits, myopathy with intrasarcoplasmic accumulation of dense granulofilamentous material, and h-IBM with early respiratory failure.[285] In addition, some cases previously diagnosed with other forms of distal myopathy (Markesbery–Griggs distal myopathy) actually have MFM.[271] MFM has been classified by some in the past as congenital myopathies but are probably best considered a form of muscular dystrophy.

Clinical Features

As mentioned, MFM is associated with a wide spectrum of clinical phenotypes.[285–288,290–293,295,297] Most affected individuals develop weakness between 25 and 45 years of age, although weakness may be noticeable in infancy or may present later in adulthood. Weakness can be predominantly proximal, distal, or generalized. In addition, some patients have a facioscapulohumeral or scapuloperoneal distribution of weakness. Facial and pharyngeal muscles can also be affected in some individuals. Rigidity of the spine can also be seen.

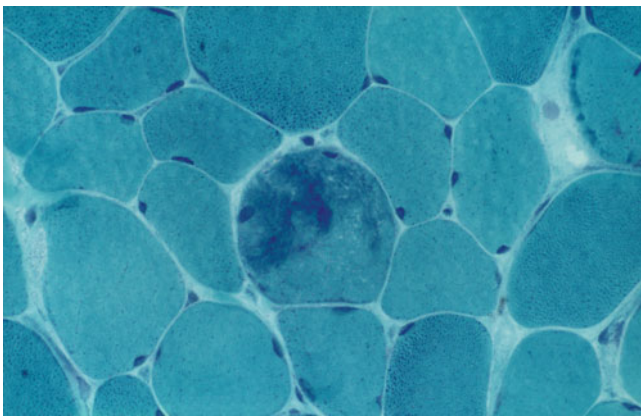
In addition to skeletal muscle, the heart can also be affected and cardia arrhythmias and congestive heart failure may be the predominant features of the disease. In severe cardiomyopathies, pacemaker insertion or cardiac transplantation may be required. In addition, severe respiratory muscle involvement can develop in MFM. Also, smooth muscle may be involved and may lead to intestinal pseudo-obstructions.

Laboratory Features

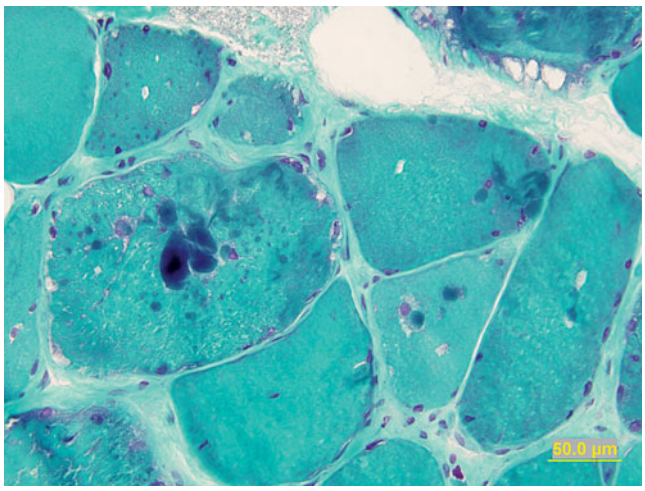
Serum CK is normal or usually only slightly increased in MFM. EKGs may demonstrate conduction defects or arrhythmia, while echocardiograms may reveal a dilated or hypertrophic cardiomyopathy. Nerve conduction studies are usually normal, although low amplitudes of motor and sensory potentials and slowing of conduction velocities can be seen. Needle EMG reveals increased insertional and spontaneous activity with fibrillation potentials, positive sharp waves, pseudomyotonic potentials, complex repetitive discharges, and early recruitment of short-duration, small-amplitude, polyphasic MUAPs. Long-duration, large-amplitude MUAPs may also be seen, owing to the chronicity of the disorder.

Histopathology

Muscle biopsies reveal variability in fiber size, increased internalized nuclei, occasionally type 1 fiber



A



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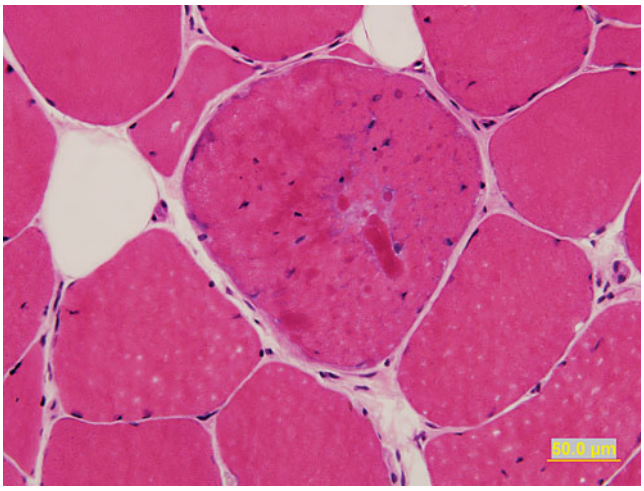

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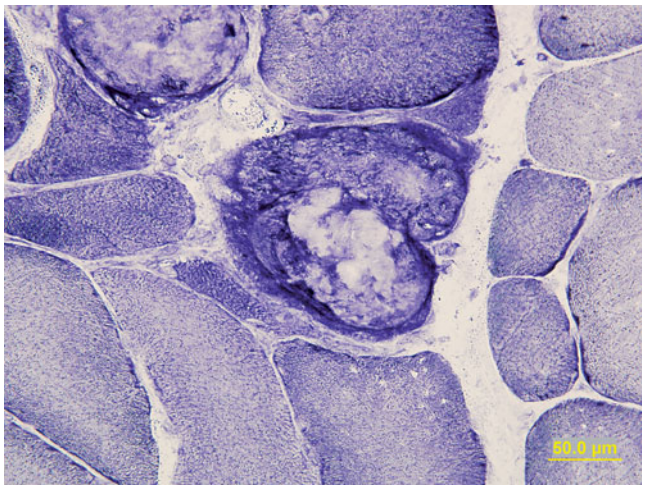

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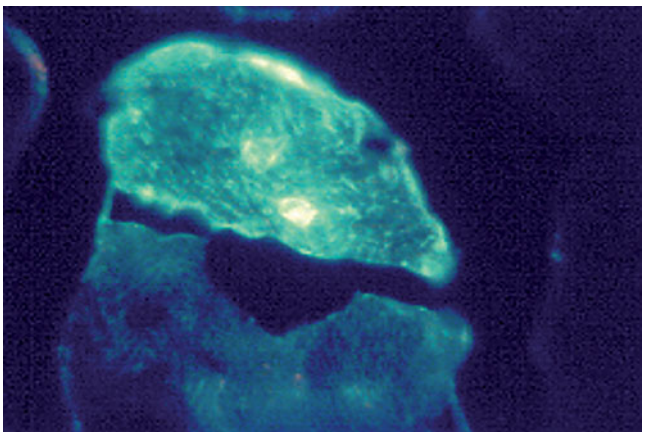

E

Figure 24–19. Myofibrillar myopathy. Nonhyaline lesions appear as amorphous accumulation of reddish-purple or dark green material (A), while the hyaline lesions are more dense and can have the appearance of cytoplasmic or spheroid bodies (B) on Trichrome stain. The hyaline lesions are eosinophilic on H&E but less well seen than on the trichrome stains (C). The hyaline and nonhyaline lesions do not stain with NADH-TR (D). Immunostaining reveals that the lesions are immunoreactive to desmin (E).

predominance, and, in some cases, scattered fibers with rimmed vacuoles. In addition, Nakano et al. defined two major types of lesions on light and electron microscopy that characterize MFM: hyaline structures and nonhyaline lesions (Fig. 24–19).[293] The hyaline structures are cytoplasmic granular inclusions, which are typically eosinophilic on H&E and dark blue-green or occasionally red on modified Gomori trichrome stains. They do not stain for NADH. On EM, the hyaline lesions resemble cytoplasmic, spheroid, or Mallory bodies. The nonhyaline lesions appear as dark green areas of amorphous material on Gomori trichrome stains. On EM, these nonhyaline lesions correspond to foci of myofibrillar destruction and consist of disrupted myofilaments, Z-disk-derived bodies, dappled dense structures of Z-disk origin, and streaming of the Z-disk.[293,295] In addition, larger-size tubulofilaments (14–20 nm) typical of the inclusion body myopathies may accumulate.

Immunohistochemistry reveals that both the hyaline and the nonhyaline lesions contain desmin and numerous other proteins.[22,285–288,290–293,295,297] Abnormal accumulation of desmin is not specific for MFM and can be seen in a variety of neuromuscular conditions, including X-linked myotubular myopathy, congenital myotonic dystrophy, spinal muscular atrophy, nemaline rod myopathy, fetal myotubes, inclusion body myositis, and in regenerating muscle fibers of any etiology.[290] Abnormal accumulation of desmin has been demonstrated in cardiac muscles in MFM patients with cardiomyopathy. Immunohistochemistry also reveals that the nonhyaline lesions react strongly for desmin, dystrophin, gelsolin, N terminus of β-amyloid precursor protein, and NCAM in addition to desmin. However, the nonhyaline lesions are depleted of actin, α-actinin, myosin, and, less consistently, titin and nebulin. In contrast, the hyaline structures are composed of compacted and degraded remnants of thick and thin filaments and react to actin, α-actinin, and myosin in addition to dystrophin, gelsolin, filamin c, and the N terminus of β-amyloid precursor protein; they do not react to NCAM and react variably to desmin. Both types of lesions also react for αB-crystallin, α-1 antichymotrypsin, and ubiquitin and can be congophilic. The abnormal muscle fibers also abnormally express several cyclin-dependent kinases (CDC/CDK) in the cytoplasm, including CDC2, CDK2, CDK4, and CDK7.[285,297]

Nerve and intramuscular nerve biopsies have demonstrated enlarged axons with accumulation of intermediate-sized neurofilaments and formation of axonal spheroids in some patients.[298,299]

Molecular Genetics and Pathogenesis

The pathogenesis of MFM is likely related to disruption of the Z-disk.[20,21,285,294,295] Mutations have been identified in desmin, αB-crystallin, myotilin, filamin c, and ZASP (Z-band alternatively spliced PDX motif-containing protein)—all of which are Z-disk-related proteins. Most familial cases demonstrate autosomal-dominant inheritance, although autosomal-recessive and possible X-linked inheritances occur. Mutations in the desmin gene located on chromosome 2q35 have been identified in several families with autosomal-dominant MFM as well as in a few sporadic cases.[287,291,295,300] Mutations in the desmin gene were subsequently demonstrated in the initial family reported with scapuloperoneal myopathy.[212] In addition, a homo- or hemizygous mutation involving a 21 base pair deletion in the first exon of the desmin gene was reported in a patient with presumed autosomal-recessive inheritance of MFM.[300] Desmin is an intermediate filament protein of skeletal, cardiac, and some smooth muscle cells. This cytoskeletal protein links Z-bands with the sarcolemma and the nucleus. The intermediate filament network is important in the stability of the muscle fiber and during mitosis/regeneration of muscle cells. These abnormal desmin filaments form insoluble aggregates, which prevent the genesis of the normal filamentous network.[301]

Mutations in the αB-crystallin gene on chromosome 11q21–23 have been demonstrated in some other autosomal-dominant kinships.[294–296] Alpha B-crystallin possesses "molecular chaperone" activity and is felt to interact with desmin in the assembly of the intermediate filament network.

Missense mutations in the myotilin gene located on chromosome 5q22–31 were identified in six of 57 patients with MFM; thus, some cases of late-onset MFM are allelic to LGMD 1A.[20] These patients had late onset of distal greater than proximal weakness, polyneuropathy, and cardiopathy. Myotilin is a component of the Z-disk where it interacts with α-actinin, actin, and filamin-c and probably plays a fundamental role in myofibrillar assembly.

In addition, missense mutations were demonstrated in the ZASP gene located on chromosome 10q22.3–10q23.2 in 11 patients.[21] Dominant inheritance was seen in seven of these patients. Patients developed a distal greater than proximal pattern of weakness at 44–73 years of age. Some had a cardiomyopathy with arrhythmia or low ejection fractions or a polyneuropathy. The kinship with late-onset distal myopathy initially reported by Markesbery and colleagues has also recently been found to be due to mutations in ZASP.[271] ZASP is expressed in skeletal and cardiac muscle and it binds to α-actinin, a component of the Z-disk that in turn cross-links thin filaments of adjacent sarcomeres.[21]

Further, mutations in the selenoprotein N gene (*SEPN1*) located on chromosome 1p36 were identified in autosomal-recessive MFM associated with Mallory-body-like inclusions.[184] These patients had an early onset of axial muscle weakness, respiratory weakness, and rigidity of the spine. Of note, mutations in *SEPN1* gene located on chromosome 1p36 have been identified in cases of MDC with rigid spine and multi/minicore myopathy.

Recently, nonsense mutations were identified in an autosomal-dominant form of MFM in the filamin-c gene (*FLNC*) located on chromosome 7q32.[22] Filamin-c binds actin and is involved in the formation of the Z-disk. In addition, filamin-c also binds γ- and δ-sarcoglycan at the sarcolemmal membrane and may also play a role involved in signaling pathways from the sarcolemma to the myofibril.[22]

Treatment

There is no proven medical therapy to improve skeletal muscle weakness. Antiarrhythmic and cardiotropic medications are sometimes necessary in patients with cardiopathy. Cardiac transplantation can be life saving in patients with severe cardiomyopathy.

HEREDITARY INCLUSION BODY MYOPATHIES

Clinical Features

There are autosomal-dominant and autosomal-recessive forms of hereditary inclusion body myopathy (h-IBM).[276,279,302,303] Autosomal-recessive h-IBM was initially reported in Iranian-Jewish families but was subsequently described in Iranian-Kurds, Afgani-Jewish, and North American families. As noted in the distal myopathy section, autosomal-recessive h-IBM was demonstrated to be allelic with the Nonaka myopathy.

The age of onset and pattern of weakness in h-IBM are different from that of sporadic inclusion body myositis (s-IBM). Most patients with s-IBM present over the age of 50 years with weakness of quadriceps and wrist and finger flexors. In contrast, most patients with autosomal-recessive h-IBM present in the second or third decade of life, with anterior tibial involvement leading to foot drop. There is insidious progression with gradual involvement of the iliopsoas, thigh adductors, and to a lesser extent the glutei muscles. Importantly, in differentiating from s-IBM, the quadriceps are usually normal or relatively spared.[276–279] However, rarely the quadriceps can be affected. The proximal arms and neck flexors can also become affected. There can be asymmetry of muscle weakness. Progression is variable, with some patients becoming wheelchair dependent with a few years of onset, while others are ambulatory several decades later.

Autosomal-dominant h-IBM is less common than recessive h-IBM.[279] Although the pattern of weakness is variable in autosomal-dominant h-IBM, most patients have a limb-girdle distribution of muscle involvement. Distal muscles can occasionally be involved. Extraocular and bulbar muscles are spared. Sensation and deep tendon reflexes are usually normal.

There are a few reports of familial cases of s-IBM in which siblings, even twins, had the characteristic clinical phenotype and histological features of s-IBM.[279,304,305] These cases do not represent h-IBM. Rather, there may be a familial predisposition for development of s-IBM, similar to that described for other autoimmune disorders.

Laboratory Features

Serum CK levels are normal or only mildly elevated. Motor and sensory nerve conduction studies are usually normal. EMG demonstrates fibrillation potentials, positive sharp waves, and complex repetitive discharges. There is a mixture of small-amplitude, short-duration polyphasic MUAPs with large-amplitude, long-duration polyphasic MUAPs.

Histopathology

Muscle biopsies of the autosomal-recessive and autosomal-dominant h-IBMs are similar to s-IBM, except for the lack of endomysial inflammation and invasion of non-necrotic muscle fibers.[276,279,302,303] Fiber size variability, split fibers, increased central nuclei, and fibers with rimmed vacuoles are evident. Amyloid and other "Alzheimer characteristic proteins" are seen in vacuolated muscle fibers, although they are much less frequent compared to s-IBM. As in s-IBM, EM demonstrates the abnormal accumulation of 15–18-nm tubulofilaments in the cytoplasm and nuclei of muscle fibers.

Molecular Genetics and Pathogenesis

Nonaka-type distal myopathy and autosomal-recessive h-IBM are allelic disorders caused by mutations in the gene that encodes for GNE on chromosome 9p1–q1.[276,278,280] GNE is involved in the posttranslational glycosylation of proteins to form glycoproteins. Disturbed glycosylation is therefore now recognized as a newly identified molecular genetic defect for the muscular dystrophies. However, other mechanisms may be involved in the pathogenesis of this myopathy.

Treatment

There is no medical treatment available for h-IBM. Patients with distal lower limb weakness may benefit from bracing.

H-IBM WITH CEREBRAL HYPOMYELINATION

This autosomal-recessive h-IBM is associated with an infantile onset of progressive proximal greater than distal weakness, legs worse than arms, and marked cerebral white matter abnormalities on CT and MRI.[306] Despite the apparent leukoencephalopathy on radiological imaging, intellectual function was normal in all the cases. Motor nerve conduction studies were mildly slow, suggesting dysmyelination of the peripheral nerves as well.

H-IBM WITH PAGET DISEASE AND FRONTOTEMPORAL DEMENTIA

h-IBM associated with Paget disease of the bone and frontotemporal dementia, or IBMPFD, is a rare autosomal-dominant disorder caused by mutations in the gene encoding valosin-containing protein (VCP).[307,308] It is characterized by adult onset of proximal and distal muscle weakness. There also appears to be a mild asymmetry and variability in the patterns of muscle weakness. In addition, early-onset Paget disease and/or early-onset frontotemporal dementia occur in over one-third cases. EMG shows myopathic changes in the latter stages of the disease, and muscle biopsies reveal nonspecific myopathic changes or rimmed vacuoles in the cytoplasm. Serum CK levels are normal to slightly elevated but are

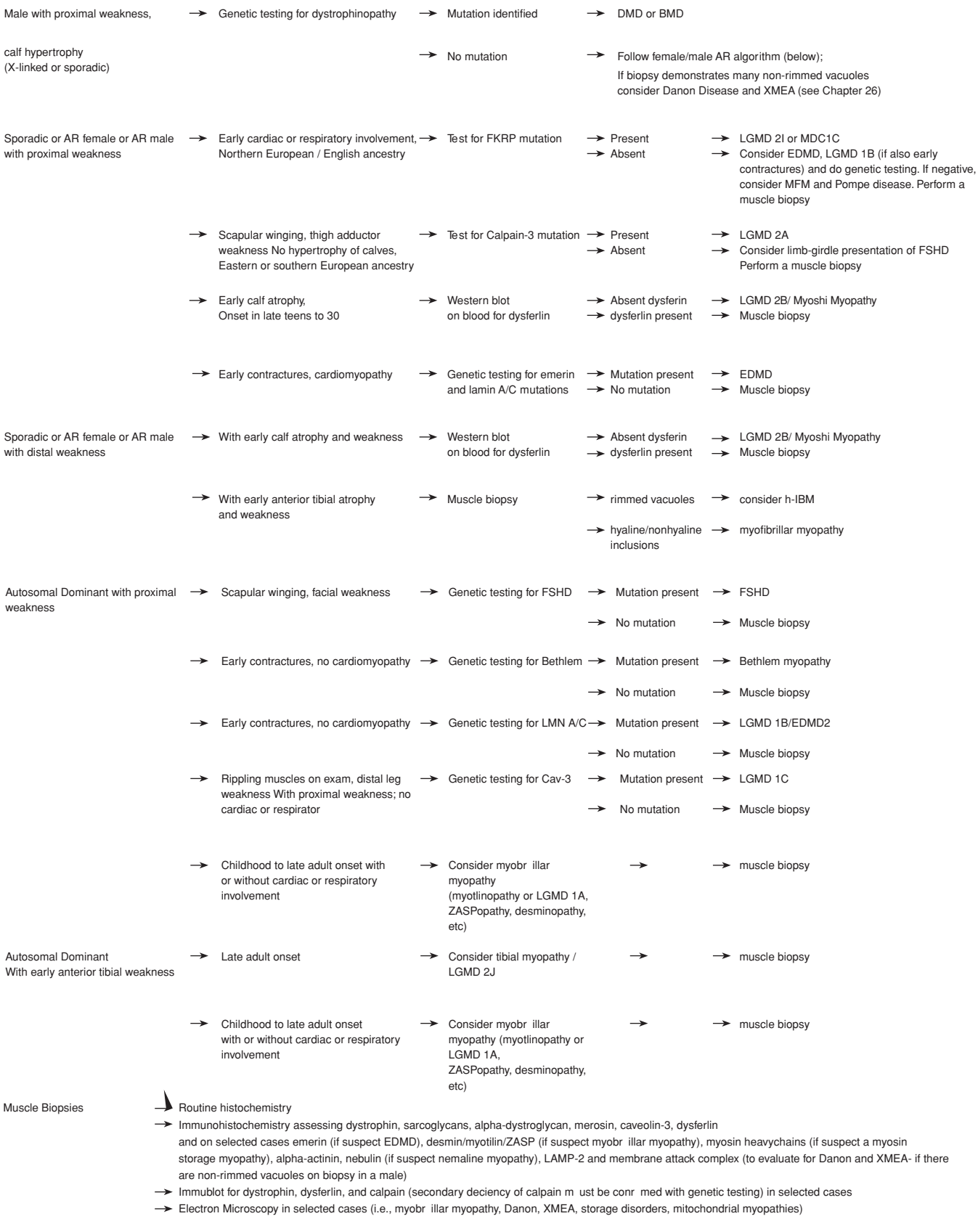

Figure 24–20. Approach to patients with muscular dystrophy.

not significantly elevated enough for use as a diagnostic method. Ultimately, the cause of death is through progressive muscle weakness and respiratory failure. Age of onset ranged 3–66 years (mean 43 years).

The disorder is caused by mutations in the gene encoding VCP, a member of the AAA-ATPase superfamily.[307,308] VCP is associated with a variety of cellular activities, including cell-cycle control, membrane fusion, and the ubiquitin–proteasome degradation pathway. VCP normally localizes to nuclei and specifically near nucleoli. Mutations in VCP gene may disrupt in nuclear structure or function.

HEREDITARY IBM TYPE 3

This myopathy usually presents with congenital arthrogryposis, ophthalmoparesis, and mild proximal weakness beginning in adulthood. As muscle biopsies may demonstrate rimmed vacuoles and tubulofilamentous inclusions, this disorder has also been called h-IBM type 3.[19,309] Mutations have been identified in the *MYH2* gene located on chromosome 17p13.1, which encodes for MyHC IIa.[19,305,310] The MyHC IIa isoform of MyHCs is expressed in type 2A muscle fibers. Both the Laing-type distal myopathy that is caused by mutations in *MYH7*and the h-IBM type 3 could be considered forms of myosin storage disease.

▶ SUMMARY

With so many different types of muscular dystrophies and the variability of clinical phenotypes associated with specific forms of dystrophy, even within individual families, the evaluation of patients presenting with weakness can be quite daunting. However, rather than ordering every genetic test possible or doing a muscle biopsy initially on every patient, an approach to ordering tests based on clinical phenotype (inheritance pattern, age of onset, pattern of weakness, and associated manifestations—early contractures and cardiac or respiratory involvement) can very useful (Fig. 24–20). Unfortunately, there are limited medical treatments of benefits, other than corticosteroids for children with DMD, that have been demonstrated to be beneficial. Still with supportive treatments (physical and occupational therapy, bracing, respiratory, and cardiac) the quality of life can be improved in patients. More work needs to be done to further understand the pathogenesis of these disorders and discover better treatments.

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CHAPTER 25

Congenital Myopathies

The term "congenital myopathy" was originally used to describe a group of myopathic disorders presenting preferentially, but not exclusively, at birth and distinct from congenital muscular dystrophies (Table 25–1). However, disorders that were once considered forms of muscular dystrophy are now known to be allelic to those some types of congenital myopathy. For example, congenital muscular dystrophy with rigid spine syndrome, multi/minicore, and some cases of myofibrillary myopathy are caused by selenoprotein N1 mutations sarcotubular myopathy and limb girdle muscular dystrophy 2H (LGMD 2H) are due to mutations in TRIM32; reducing body myopathy is probably a form of myofibrillar myopathy, which is now considered a type of LGMD. Additionally, some disorders caused by mutations in sarcomeric proteins are classified as forms of LGMD (e.g., titinopathies, myotilinopathies, ZAS Popathies) while others (e.g., actinomyosin, tropomyosin, alpha actin, and troponin) are forms of congenital myopathy. Thus, the nosology of what distinguishes a "congenital myopathy" from a "muscular dystrophy" on histopathological grounds is not at all clear.

Usually the congenital myopathies present in infancy as generalized hypotonia and weakness. Motor milestones are typically delayed. Affected infants are usually hypotonic and display delayed motor development. Some congenital myopathies can present later in childhood or even in early adulthood. The congenital myopathies were initially considered as nonprogressive, although it is now clear that progressive weakness can occur.

Congenital myopathies can be inherited in an autosomal-dominant, autosomal-recessive, or X-linked pattern. Within families, there can be considerable variation with respect to disease presentation and degree of muscle involvement. The serum creatine kinase (CK) levels are either normal or only mildly elevated. The classification of congenital myopathies has been based almost exclusively on clinical presentation and light/electron microscopic structural alterations of the muscle biopsy specimen (Table 25–1).

▶ CENTRAL CORE MYOPATHY

CLINICAL FEATURES

Central core myopathy usually manifests at birth or early childhood as generalized weakness and hypotonia.[1–5] The degree of muscle weakness can vary even within families.[3] Muscle weakness is stable or only slowly progressive. Motor milestones, such as the ability to sit and walk, are delayed. Some individuals who are affected never achieve independent ambulation, while others have only mild weakness. The proximal muscles, legs more than arms, are preferentially affected, leading to a wide-based hyperlordotic gait. Individuals who are affected may also demonstrate Gower sign when arising from the floor. There may be mild facial and neck flexor weakness. However, patients do not exhibit ptosis or extraocular muscle weakness—clinical features that can help distinguish central core myopathy clinically from centronuclear and nemaline myopathies. Muscle atrophy or hypertrophy is usually not seen in central core disease. Contractures are uncommon. Muscle stretch reflexes are normal or reduced. There are no apparent central nervous system abnormalities. Patients who are affected may exhibit mild-to-moderate skeletal deformities including pes planus, pes cavus, kyphoscoliosis, and congenital hip dislocation. Mild respiratory muscle weakness with reduced forced vital capacity and nocturnal hypoxemia is seen in some patients.[3]

LABORATORY FEATURES

The serum CK levels are normal or slightly elevated. Motor and sensory nerve conduction studies (NCS) are usually normal. Electromyography (EMG) may reveal fibrillation potentials and positive sharp waves in weak muscles of patients with long-standing disease and myopathic appearing motor unit action potentials (MUAPs) that recruit early.[6] A few long-duration, polyphasic MUAPs and units with satellite potentials may also be appreciated.

HISTOPATHOLOGY

The characteristic histological features are the structural alterations within the center of muscle fibers.[7] These cores appear only in type 1 muscle fibers and are particularly noticeable on nicotinomide adenine dinucleotide tetrazolium reductase (NADH-TR) stains where these regions are devoid of stain (Fig. 25–1). The cores can occasionally be eccentric and multiple within a given muscle fiber. The distinction between central core and multi/minicore is that in central core disease the "cores"

▶ TABLE 25–1. CONGENITAL MYOPATHIES

Disease	Inheritance	Gene/Chromosome	Clinical Features
Central core myopathy	AD	Ryanodine receptor (RYR1)/ 19q13.1	Onset: infancy or childhood, occasionally adulthood; proximal limbs and mild facial weakness; skeletal anomalies; risk for MH
Multi/minicore myopathy	AD, AR, and sporadic	Selenoprotein N1/ 1p36 in some AR	Onset: infancy or childhood; proximal and facial muscles; rare EOM weak; cardiomyopathy and respiratory weakness; skeletal anomalies; risk for MH
Nemaline myopathy	AR AR/AD AR/AD AD AR AR/AD AD	Nebulin (NEM2)/2q21.2–q22 α-Actin (ACTA1)/1q42 α-Tropomyosin (TMP3)/1q21–q23 β-Tropomyosin (TPM2) 9q13 Slow troponin T (TNNT1)/19q13 α-Tropomyosin (TMP1)/15q21–23 cofilin-2 (CFL2)/14q12	Severe infantile form: Infantile onset: severe generalized hypotonia/weakness; respiratory weakness; skeletal anomalies; usually fatal in first year of life Mild early onset form: Most common subtype Onset: infancy or childhood; mild generalized hypotonia and weakness; facial muscles; rare ptosis, EOM weak; dysmorphic facies and skeletal anomalies Adult onset form: onset in adult life; mild proximal and occasionally distal weakness; no facial or skeletal anomalies
Centronuclear/myotubular myopathy; severe neonatal type	X-linked	Myotubularin/Xp28	Severe neonatal hypotonia and weakness; respiratory weakness; ptosis and EOM weak; poor prognosis in most
Centronuclear myopathy; neonatal or late infantile type	Sporadic, AR, AD	Dynamin-2 (allelic to dominant intermediate Charcot–Marie–Tooth disease type B or DI-CMTB)/19p13.2	Most common subtype: Onset: late infancy or early childhood; generalized weakness and hypotonia; facial and EOM weakness, ptosis; facial anomalies
Centronuclear myopathy; late childhood/adult type	AD	Dynamin-2 (allelic to dominant intermediate or DI-CMTB)	Onset in late childhood or adulthood; mild proximal and/or distal predominance; ptosis is common; facial and EOM muscles variable involved; no skeletal or facial anomalies; mild sensory abnormalities
Congenital fiber-type disproportion	Sporadic	Most unknown Some caused by *ACTA1* or Selenoprotein N-1 mutations	Onset in infancy; generalized nonprogressive weakness; occasional respiratory weakness; skeletal and facial anomalies
Reducing body myopathy	AR or sporadic	Unknown. May be same entity as MFM	Onset in infancy to adulthood; generalized or proximal weakness; may have facial, respiratory or asymmetric weakness; skeletal anomalies
Fingerprint body myopathy	Most sporadic	Unknown	Infantile onset; slow or nonprogressive proximal weakness
Sarcotubular myopathy (allelic to LGMD 2H)	AR	TRIM 32/9q31–33	Onset: infancy; slow progressive proximal +/− distal weakness
Trilaminar myopathy	Unknown; single case	Unknown	Infantile onset: generalized weakness; skeletal anomalies

(*continued*)

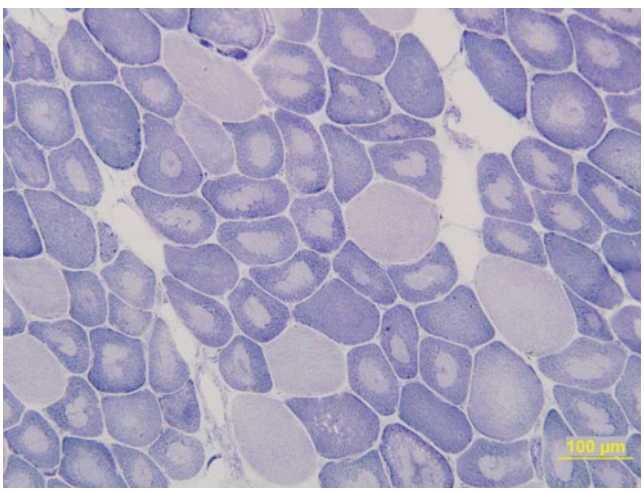
▶ **TABLE 25–1. (CONTINUED)**

Disease	Inheritance	Gene/Chromosome	Clinical Features
Hyaline body myopathy/ familial myopathy with lysis of myofibrils/ myostin storage myopathy	AD or AR	AD: slow/beta-cardiac myosin heavy chain (MYH7)/14q11.2 AR: unknown/3p22.2–p21.32	Onset in infancy or adults; limb-girdle or scapuloperoneal weakness or distal
H-IBM 3/myosin storage myopathy	AD	Myosin heavy chain type IIa (MYH2)/17p13.1	Congenital arthrogryposis; ophthalmoparesis; adult onset of mild proximal weakness and myalgias; rimmed vacuoles and inclusions on muscle biopsy (H-IBM type 3)
Cap myopathy	AD	Tropomyosin (TPM2) 9q13	Onset in infancy; generalized weakness; skeletal anomalies
Zebra body myopathy	Unknown	Possibly alpha-actin (ACTA1)/1q42	Onset in infancy or childhood; Generalized weakness—may be asymmetric and worse in arms
Tubular aggregate myopathy			
Type 1	AD	Unknown	Onset: childhood or early adulthood; limb-girdle weakness
Type 2	AR	Unknown	Onset: infancy; congenital myasthenia; fatigable weakness
Type 3	Sporadic	Unknown	Adult onset: myalgia

AD, autosomal dominant; AR, autosomal recessive; EOM weakness, ophthalmoparesis; MH, malignant hyperthermia; H-IBM, hereditary inclusion body myopathy; ZASP, Z band alternatively spliced PDZ motif-containing protein.

extend along the entire length of the muscle fibers on longitudinal section. However, in some cases, the distinction between central cores and multi/minicores is not clear as there can be typical multi/minicores in patients with central core myopathy,[3,7] and repeat biopsies in patients initially diagnosed with minicores may subsequently reveal on central cores.[8] In addition, muscle biopsies reveal variation in fiber size, increased internalized nuclei, and often a predominance of type 1 fibers. Increased endomysial fibrosis and fat may be present,[7] but the other features help distinguish the disorder from muscular dystrophies.

On electron microscopy (EM), the cores may be "structured" or "unstructured" (Fig. 25–2). In structured cores, there is steaming of the Z-band but the sarcomeres are preserved. In unstructured cores, there are severe



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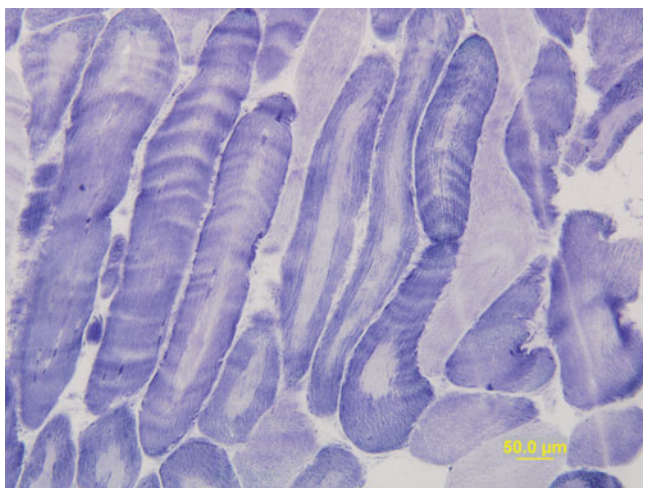
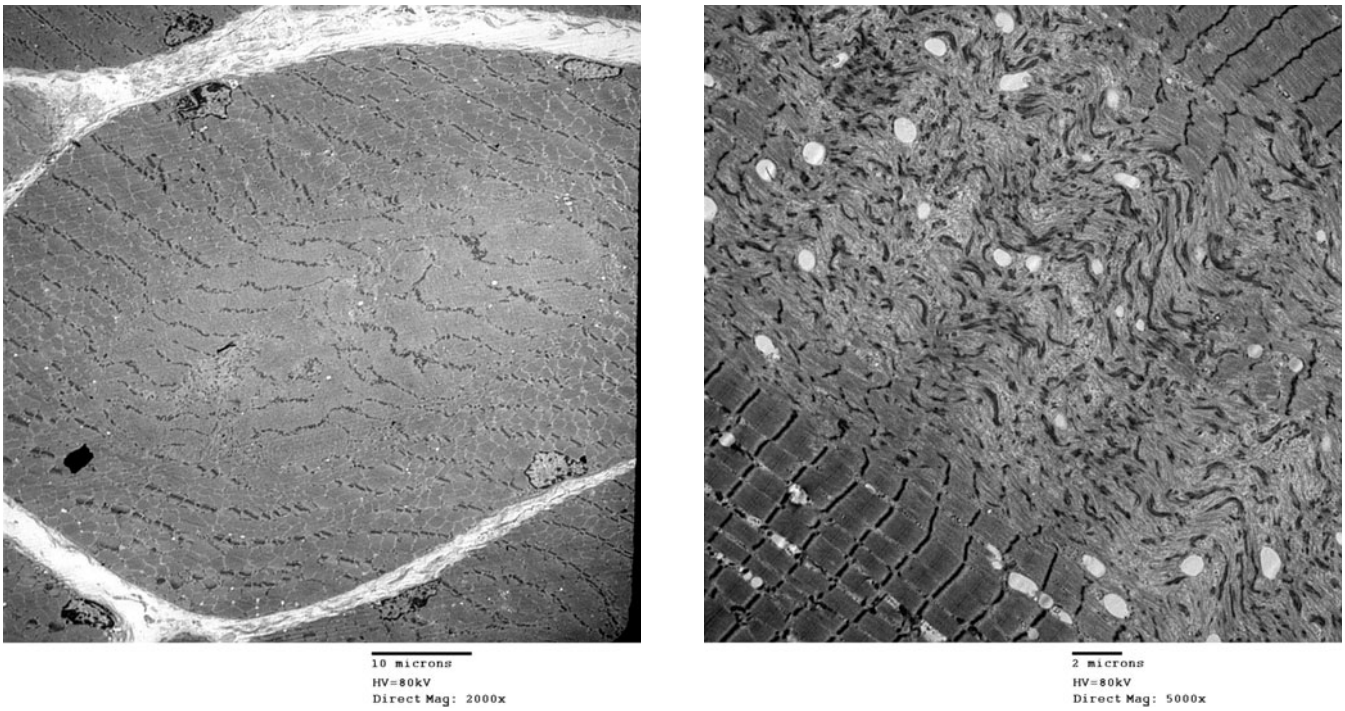


B

Figure 25–1. Central core myopathy. Nicotinomide adenine dinucleotide tetrazolium reductase (NADH-TR) stain demonstrates areas devoid of oxidated enzyme activity in the center of the fibers or sometimes eccentric regions (A) that extend the length of the fiber longitudinally (B).



A B

Figure 25–2. Central core myopathy. Electron microscopy reveals areas with poorly aligned sarcomeres and reduced glycogen and mitochondrial in an "unstructured" core (A) A core can be seen to extend over a large length of the fibers on a longitudinal section (B).

myofibrillar disruption and loss of the normal sarcomere organization. In both structured and unstructured cores, mitochondria and glycogen granules are reduced or absent. The cores appear to contain desmin, dystrophin, actin, α-actinin, gelsolin, nebulin, myotilin, β-amyloid precursor protein, NCAM, and various cyclin-dependent kinases on the basis of immunocytochemistry, and the cores are also variably congophilic.[9]

MOLECULAR GENETICS AND PATHOGENESIS

Central core myopathy is an autosomal-dominant disorder caused by mutations in the ryanodine receptor gene (RYR1) on chromosome 19q13.1. Of note, this same gene is mutated in one form of familial malignant hyperthermia; thus, patients with central core myopathy are at risk of malignant hyperthermia (Table 25–1).[10] Why these "cores" form in the center of the muscle fibers is unknown. The ryanodine receptor is a tetramere of RYR1 proteins, which bridges the gap between the sarcoplasmic reticulum and the T-tubules in skeletal muscle and forms a calcium-release channel. Thus, the ryanodine receptor likely plays an important role in excitation–contraction coupling. In experimental studies of mutant myotubes, voltage-gated calcium release was reduced by approximately 90%, while caffeine-induced Ca^{2+} release was only marginally reduced in mutant myotubes, indicating the disruption of voltage-sensor activation of calcium release.[11,12]

TREATMENT

There is specific medical treatment available for central core myopathy. Patients may benefit from physical therapy and orthotic devises. Patients with central core disease and their families should be informed of their risk of developing malignant hyperthermia with general anesthesia. Appropriate precautions and avoidance of certain anesthetic agents (e.g., halothane) and neuromuscular blocking agents (succinylcholine) need to be taken during surgical procedures.

▶ MULTI/MINICORE MYOPATHY

CLINICAL FEATURES

Although it is generally agreed that multi/minicore disease (MmD) constitutes a distinct entity, the morphological lesions defining it are nonspecific, and the clinical expression of the disease is highly variable.[13–18] MmD usually presents in infancy or early childhood, but adult-onset cases have been reported as well. Affected infants are usually hypotonic and weak. Motor milestones are delayed, but ambulation is usually achieved. Most patients have generalized muscle weakness and atrophy

predominantly affecting proximal muscles. Distal muscles are usually normal or only slightly involved. However, there may be a subgroup of MmD that manifests with predominantly distal hand weakness.[14,15] Facial muscle weakness, ptosis, and occasionally ophthalmoparesis can also been seen. It is unclear if these patients represent a distinct subgroup of MmD.

Muscle contractures and multiple skeletal deformities such as kyphoscoliosis, high-arched palate, and club feet are common findings. Weakness is usually stable or only slowly progressive.[15] Neck extensors and trunk muscles are frequently contracted, leading to rigidity of the spine. Cardiomyopathy and ventilatory muscle involvement can also develop.[16,18] Respiratory involvement is disproportionate to the degree of scoliosis.[14,15] Patients may require intermittent or continuous positive-pressure ventilation.

Laboratory Features

Serum CK is usually normal or only slightly elevated. Pulmonary function tests often reveal reduced forced vital capacities. Polysomnographic studies may disclose nocturnal desaturations and short apnea periods. NCS are normal. EMG usually reveals normal insertional and spontaneous activity, although early recruitment of short-duration, small-amplitude MUAPs may be appreciated.

Histopathology

Muscle biopsies reveal multiple small regions within muscle fibers of variable size (minicores) formed by disorganization of the myofibrils (Fig. 25–3).[14,15] These minicores are similar to central cores but are much smaller and do not extend the entire length of the muscle fiber as do central cores. In addition, minicores can occur in either type 1 or type 2 muscle fibers. Type 1 fiber predominance and atrophy as well as fiber size variation are also noted. There can be increased endomysial connective tissue as well. EM demonstrates myofibrillar disruption similar to that seen in central cores (Fig. 25–4).

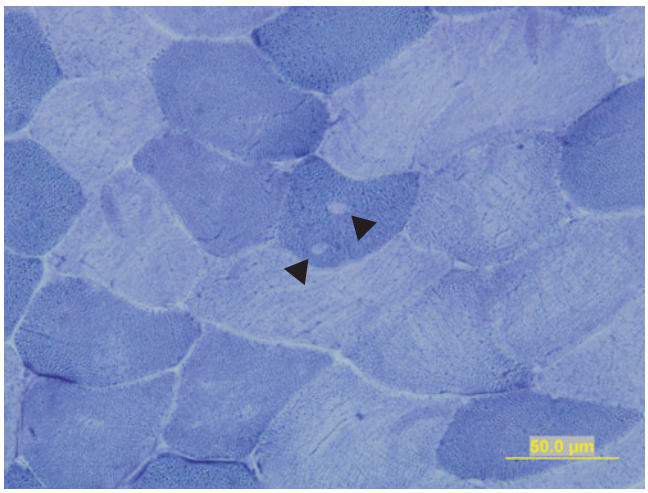


Figure 25–3. Multi/minicore myopathy. NADH stain demonstrates small areas devoid of oxidative enzyme activity.

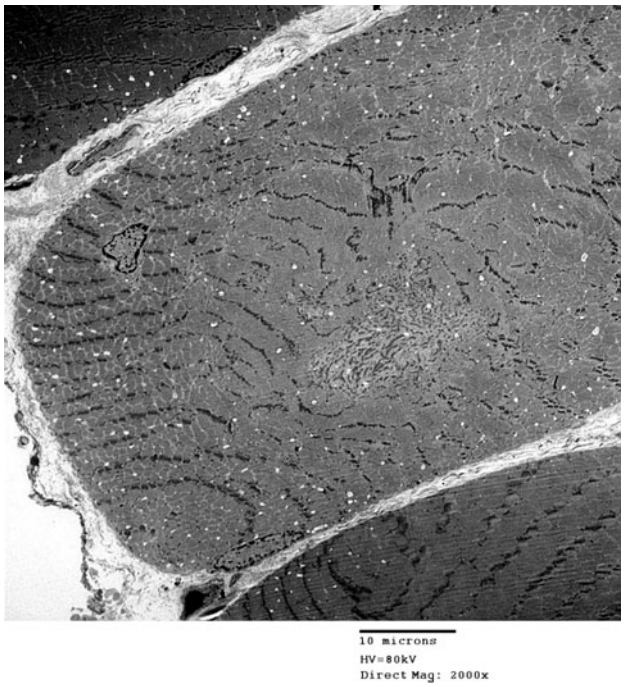


Figure 25–4. Multi/minicore myopathy. Electron microscopy reveals small areas of myofibrillar disarray similar to central core myopathy but much smaller.

MOLECULAR GENETICS AND PATHOGENESIS

This is a genetically heterogeneic group of disorders. The absence of clear dominant transmission in any well-established case and the presence of several consanguineous families strongly suggest that MmD usually is an autosomal-recessive entity or secondary to spontaneous mutations.[15] However, some patients with suspected MmD have demonstrable mutations in the RyR1 gene similar to central core myopathy an autosomal dominant disorder.[3,8,10,19,20] Mutations in the selenoprotein N gene (SEPN1), which is located on chromosome 1p36 (RSMD1 locus), have been demonstrated in some patients with classic MmD.[21] Of note, this is the same gene responsible for the congenital muscular dystrophy with rigid spine syndrome and some cases of myofibrillary myopathy.[21] The dystrophic changes and histological features of myofibrillar myopathy apparent on some muscle biopsies and SEPN1 mutations identified in some cases of MmD highlight the difficult nosological boundaries between various types of congenital myopathies and muscular dystrophies. In addition, mutations in coiflin-2 gene encoded on chromosome 14q13 have been reported in two siblings that had nemaline rods and minicores on muscle biopsy.

TREATMENT

No specific medical treatment is available. Patients may be at risk of malignant hyperthermia and should be counseled accordingly (see central core myopathy).[10,22,23] Early-onset scoliosis is common and may require extensive arthrodesis. Patients may require intermittent or continuous positive-pressure ventilation.

▶ NEMALINE MYOPATHY

CLINICAL FEATURES

Nemaline myopathy is clinically and genetically heterogenous. It can be inherited in an autosomal-dominant or autosomal-recessive fashion. There are three major clinical presentations of nemaline myopathy: (1) a severe infantile form, (2) a static or slowly progressive form, and (3) an adult-onset form.[24–34]

The severe infantile form is characterized by severe generalized weakness and hypotonia at birth. Muscle stretch and Moro reflexes are usually absent. Affected infants have a weak cry and suck. Because of ventilatory muscle involvement, they often need to be mechanically ventilated. Most children with this severe infantile-onset form of nemaline myopathy die in the first year of life due to ventilatory complications. Arthrogryposis, neonatal ventilatory failure, and failure to achieve early motor milestones are associated with early mortality.[29] Most are inherited in an autosomal-recessive inheritance pattern, but autosomal-dominant inheritance can also occur.[34]

More commonly, nemaline myopathy manifests as mild, nonprogressive, or slowly progressive weakness beginning in infancy or early childhood. Both proximal and distal extremity muscles are affected and associated with generalized reduced muscle bulk. Some patients have a facioscapuloperoneal distribution of weakness. Motor milestones are often delayed, and the children may exhibit a wide-based, waddling, hyperlordotic gait. Slight facial and masticatory muscle weakness may be appreciated, but ptosis and extraocular weakness are not typical. Many have a characteristic dysmorphic narrow facies with high-arched palate and micrognathia. In addition, multiple skeletal deformities such as pectus excavatum, kyphoscoliosis, pes cavus, or club feet are common. Deep tendon reflexes are reduced or absent. Most cases are inherited in an autosomal-dominant pattern, although autosomal-recessive inheritance is also seen.

The adult-onset type of nemaline rod myopathy is mild proximal and occasionally distal muscle weakness presenting in adulthood. Some patients have minimal skeletal muscle weakness but manifest with a cardiomyopathy. The adult-onset form is not associated with dysmorphic facial features or skeletal deformities typical of the early-onset forms.

Laboratory Features

The serum CK level is normal or slightly elevated. NCS are usually normal. Early recruitment of small-amplitude, short-duration MUAPs are appreciated in weak muscles on EMG. In the severe infantile forms, EMG may demonstrate increased insertional and spontaneous activity in the form of fibrillation potentials and positive sharp waves. Such abnormal spontaneous activity is usually not appreciated in the more benign forms of the myopathy.

Histopathology

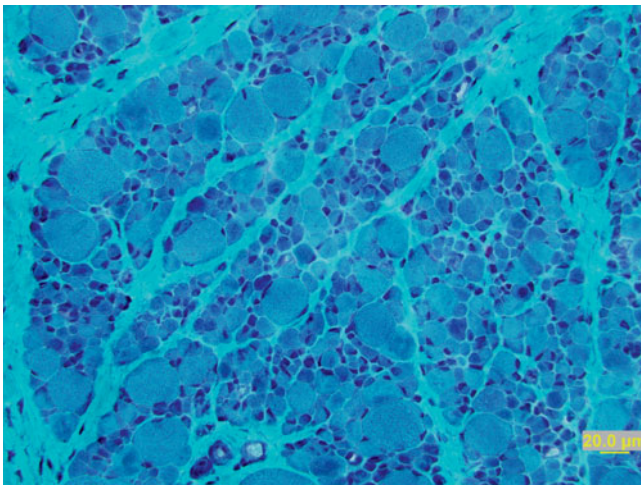
Muscle biopsies often reveal type 1 fiber predominance and hypotrophy in the congenital forms but not in the adult-onset form of the disease. On routine histochemistry, the nemaline rods are best appreciated on modified Gomori-trichrome stain, on which the rods appear as small, red-staining bodies in the subsarcolemma and occasionally perinuclear regions (Fig. 25–5). On EM, the typical "rod bodies" measure 3–6 μm in length and 1–3 μm in diameter, giving the appearance of threads (nemaline: Greek for "thread like").The nemaline rods have a density similar to the Z-disk (Fig. 25–6). Intranuclear rods may be observed, and early reports suggested that these represent a marker for this severe form of the disease (Fig. 25–7).[35–37] However, intranuclear rods are not demonstrated in all severe infantile cases and can also be found in milder adult-onset cases of nemaline myopathy.[28] Immunohistochemistry reveals that the rods and Z-disk are strongly immunoreactive for α-actinin.[38] Rods are not specific for congenital nemaline myopathy and have been reported following tenotomy; in HIV-associated myopathy, myofibrillar myopathy, myositis, and hypothyroidism.

MOLECULAR GENETICS AND PATHOGENESIS

Nemaline rods arise secondary to a derangement of proteins necessary to maintain normal Z-disk structure. The myopathy is genetically heterogeneic, with mutations having been identified in the genes that encode for α-tropomyosin (TPM3), beta-tropomyosin (TPN2), nebulin (NEM2), troponin T (TnT1), and α-actin (ACTA1) (Table 25–1).[34]

Autosomal-dominant nemaline myopathy has been linked to mutations in α-tropomyosin (TPM3) on chromosome 1q21–q23.[19,39,40] The severity of cases with TPM3 mutations vary from severe infantile to late childhood-onset, slowly progressive forms. Mutations in the beta-tropomyosin (TPN2) gene on chromosome 9p13 have also been demonstrated in some autosomal-dominant cases.[41]

Most of the autosomal-recessive cases are caused by mutations in the nebulin gene (NEM2) located on



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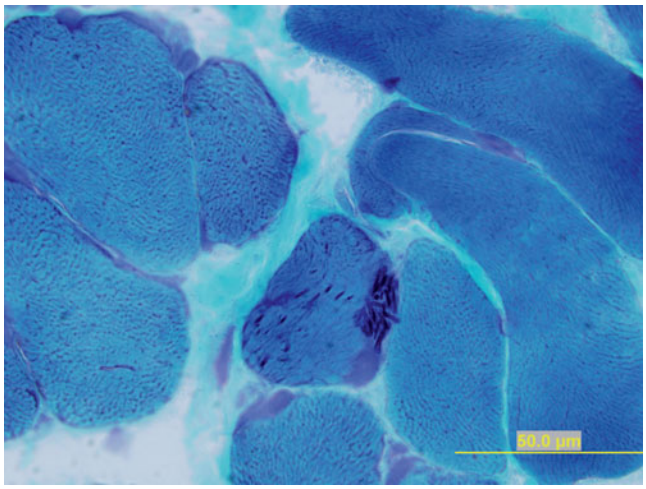

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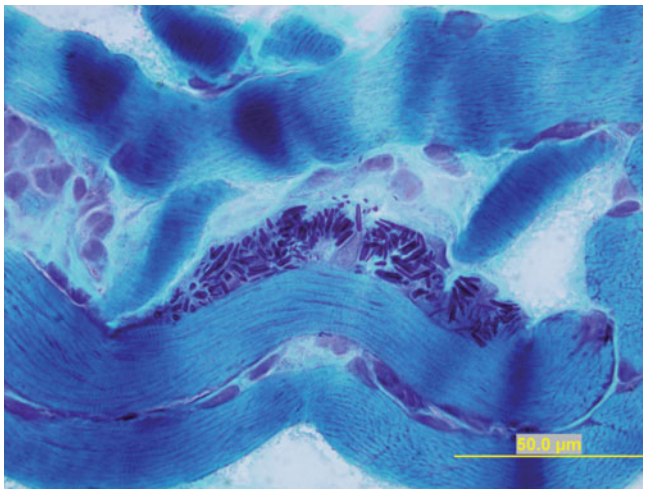


C

Figure 25–5. Nemaline myopathy. Infantile nemaline myopathy demonstrates many hypotrophic fibers (A). In an adult-onset nemaline myopathy, high-power light microscopy reveals subsarcolemmal cluster of reddish-purple staining rods in cross section (B) and on longitudinal sections (C). Modified Gomori-trichrome stain.

chromosome 2q21.2–q22.[42–45] In addition, a severe infantile form of autosomal-recessive nemaline myopathy found in Amish communities is caused by mutations in the muscle troponin T (TnT1) gene on chromosome 19q13.[46]

Mutations in the α-actin gene (ACTA1) located on chromosome 1q42 have been associated with autosomal-recessive and autosomal-dominant nemaline myopathy.[24,30,47,49] The severity of the disease caused ranges from lack of spontaneous movements at birth requiring immediate mechanical ventilation to mild disease compatible with life to adulthood. There are rare reported cases with adult onset as well.[24] Mutations in the ACTA1 gene are also responsible for previously reported cases of "congenital myopathy with excess of thin filaments."[30,48]

Mutations in the gene that encodes for the actin-binding protein, coiflin-2, located on chromosome 14q13 has been identified in two siblings with nemaline myopathy and minicores. In addition, a variant of nemaline myopathy and core-like lesions to was linked chromosome 15q21–q23 in two unrelated families.[22] The alpha-tropomyosin-1 gene (TPM1) located within this region is a strong candidate gene.

TREATMENT

No specific medical treatment is available. Morbidity from respiratory tract infections and feeding difficulties frequently diminish with increasing age; therefore, aggressive early management is warranted in most cases of severe infantile nemaline myopathy. Individuals who are affected may benefit from physical therapy and bracing.

▶ LATE-ONSET NEMALINE MYOPATHY

CLINICAL FEATURES

This myopathy is likely distinct from the truly congenital, hereditary myopathies and may be acquired as discussed below. The myopathy usually presents after the age of 40 years and can begin as late as the ninth decade.[5,50–52] Proximal, distal, or generalized muscle involvement can

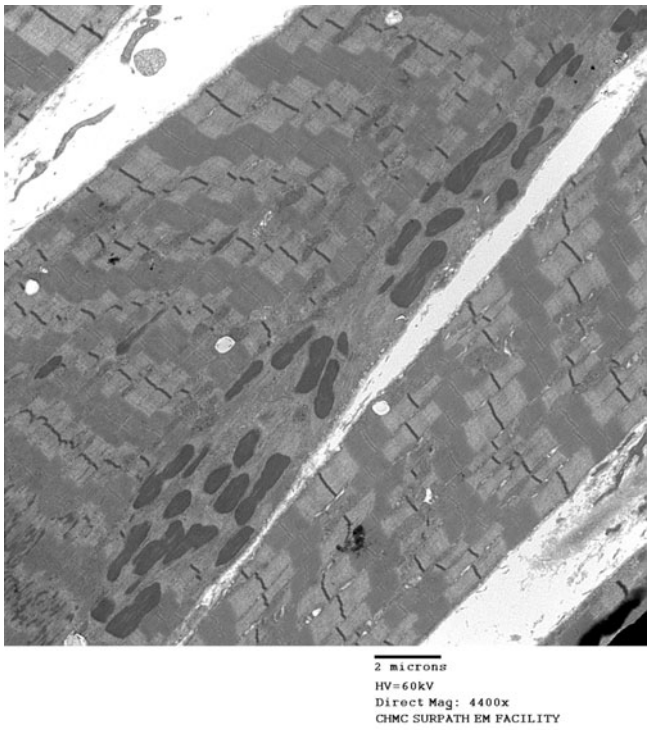


Figure 25–6. Nemaline myopathy. Electron microscopy reveals rods appearing as osmiophilic bodies, which have the same density as the Z-disks.

occur. Some patients may present with isolated neck weakness. Respiratory muscle involvement may ensure and be cause of death, particularly in cases associated with a monoclonal gammopathy.

LABORATORY FEATURES

Serum CK is usually normal. Motor and sensory NCS are normal. EMG reveals increased insertional and spontaneous activity in the form of positive sharp waves, fibrillation potentials, and early recruitment of short-duration, small-amplitude MUAPs. About 50% of cases are associated with a monoclonal gammopathy of undetermined significance.[5,50–52]

HISTOPATHOLOGY

Routine light and electron microscopy demonstrates typical nemaline rods. The rods may be very short and therefore may be missed on routine light microscopy if thickness of the sections is greater that 3 μm.[50] However, the rods are almost always appreciated on EM.

MOLECULAR GENETICS AND PATHOGENESIS

This appears to be a sporadic disorder, and no genetic mutations have been reported. It may be an acquired myopathy as opposed to a hereditary disease. The relationship between the nemaline myopathy and the monoclonal gammopathy is not clear.

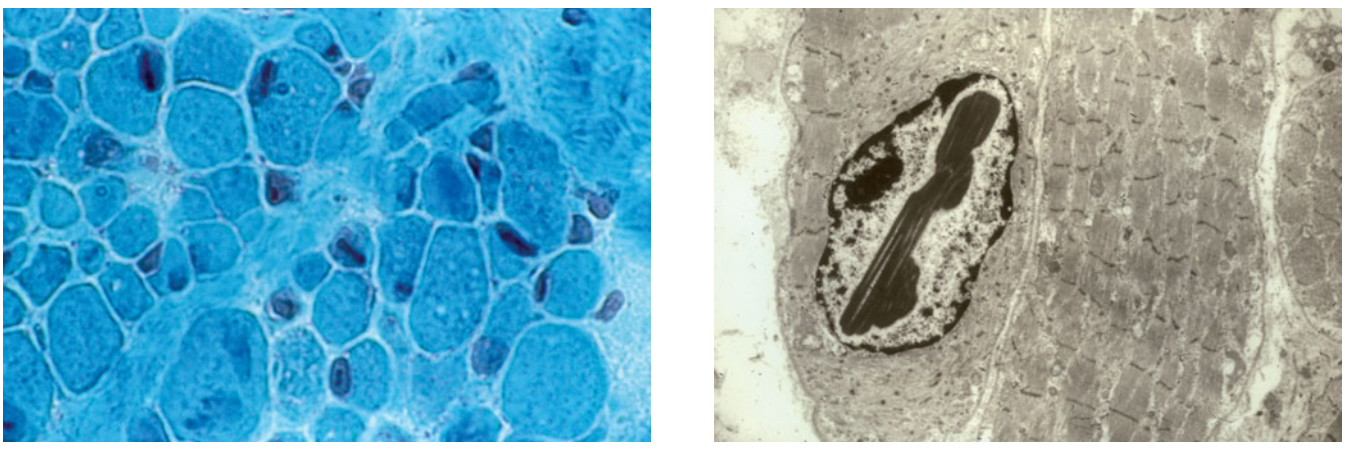
TREATMENT

The response to treatment with various immunotherapies in patients with late-onset nemaline myopathy with a monoclonal gammopathy appears to be poor.

▶ CENTRONUCLEAR MYOPATHY

CLINICAL FEATURES

Spiro and colleagues first introduced the term "myotubular myopathy" to describe this myopathy, given its resemblance to myotubes on muscle biopsies.[53] However, this myopathy is not caused by an arrest of



A B

Figure 25–7. Nemaline myopathy. Intranuclear rods are apparent on this modified Gomori trichrome stain (A) and on electron microscopy (B).

myotubes and the term "centronuclear myopathy" is more appropriate. At least three clinically different forms of the disease are recognized: (1) a slowly progressive, infantile–early childhood type; (2) a severe X-linked neonatal type; and (3) a late childhood or adult-onset type.[54–57]

The slowly progressive, infantile–early childhood type is the most common presentation. These cases may be inherited in an autosomal-recessive or autosomal-dominant fashion. Children who are affected are usually the product of a normal pregnancy and delivery. Mild hypotonia and generalized weakness are apparent in infancy or early childhood, and motor milestones are typically delayed. Ambulation is usually achieved, but the gait may be wide based and hyperlordotic. As with nemaline myopathy, generalized muscle atrophy, elongated narrow facies, and high-arched palate are often appreciated. Unlike other forms of congenital myopathy, ptosis and ophthalmoparesis are common in centronuclear myopathy. Muscle stretch reflexes are depressed or absent, but sensation is completely normal. Some children have mental retardation and seizures.

The X-linked recessive myotubular myopathy presents at birth with severe hypotonia and generalized weakness. Affected infants usually require ventilatory support and feeding tubes. Polyhydramnios is a frequent complication of the mother's pregnancy. Ptosis and ophthalmoparesis may not be apparent initially but become more prominent after the newborn period. Arthrogryposis may be evident. X-linked myotubular myopathy is usually fatal in infancy; however, the prognosis is not invariably poor.[56,57] In a review of 40 cases, six affected boys were alive between the ages of 6 months and 27 years (mean 10 years).[57] All but one had respiratory difficulties at birth, and two still needed mechanical ventilation at the ages of 8 and 10 years. Yet, four boys eventually were able to walk and three had no significant disabilities at the ages of 6 months, 5 years, and 7 years. With aggressive medical intervention, the survival rate has increased.[56]

Interestingly, there have been a few well-described cases of manifesting females with proven X-linked (myotubularin deficiency) centronuclear myopathy.[58–60] Affected woman can present with axial and proximal weakness, bilateral ptosis, and external ophthalmoplegia with onset in childhood or adult. The mechanism may be akin to skewed inactivation, as sometimes seen in manifesting female carriers of dystrophin mutations.

A more benign form of centronuclear myopathy can present in late childhood or adulthood. Muscle weakness is usually mild and only slowly progressive. The pattern of muscle weakness is quite variable, with some patients having predominantly proximal weakness, while the distal muscles are more affected in others. Facial muscles may be weak, and some have ptosis and ophthalmoparesis. A facioscapulohumeral pattern of weakness has also been described.[61] Unlike infantile- and childhood-onset cases, dysmorphic facial features and skeletal anomalies are not associated with the adult-onset form of centronuclear myopathy. Some of these cases are felt to be autosomal-dominantly inherited.

LABORATORY FEATURES

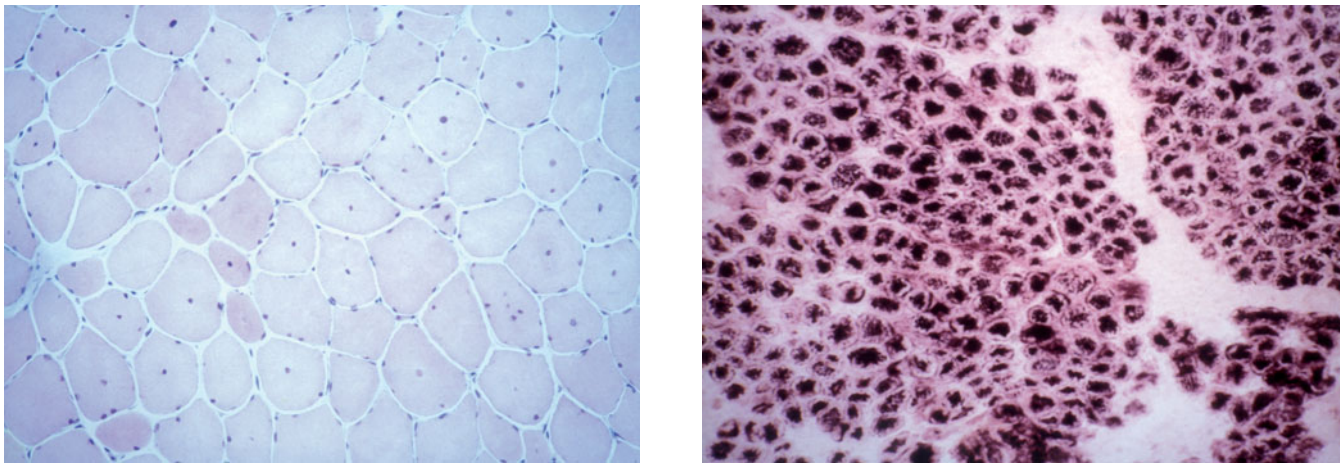
Serum CK is normal or slightly elevated. Motor and sensory NCS are normal. However, EMG is usually very abnormal, particularly in the severe X-linked infantile-onset form, revealing increased insertional and spontaneous activity in the form of positive sharp waves, fibrillation potentials, complex repetitive discharges, and even myotonic discharges.[6] Early recruitment of short-duration, small-amplitude MUAPs are evident in weak muscles. Reduced amplitudes and mild slowing of motor and sensory NCS have been noted in some individuals with mutations in dynamin 2 gene (discussed in "Pathogenesis" section), which is not surprising as this is also a cause of dominant intermediate Charcot–Marie–Tooth disease type B(DI-CMTB).

HISTOPATHOLOGY

Muscle biopsies reveal myonuclei in the center of muscle fibers, often forming chains when viewed longitudinally.[55] Occasionally, the nuclei cluster in the center of the fiber rather than forming longitudinal chains. On transverse section, the number of muscle fibers with central nuclei range from 25% to 95% (Fig. 25–8). The central nuclei appear in both fiber types. On ATPase stains, there is small perinuclear halo devoid of ATPase activity. With oxidative enzyme stains, center of muscle fibers appear dark and there is a radial arrangement of the intermyofibrillar network, which resembles spokes on a wheel. The type 1 fibers predominate and appear hypotrophic, while the type 2 fibers are normal in size. Muscles biopsies of obligate female of X-linked myotubular myopathy may also show mild abnormalities.[57] On EM, there are reduced myofibrils and an excess of mitochondria and glycogen granules in the center of muscle fibers that are not occupied by nuclei.

MOLECULAR GENETICS AND PATHOGENESIS

As noted previously, there is genetic heterogeneity between the different forms of centronuclear myopathy (Table 25–1). The severe X-linked neonatal form is caused by mutations in the myotubularin gene (*MTM1*).[62,63] Myotubularin is a dual-specificity phosphatase, which plays a role in muscle cell growth and differentiation. Terminal muscle fiber differentiation is dependent on the hypophosphorylation of specific gene-regulating proteins.[64] Myotubularin is thought to dephosphorylate these regulating proteins, and



A B

Figure 25–8. Centronuclear myopathy. Increased number of internalized nuclei often in the center of the muscle fiber is appreciated (A), hematoxylin and eosin (H&E). Late childhood- and adult-onset cases often have increased nuclei more randomly located throughout the fibers. Central areas appear dark on NADH-TR (B).

mutations in the myotubularin gene lead to loss of function of this phosphatase activity, resulting in maturational disturbances of muscle.

Some autosomal-dominant cases of late-onset centronuclear myopathy characterized by prominent distal limb weakness and ptosis have been linked to mutations in the *DNM2* gene on chromosome 19p13.2, which encodes for dynamin-2.[54,65] Recently, mutations in this gene have also been reported in 5 sporadic cases of severe neonatal centronuclear myopathy. Of note, mutations in this gene cause dominant intermediate Charcot-Marie-Tooth disease B(DI-CMTB),[66] thus explaining some of the overlapping features (distal weakness, mild sensory abnormalities) that might be seen. Dynamin-2 belongs to the family of large GTPases and is important in endocytosis, membrane trafficking, actin assembly, and centrosome cohesion.[54]

The autosomal-recessive forms of centronuclear myopathy have not been genetically linked.

TREATMENT

Infants with the X-linked form of the disease often require mechanical ventilation and tube feedings to support life. With such aggressive medical intervention, the survival rate has increased.[56]

▶ CONGENITAL FIBER-TYPE DISPROPORTION

CLINICAL FEATURES

Congenital fiber-type disproportion usually manifestes as generalized hypotonia and weakness along with a weak cry and suck in infancy.[6] Motor milestones are delayed, but muscle weakness is usually nonprogressive and functional status improves with age attained. However, there are cases with a progressive and sometimes fatal course secondary to respiratory muscle insufficiency.[67] Some children who are affected display dysmorphic facial features with a high-arched palate, congenital hip dislocations, kyphoscoliosis, arthrogryposis, and a rigid spine. Muscle stretch reflexes are reduced. Approximately one-third of patients have some type of central nervous system abnormalities; some of these cases may represent forms of congenital muscular dystrophy with impaired glycosylation of alpha-dystroglycan (see Chapter 24).

LABORATORY FEATURES

The serum CK is normal or mildly elevated. NCS are normal. EMG can be normal or can reveal increased insertional and spontaneous activity and early recruitment of myopathic MUAPs.[6]

HISTOPATHOLOGY

Muscle biopsies reveal a disproportion in the size of type 1 compared to type 2 fibers.[67] While type 1 fibers are more numerous, they are typically less than 15% the diameter of type 2 fibers, which appear normal in size or slightly hypertrophic (Fig. 25–9). However, type 1 fiber predominance and hypotrophy are not specific for this myopathy, and these are also common in centronuclear and nemaline myopathy and may also be found in congenital muscular dystrophies, spinal muscular atrophy,

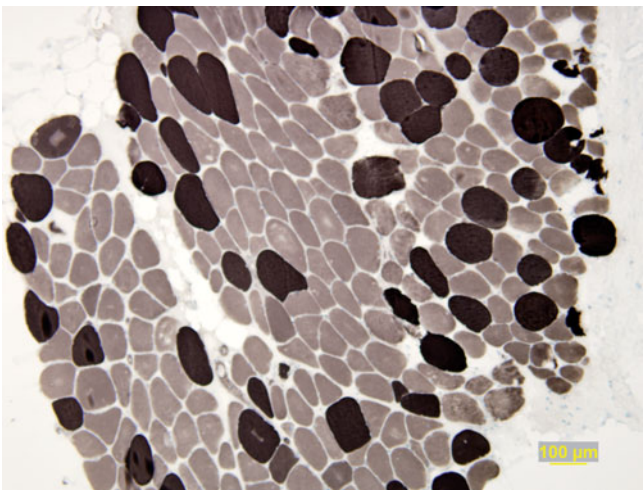


Figure 25–9. Congenital fiber-type disproportion. Type 1 fibers are more numerous but smaller in diameter than the type 2 fibers. However, type 1 fiber predominance and hypotrophy are not specific for this myopathy, and these are also common in other forms of congenital myopathy and congenital muscular dystrophy. ATPase 9.4.

and central nervous system disease. With sequential muscle biopsies, nemaline rods or central nuclei may become apparent.[68] No consistent ultrastructural abnormalities have been noted.

MOLECULAR GENETICS AND PATHOGENESIS

Most cases are sporadic in occurrence, although there are some cases that appear to be inherited in an autosomal-dominant and others in an autosomal-recessive fashion. Some cases have been linked to mutations in ACTA1 gene, suggesting that these were in fact nemaline myopathies in which the rods were not apparent on the muscle biopsies, and others have been found to have selenoprotein N1 mutations.[69]

TREATMENT

Supportive measures in regard to mechanical ventilation and tube feeding may be temporarily required in some patients. Physical therapy and orthotic devises may be beneficial.

▶ SARCOTUBULAR MYOPATHY

CLINICAL FEATURES

Sarcotubular myopathy was initially reported in two Hutterite brothers of a consanguineous marriage.[70] Subsequently, it has been demonstrated that this disorder is allelic to LGMD 2H.[71] Patients can present with exertional myalgias or proximal muscle weakness in infancy or adult life. Scapular winging, calf hypertrophy, foot drop, and mild facial weakness may be appreciated. Muscle stretch reflexes are usually diminished.

Laboratory Features

Serum CK levels have ranged from normal to 20-fold elevated.[70,71] EMG may be normal or may reveal myopathic features.

Histopathology

Muscle biopsy revealed increase in internal nuclei, muscle fiber splitting, and many fibers (mostly type 2) with small vacuoles.[70,71] These vacuoles abutt T-tubules, appear to be membrane bound, and are empty or contain a small amount of amorphous debris on EM. The vacuoles immunostain for sarcoplasmic reticulum-associated ATPase.

MOLECULAR GENETICS AND PATHOGENESIS

Mutations in *TRIM 32*, the gene encoding the tripartite motif-containing protein 32, have been demonstrated in two families; thus, this disorder is allelic to LGMD 2H.[71] TRIM 32 may be critical for the recognition of protein(s) targeted to be ubiquinated by this ligase enzyme.

TREATMENT

There is no specific medical treatment.

▶ FINGERPRINT BODY MYOPATHY

CLINICAL FEATURES

Fingerprint body myopathy is a rare disorder and typically presents as generalized hypotonia, weakness, and muscle atrophy in infancy or early childhood.[72–74] Muscle strength is stable or only slowly deteriorates over time. Muscle stretch reflexes are reduced or absent. Some individuals have a reduced intelligence and febrile seizures. In addition, kyphoscoliosis and pectus excavatum may be evident in some cases.

LABORATORY FEATURES

Serum CKs are normal or slightly elevated. NCS are normal. EMG may be normal or may demonstrate short-duration, low-amplitude MUAPs without abnormal insertional or spontaneous activity.

Histopathology

Muscle biopsy reveals type 1 fiber predominance with type 1 fiber hypotrophy and type 2 fiber hypertrophy. On oxidative enzyme stains, there is reduced activity in the subsarcolemma and perinuclear regions in type 1 fibers. EM and phase-contrast microscopy demonstrate a complex lamellar pattern resembling fingerprints that are evident in these areas; these fingerprint bodies appear to be composed of cytoskeletal proteins.[72–74] Fingerprint bodies are nonspecific and have also been noted in myotonic dystrophy, various distal myopathies, nemaline myopathy, dermatomyositis, oculopharyngeal dystrophy, and muscle biopsies from patients with uremia and chronic pulmonary disease.

MOLECULAR GENETICS AND PATHOGENESIS

Most of the cases have been sporadic, although the disease was reported in a pair of male identical twins[72] and in two siblings.[74] The pathogenic mechanism for the formation of the fingerprint bodies is not known.

Treatment

There is no specific medical treatment.

▶ TRILAMINAR MYOPATHY

CLINICAL FEATURES

A single infant with rigidity of its trunk and limbs, decreased spontaneous movements, weak suck and swallowing, and numerous joint contractures has been reported with this disorder.[75] Sensation appeared normal and deep tendon reflexes were intact. By 10 months of age, the infant had some head control but was still unable to sit. Subsequently, the patient was able to ambulate, albeit with difficulty.

LABORATORY FEATURES

Serum CK was markedly elevated at birth (approximately 40 times normal). EMG and NCS were normal.

HISTOPATHOLOGY

Muscle biopsy demonstrated variability in fiber size. The unique feature was that approximately 25% of fibers were hypertrophic and had three concentric zones that displayed a differential staining pattern.[75] The inner and outer zones stained intensely with Gomori-trichrome and NADH stains, while the inverse pattern was seen on ATPase staining. On EM, the innermost zone demonstrated myofibrillar disarray and densely packed mitochondria, glycogen granules, and myofilaments. The intermediate zone revealed Z-band streaming. The outer zone was composed of disorganized myofibrils, mitochondria, lipid droplets, and vesicles.

MOLECULAR GENETICS AND PATHOGENESIS

The pathogenesis is unknown.

TREATMENT

No specific medical treatment is available.

▶ HYALINE BODY MYOPATHY/FAMILIAL MYOPATHY WITH LYSIS OF MYOFIBRILS

CLINICAL FEATURES

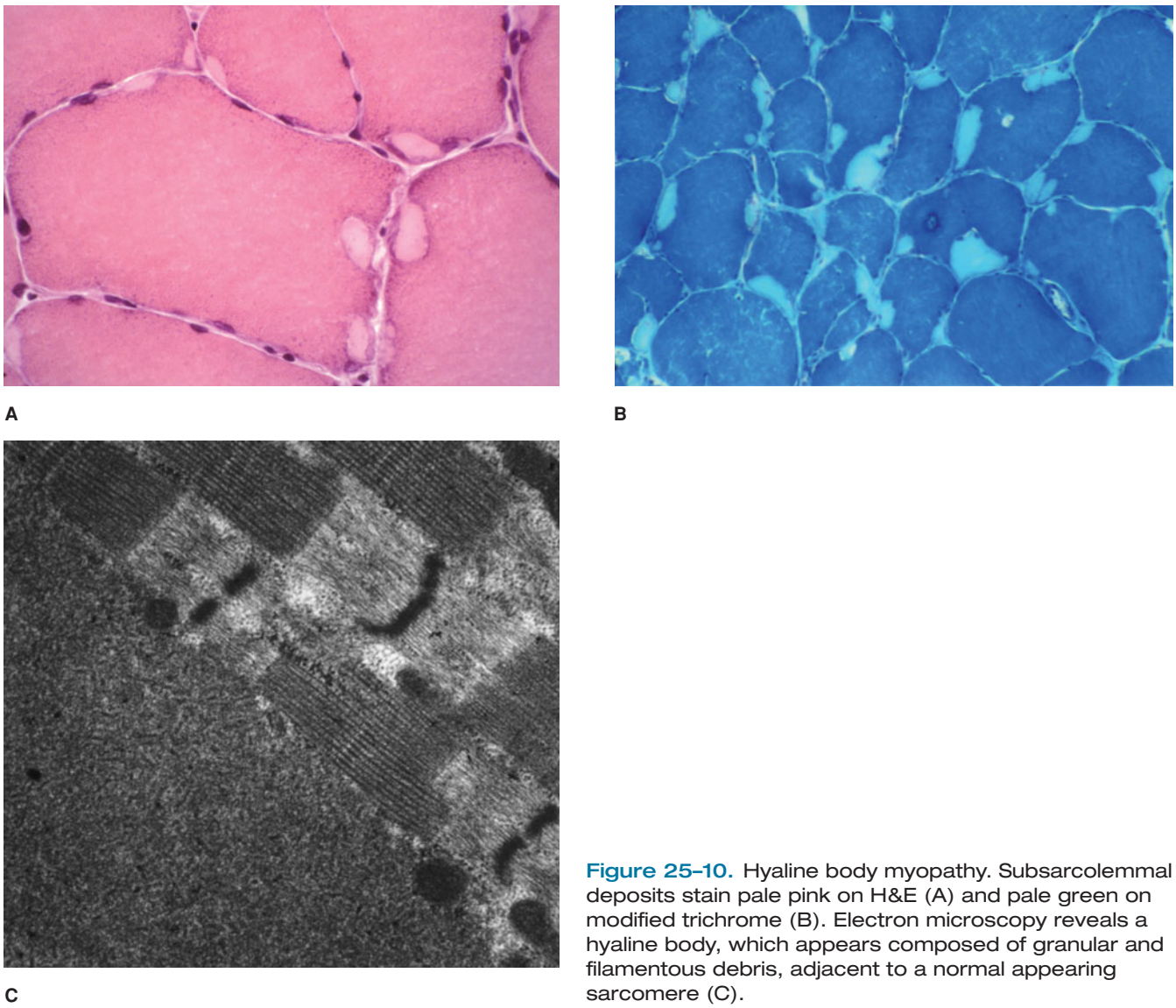
Hyaline body myopathy is a rare congenital myopathy, which can present in infancy to as late as the fifth decade of life with limb-girdle or scapuloperoneal pattern of weakness.[5,76–82] Muscle strength is stable or only slowly deteriorates and is nonprogressive. Rare patients have a cardiomyopathy.[81] Muscle stretch reflexes are preserved. Hyaline body myopathy has been reported as occurring sporadically as well as being inherited in an autosomal-dominant or autosomal-recessive fashion. There is variability in the severity of the course even within families.

LABORATORY FEATURES

Serum CK levels can be normal or mildly elevated, while EMG studies may be normal or may reveal an increased number of small-duration, low-amplitude, polyphasic MUAPs.[14,81] Echocardiograms may reveal a dilated cardiomyopathy with reduced ejection fraction.[81]

HISTOPATHOLOGY

Muscle biopsies reveal subsarcolemmal "hyaline" bodies that stain pale green on modified Gomori-trichrome and pale pink on H&E stains (Fig. 25–10).[5,76–82] The hyaline bodies occur in type 1 fibers, which are hypotrophic. The hyaline bodies do not stain with oxidative enzymes or periodic acid Schiff (PAS) but demonstrate intense ATPase activity. Angulated neurogenic fibers and fiber-type grouping may also be appreciated. Immunostaining demonstrates strong reactivity for slow myosin heavy chain (MyHC) in some but



A B C

Figure 25–10. Hyaline body myopathy. Subsarcolemmal deposits stain pale pink on H&E (A) and pale green on modified trichrome (B). Electron microscopy reveals a hyaline body, which appears composed of granular and filamentous debris, adjacent to a normal appearing sarcomere (C).

not all hyaline bodies.[78,82] The hyaline bodies are nonreactive for alpha-B-crystalin, ubiquitin, tropomyosin, actins, desmin, and components of sarcolemma. On EM, the hyaline bodies appear to be composed of granulofilamentous debris often with fragments of sarcomeres and surrounded by a zone of sarcomeric disorganization.[78]

MOLECULAR GENETICS AND PATHOGENESIS

Missense mutations in the MYH7 gene on chromosome 14q11.2 that encodes for slow/beta-cardiac MyHC have been identified in several different families with autosomal-dominant hyaline body myopathy.[77,79,82] Mutations in this gene also have been associated with a familial form of cardiomyopathy. Interestingly, despite extensive workup, cardiomyopathy has not been reported in patients with hyaline body myopathy harboring mutations in this gene.[77,82] This disorder appears to be genetically heterogeneic, as one family with two affected siblings localized to chromosome 3p22.2–p21.32.[81] Within this region lies a candidate who exhibits homology to the MyHC. It appears that normal MyHC is essential for the assembly of thick filaments in skeletal muscle.

TREATMENT

There is no specific medical treatment available.

▶ OTHER MYOSIN STORAGE DISORDERS

Another autosomal-dominant myopathy characterized by mild weakness and myalgias with onset in childhood or early adult life has been linked to mutations

in the *MYH2* gene located on chromosome 17p13.1, which encodes for MyHC IIa.[83,84] The MyHC IIa isoform of MyHCs is expressed in type 2A muscle fibers. Other families present with congenital arthrogryposis, ophthalmoplegia, and mild proximal weakness beginning in adulthood. As muscle biopsies may demonstrate rimmed vacuoles and tubulofilamentous inclusions, this disorder has also been called hereditary inclusion body myopathy type 3 (see Chapter 24).[85,86].

▶ CAP DISEASE

CLINICAL FEATURES

This rare myopathy is associated with neonatal onset of generalized muscle weakness and hypotonia associated with skeletal deformities and reduced muscle stretch reflexes.[87] Respiratory muscles are also frequently affected.

LABORATORY FEATURES

Serum CK is normal. NCS are normal, while EMG demonstrates myopathic MUAPs.

HISTOPATHOLOGY

Muscle biopsies reveal many muscle fibers that contain a peripheral crescent that reacts strongly to NADH-TR, PAS, and phosphorylase but not to SDH or myofibrillar ATPase. Immunohistochemistry reveals that these "caps" display increased fast myosin activity, desmin, tropomyosin, and alpha-actinin.[88] On EM, there is widened Z-bands, disarray of the myofibrils, and lack of thick filaments.

MOLECULAR GENETICS AND PATHOGENESIS

This myopathy has recently been reported to be caused by mutations in beta-tropomyosin (TPN2) gene which also cause a type of nemaline myopathy.

TREATMENT

There is no specific medical treatment available.

▶ ZEBRA BODY MYOPATHY

CLINICAL FEATURES

Only a few of cases of zebra body myopathy have been reported.[89,90] One child presented with generalized weakness and atrophy from birth.[89] The second report involved a child with severe hypotonia, dysphagia, and asymmetric weakness of the upper limbs.[90] Muscle weakness was stable or only slowly progressive.

LABORATORY FEATURES

Serum CK is two to three times normal. EMG reveals myopathic units without abnormal spontaneous activity.

HISTOPATHOLOGY

Muscle biopsies demonstrate variability in muscle fiber size, increased internal nuclei, and occasional vacuoles. The Z-bodies appear on EM as osmiophilic 270-mm stria, with a periodicity such that these resemble stripes on a zebra.[89,90] The density of the stria is that of Z-disks and measuring up to 2 nm in length. Streaming of the Z-bands and nemaline rods may also be appreciated.

MOLECULAR GENETICS AND PATHOGENESIS

Zebra bodies are not a specific abnormality and can be found in normal individuals at myotendonous junctions, in intrafusal fibers (muscle spindles), in extraocular muscles, and in cardiac muscles. These may also be found in other pathologic conditions (e.g., myofibrillar myopathy). The pathogenic basis for the disease is not known but may be secondary to mutations alpha-actin gene (ACTA1).

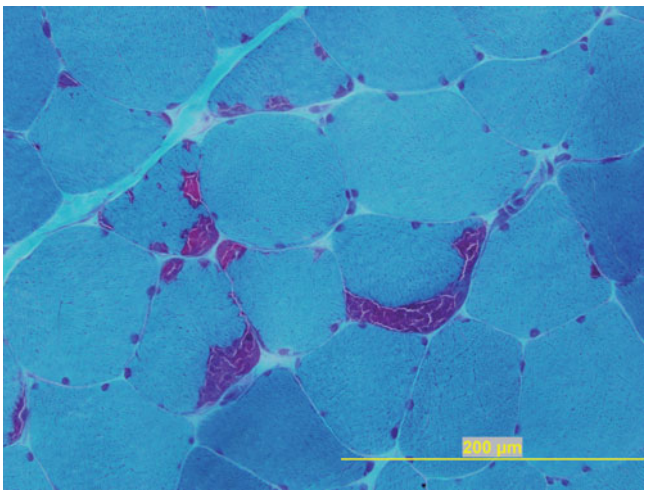
TREATMENT

There is no specific medical treatment available.

▶ TUBULAR AGGREGATE MYOPATHY

CLINICAL FEATURES

Tubular aggregates are a nonspecific histological abnormality, which may be found in muscle biopsies of patients with hereditary periodic paralysis, hyperthyroidism, congenital myasthenia (slow channel syndrome), hypoxia, and some toxic myopathies. In addition, tubular aggregates are also found on muscle biopsy of patients with no symptoms or signs of a myopathy. However, there are three clinical syndromes in which the primary pathologic feature is tubular aggregates on muscle biopsy.[85,91,92] Individuals who are affected may have slow progressive limb-girdle weakness beginning in childhood or early adulthood. Additionally,



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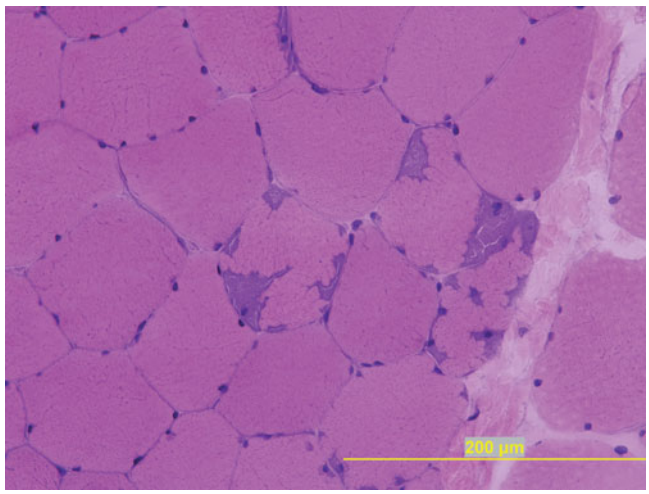

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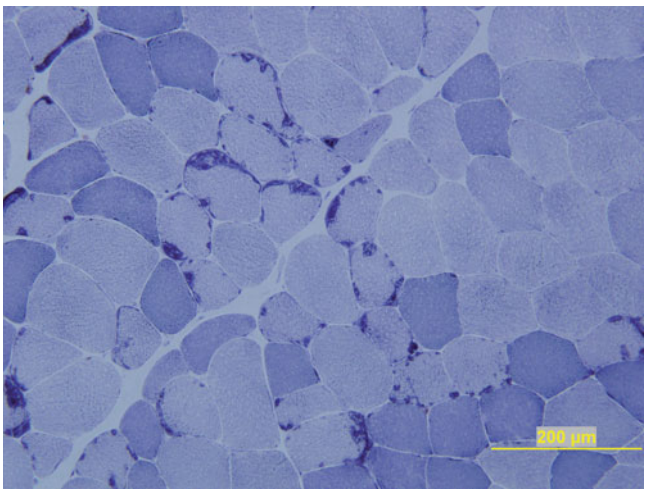

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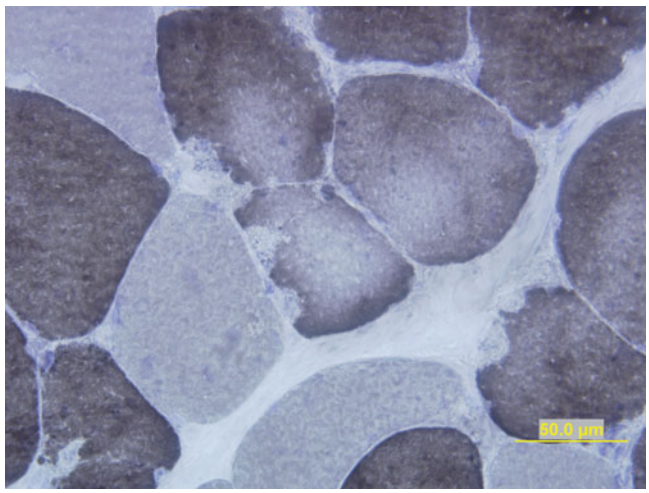

D

Figure 25–11. Tubular aggregates. Tubular aggregates appear as subsarcolemmal masses of reddish material on modified trichome (A) and are bluish on H&E (B). The tubular aggregates occur only in type 2 fibers and appear densely staining on NADH-TR (C), but do not stain with ATPase 9.4 (D).

there is a form that resembles congenital myasthenia, which presents as a slowly progressive muscle weakness from infancy.[91] These patients demonstrate fatigable weakness, which improves with anticholinesterase medications. Another clinical subgroup comprises patients with generalized myalgias, which are worse with exertion.[85,92] Muscle tone, bulk, and strength are normal as is the rest of the physical examination.

LABORATORY FEATURES

Serum CK is normal or mildly increased. Routine motor and sensory NCS are normal. Patients with the myasthenic syndrome demonstrate a decremental response on repetitive stimulation, which improves with pyridostigmine. EMG can be normal or can demonstrate myopathic MUAPs and fibrillation potentials. Patients with the muscle-pain syndrome typically have completely normal electrodiagnostic findings.

HISTOPATHOLOGY

Tubular aggregates stain basophilic on H&E and are red on modified Gomori trichrome (Fig. 25–11(A)). These react intensely to NADH-TR (Fig. 25–11(B)) but not to SDH. Tubular aggregates are located subsarcolemmal and are present only in type 2 muscle fibers in the syndromes associated with periodic paralysis and muscle pain but are evident in both fiber types in the limb-girdle syndrome. On EM aggregates are composed of bundles of tubules 60–80 nm in diameter, which course in various directions with respect to the long axis of the muscle fibers (Fig. 25–12).

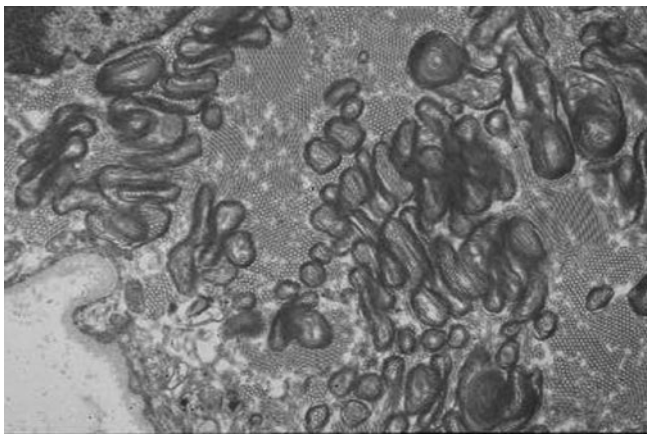

Figure 25–12. Tubular aggregates. On EM, tubular aggregates appear as subsarcolemmal aggregates of long, straight parallel tubules, which are somewhat haphazardly oriented in small bundles.

MOLECULAR GENETICS AND PATHOGENESIS

The limb-girdle syndrome may be inherited in an autosomal-dominant or autosomal-recessive manner. The tubular aggregates associated with congenital myasthenic syndrome are inherited in an autosomal-recessive pattern. Most cases of the muscle-pain syndrome are sporadic in occurrence, although families with dominant inheritance have also been described. The pathogenic basis for the formation of tubular aggregates is not known but has been postulated to represent an adaptive response of muscle fibers to injury.

TREATMENT

Patients with the congenital myasthenic syndrome may benefit from pyridostigmine. Individuals with the muscle pain syndrome may improve with dantrolene or tricyclic antidepressant medications.

▶ REDUCING BODY MYOPATHY

CLINICAL FEATURES

Reducing body myopathy is a rare disorder that has varied clinical presentations.[93–96] It can present in infancy with severe generalized weakness, hypotonia, and joint contractures. Ptosis may be apparent as well. There is an increased mortality due to associated respiratory muscle weakness. Some individuals who are affected apparently develop muscle weakness later in childhood or in adulthood. The proximal or distal muscles may be preferentially affected, and involvement can be asymmetric, particularly in the arms. The course can vary from mild stable weakness to progressive deterioration of strength, leading to death. Some patients who are affected develop contractures of the major joints, scoliosis, and rigidity of the spine.

LABORATORY FEATURES

Serum CK levels are usually normal, although a few patients have demonstrated mild elevations. NCS are normal. EMG may demonstrate myopathic features.

HISTOPATHOLOGY

The characteristic feature on muscle biopsies are "reducing bodies," named such because of their unique ability to reduce nitroblue tetrazolium when mediated by menadione.[93–96] These reducing bodies stain purple with modified Gomori-trichrome stain and pink on H&E stain and are devoid of oxidative enzyme staining. Immunohistochemistry reveals increased desmin at the periphery of some reducing bodies, but αB crystallin, α-actinin, titin, and nebulin immunostains are normal. There is usually type 1 fiber predominance as seen in most other congenital myopathies, but the reducing bodies are evident in both fiber types. On EM, the reducing bodies appear to be composed of electron-dense granules and 12–17-nm tubulofilaments.

MOLECULAR GENETICS AND PATHOGENESIS

The majority of cases appear to be sporadic in nature, although familial cases have been described. The pathogenesis is unknown. In many ways the histopathology resembles that seen in myofibrillar myopathy (discussed in Chapter 24) and may in fact be the same entity.

TREATMENT

No specific treatment is available.

▶ MYOFIBRILLAR MYOPATHY

This is a genetically heterogeneic group of disorders, which are now considered to be forms of muscular dystrophy as opposed to congenital myopathies and are discussed in detail in Chapter 24.

▶ SUMMARY

As evident from this chapter, there is significant overlap in what have previously been termed congenital myopathies and congenital and limb-girdle dystrophies. Continued advances in molecular genetics have

provided and will likely provide better insight into the classification of these myopathies. Unfortunately, there are no medications as yet available to these disorders. However, physical and occupational therapy as well as supportive therapy for respiratory or cardiac muscle involvement can be beneficial.

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CHAPTER 26

Metabolic Myopathies

The inherited metabolic myopathies are traditionally classified by their underlying biochemical abnormalities as disorders of (1) carbohydrate, (2) lipid, and (3) adenine nucleotide metabolism.[1] A fourth possible category includes the mitochondrial encephalomyopathies, but these do not cause defects in a specific biochemical pathway and will be discussed in a separate chapter. The immediate source of energy for muscles comes from the hydrolysis of adenosine triphosphate (ATP). At rest, the major substrate for muscle in terms of ATP production comes form metabolism of long-chain fatty acids. Therefore, any disorder impairing β-oxidation of long-chain fatty acids in the mitochondria can lead to a significant myopathy. During exercise, ATP is derived from metabolism of carbohydrates, fatty acids, and ketones. Early in the course of exercise (e.g., up to 45 minutes), energy is derived mainly from free glucose or glucose made available via glycogenolysis. Subsequently, there is a shift toward the metabolism of fatty acids such that after a few hours 70% of energy is derived from lipid breakdown.

Metabolic myopathies can also be viewed as static or dynamic disorders. The static myopathies are defined by the presence of fixed or progressive weakness. On the other hand, the dynamic myopathies are associated with exercise intolerance (i.e., exertional myalgias, cramps, and myoglobinuria) as the dominant clinical features. Some metabolic defects are associated with both a dynamic and a static myopathy.

▶ DISORDERS OF CARBOHYDRATE METABOLISM

Carbohydrates are stored in liver and muscle as glycogen, a highly branched polymer of glucose. Normal synthesis and breakdown of glycogen is essential to maintain adequate glucose concentration in muscle that can be further metabolized and provide energy in the form of ATP. There are 14 currently recognized glycogen storage diseases (GSDs), also called glycogenoses (Table 26–1). This is somewhat of a misnomer because some of these glycogenoses do not result in the accumulation of glycogen in tissues.

The glycogenoses predominantly affect the liver and the muscle. Since there is differential metabolism of carbohydrates in these two tissues, the individual GSDs may produce strictly liver or muscle disease, or some combination of the two. Types I (glucose 6-phosphatase deficiency) and VI (liver phosphorylase deficiency) only cause liver disease and are not further discussed. Types II (lysosomal α-glucosidase deficiency), V (phosphorylase deficiency), VII (phosphofructokinase [PFK] deficiency), X (phosphoglycerate mutase [PGAM] deficiency), and XI (lactate dehydrogenase deficiency) produce almost exclusively muscle disease, while the remaining types produce a varying mixture of muscle disease with systemic disease.

The pathophysiologic basis by which the varied enzymatic defects lead to muscle dysfunction remains largely unknown. The inability to metabolize a substrate reduces the ability of muscle cells to form ATP necessary for normal energy production. Further, the enzymatic defects may result in accumulation of metabolites, which may be toxic to muscle.

The exercise forearm test can be used to diagnose various disorders of glycolysis. The test can be adequately performed without blood pressure cuff insufflation. In fact, performing this test with the limb ischemic may be hazardous to the patient because it can induce profound muscle damage and myoglobinuria.[2] We place a butterfly needle in the antecubital fossa and draw baseline lactate and ammonia levels. The forearm muscles are exercised by having the patient rapidly and strenuously open and close the hand for 1 minute. Immediately after exercise and then 1, 2, 4, 6, and 10 minutes post exercise, blood samples are again taken and analyzed for lactate and ammonia. The normal response is for lactate and ammonia levels to rise three to four times the baseline levels. If neither the lactate nor the ammonia level increases, the test is inconclusive and implies that the muscles were not sufficiently exercised. A rise in lactate levels but not ammonia is diagnostic for myoadenylate deaminase (MAD) deficiency. In myophosphorylase, PFK, PGAM, phosphoglycerate kinase (PGK), phosphorylase b kinase (PBK), debrancher, and lactate dehydrogenase deficiencies, the ammonia levels rise appropriately, but the lactic acid does not.

TYPE II GLYCOGENOSIS (POMPE DISEASE; ACID MALTASE DEFICIENCY; α-GLUCOSIDASE DEFICIENCY)

GSD II is an autosomal-recessive disorder caused by a deficiency of lysosomal acid α-glucosidase (Table 26–1,

▶ **TABLE 26–1. DISORDERS OF CARBOHYDRATE METABOLISM**

Disorder	Enzyme Defect	Inheritance	Clinical Features
Type I (von Gierke's disease)	Glucose-6-phosphate	Autosomal recessive	No neuromuscular signs or symptoms
Type II (Pompe disease)	Acid α-1,4-glucosidase	Autosomal recessive	Infancy: hypotonia and generalized weakness Childhood/adult: progressive weakness and ventilatory failure
Type III (Cori–Forbes disease)	Debrancher (amylo-1, 6-glucosidase)	Autosomal recessive	Infancy: hypotonia and generalized weakness Childhood/adult: proximal or distal weakness, spasticity, dementia, and incontinence
Type IV (Anderson disease)	Brancher (amylo-1,4-1, 6-transglucosidase)	Autosomal recessive	Infancy: hypotonia and generalized weakness Childhood/adult: proximal or distal weakness
Type V (McArdle disease)	Myophosphorylase	Autosomal recessive	Infancy: rare weakness Childhood/adult: exercise intolerance, and rare weakness
Type VI	Liver phosphorylase	Autosomal recessive	No muscle involvement
Type VII (Tarui disease)	Phosphofructokinase (PFK)	Autosomal recessive	Childhood: exercise intolerance and rare weakness
Type VIII	Phosphorylase b kinase (PBK)	Autosomal recessive and X-linked	Infancy to adult: exercise intolerance and rare weakness
Type IX	Phosphoglycerate kinase (PGK)	X-linked	Childhood: exercise intolerance, rare weakness, hemolytic anemia, mental retardation, and seizures
Type X	Phosphoglycerate mutase (PGAM)	Autosomal recessive	Childhood–adult: exercise intolerance
Type XI	Lactate dehydrogenase	Autosomal recessive	Childhood–adult: exercise intolerance
Type XII	Aldolase	Autosomal recessive	Infancy–childhood: exercise intolerance and weakness
Type XIII	Trioesphosphate isomerase	Autosomal recessive	Infancy: hypotonia, generalized weakness, and mental retardation
Type XIV	β−Enolase	Autosomal recessive	Childhood–adult: exercise intolerance

Fig. 26–1). GSD II is more commonly referred to as Pompe disease or acid maltase deficiency may present in three major forms: a severe infantile form, a juvenile-onset type, and an adult-onset variant.[3–14] The incidence of infantile Pompe disease ranges from 1 in 31,000 to 1 in 138,000. The incidence in later onset forms is approximately 1 in 53,000.

Clinical Features

Infantile Pompe disease is characterized by generalized weakness and hypotonia, cardiomegaly, and mild-to-moderate hepatomegaly, with an onset in the first several months of life.[8,9,16–18] Infants often have an enlarged tongue (i.e., macroglossia). The weakness and cardiomyopathy are progressive. Feeding difficulties and ventilatory muscle weakness are common. The disease is invariably fatal by 2 years of age secondary to cardiorespiratory failure.

The juvenile-onset acid maltase deficiency usually manifests in the first decade of life.[8,10,14,16,19] Motor milestones may be delayed. Weakness is slowly progressive and involves proximal greater than distal muscles in the legs and arms. Children often have hypertrophy of the calf muscles, a waddling gait, and significant lumbar lordosis and demonstrate a Gower maneuver to arise from the floor. Thus, affected children are not uncommonly misdiagnosed with Duchenne or some other form of limb-girdle muscular dystrophy. Rarely, acid maltase deficiency presents with rigidity of the spine.[22] Unlike the infantile-onset acid maltase deficiency, cardiomegaly, hepatomegaly, and macroglossia are uncommon.[8] Nevertheless, it is relentlessly progressive; particularly the ventilatory muscles are affected, leading to death in the second or third decade of life.

The adult-onset acid maltase deficiency usually manifests in the third or fourth decade (range to the 70s years, mean 36.5 years).[7,8,10,11,16,23–26] Patients develop generalized proximal greater than distal muscle weakness resembling polymyositis or a type of limb-girdle dystrophy. Some patients have a scapuloperoneal distribution of weakness.[5] Weakness is occasionally asymmetric and may involve the face or tongue.[24] Nearly half of affected individuals complain of muscle pains, particularly in the thighs. Muscle stretch reflexes may be reduced. Hepatomegaly and cardiomegaly do not typically occur; however, electrocardiographic abnormalities and arrhythmias can be seen. As in the infantile and juvenile forms of the disease, there is a predilection for involvement of ventilatory muscles. In this regard,

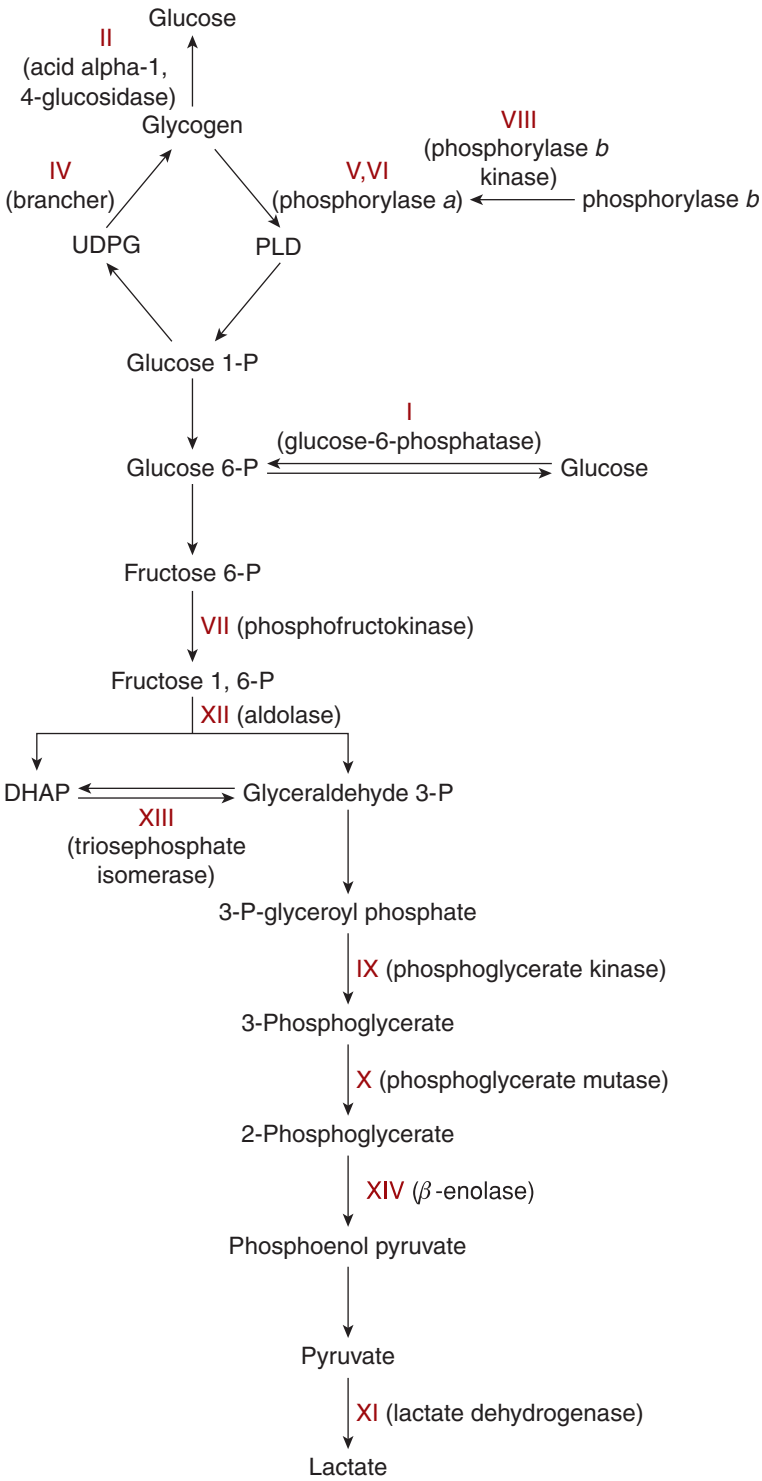


Figure 26–1. Glycolytic pathways. Glycogen metabolism disorders are caused by specific enzyme deficiencies involving each of the pathways illustrated with a Roman numeral. The enzymes corresponding to each numbered glycogen storage disorder are listed in Table 26–1. Diseases I and VI are not included, as these do not involve muscle. (With permission from Amato AA. Sweet success—a treatment for McArdle's disease. N Engl J Med 2003;349(26):2481–2482.)

16–33% of patients present with symptoms related to ventilatory insufficiency (e.g., dyspnea, frequent nocturnal arousals, morning headaches, and excessive daytime sleepiness).[8,24]

Laboratory Features

Alpha-glucosidase activity may be assayed in muscle fibers, fibroblasts, leukocytes, lymphocytes, and urine. The reduction of activity generally correlates with the severity of the myopathy, with infantile-onset disease being associated with a severe deficiency of α-glucosidase activity, while the less severe adult-onset form has residual activity, up to 30% in muscle and 53% in lymphocytes.[25] However, false-negative results on leukocyte assay can occur due to contamination with granulocytes or other sources of neutral glucosidase. A newly developed fast and sensitive test is a dried blood spot analysis of alpha-glucosidase activity and is our initial screening test.[cite the following references here: (Umapathysivam 2001; Chamoles 2004; Kallwass 2007] If the dried blood spot shows reduced enzyme activity confirmatory testing should be performed by measuring alpha-glucosidase activity activity in cultured fibroblasts or muscle tissue or by genetic testing. Serum creatine kinase (CK) levels are moderately elevated in infantile-onset, but adults may have normal CK levels.

Computer tomography and magnetic resonance imaging scans confirm the early and severe involvement of the adductor magnus and semimembranosus at the early stage of the disease and a later fatty infiltration of the long head of the biceps femoris, semitendinosus, and the anterior thigh muscles. In advanced phases, a selective sparing of sartorius, rectus, femoris and gracilis muscles and peripheral portions of the vastus lateralis are also evident.[26,27]

Motor and sensory nerve conduction studies (NCS) are normal. Electromyography (EMG) reveals increased insertional and spontaneous activity in the form of fibrillation potentials, positive sharp waves, complex repetitive discharges, and even myotonic discharges. In mild forms of the disease, these irritative discharges may be evident only in the paraspinal muscles. Motor unit action potentials (MUAPs) are myopathic in appearance and recruit early.

Electrocardiograms (EKG) may demonstrate nonspecific abnormalities including left axis deviation, short PR interval, large QRS complexes, inverted T waves, ST depression, persistent sinus tachycardia in the severe and mild forms of GSD II.[8,24] Wolfe–Parkinson–White syndrome occurs in infantile and adult forms of the disease.[28,29] Echocardiograms can show hypertrophic cardiomyopathy. Pulmonary function tests show a restrictive defect with decreased forced vital capacity, reduced maximal inspiratory and expiratory pressures, and early fatigue of the diaphragm.[30]

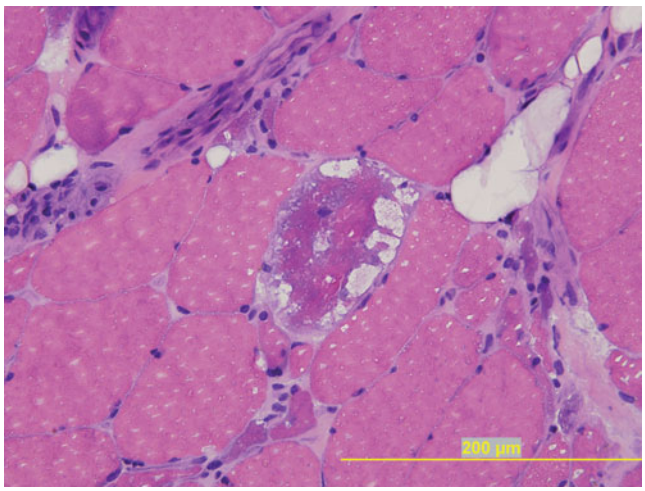
Histopathology

Biopsies characteristically demonstrate glycogen-filled vacuoles within muscle fibers (Fig. 26–2).[4,5,7,8,11,16,23] These vacuoles are very prominent in the infantile form, but, in the childhood and adult forms, these are apparent in only 25–75% of fibers in clinically affected muscles and may be absent in clinically unaffected muscle groups.[8] Muscle biopsy may show only slight, nonspecific abnormalities in late-onset case. When present, the vacuoles react strongly to periodic acid Schiff (PAS), are sensitive to diastase, and stain intensely with acid phosphatase, confirming that the vacuoles are secondary lysosomes filled with glycogen. Glycogen can also be found free in the cytoplasm on electron microscopy (EM). Muscle biopsies also reveal necrotic and regenerating muscle fibers, variation in fiber size and fiber splitting. In later stages, muscle fiber atrophy and increased endomysial connective tissue may be present. Occasionally, fiber-type grouping and group atrophy may be evident, owing to motor neuron degeneration.[8,11] In this regard, glycogens accumulates in anterior horn cells and bulbar nuclei as well as Schwann cells accounting for the superimposed neurogenic findings in some patients.[8,9,31,32]

Molecular Genetics and Pathogenesis

Missense, nonsense, and frame-shift mutations have been identified in the α-glucosidase gene located on chromosome 17q21–23 in infantile-, childhood-, and adult-onset cases.[33,34] Prenatal diagnosis is possible with amniocentesis or chorionic villous sampling.[33–35] Acid alpha-glucosidase is a lysosomal enzyme, which cleaves 1,4 and 1,6 linkages in glycogen, maltose, and isomaltose.[36] Glycogen within lysosomes is degraded to glucose by acid maltase, and the deficiency of the enzyme results in glycogen accumulation. There appears to be an inverse correlation between residual acid alpha-glucosidase activity and the clinical severity.[34,37] However, there are cases associated with an adult-onset Pompe disease who may have very little residual enzyme activity, so the relationship between disease activity and clinical severity is not 100% accurate.[5] Interestingly, there may be phenotypic variability in severity within families.[5,17,38]

How acid alpha-glucosidase leads to muscle fiber dysfunction is not completely understood. The accumulating glycogen that results from the deficiency may displace or replace important cellular organelles. Alternatively, the lysosomes filled with glycogen may rupture, thereby releasing proteases that degrade myofibrils and other important muscle proteins. Muscle catabolism is increased by 31% in Pompe disease compared to normal controls, and mean protein balance is reduced.[15] Furthermore, resting energy expenditure in Pompe



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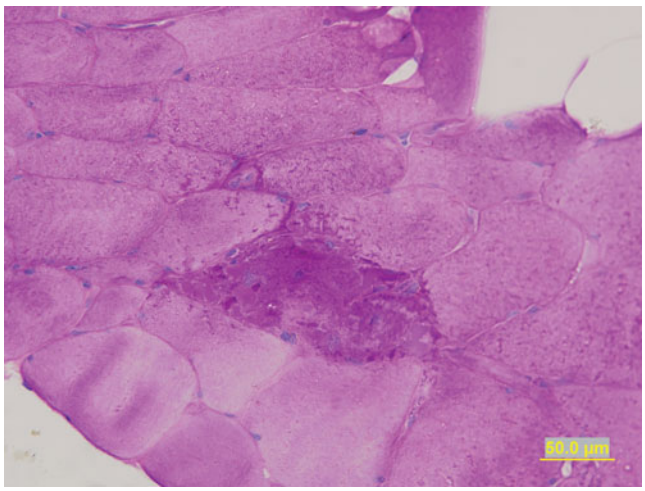
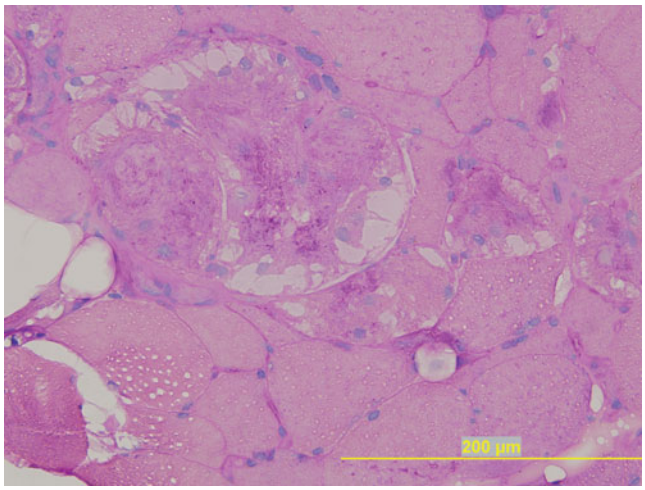


B



C

Figure 26–2. Pompe disease. Muscle biopsy in a patient with adult-onset acid maltase deficiency reveals one or more vacuoles within many muscle fibers, hematoxylin and eosin (H&E) (A). These vacuoles are filled with glycogen, which stain intensely red on periodic acid-Schiff (PAS) stain (B) and are digested by diastase (C).

disease is increased.[15] Patients do not exhibit exercise intolerance or myoglobinuria because metabolism of non-membrane-bound glycogen and glucose for energy metabolism is not impaired.

Treatment

In the past, there were no specific treatments for acid maltase deficiency other than supportive therapy for associated cardiorespiratory complications. Low carbohydrate and ketogenic diets are ineffective. A small study reported that 4/16 patients treated with high-protein diet demonstrated improvement in muscle and respiratory function.[15] Intravenous recombinant α-glucosidase enzyme appears to be safe and beneficial in children and perhaps adults with Pompe disease and has received approval by the US Food and Drug Administration (FDA).[39–41] A trial enrolling 18 patients with infantile onset Pompe disease showed that enzyme replacement therapy reduced the risk of death by 99% and the risk of death or invasive ventilation by 92%.[cite reference #40] The recommended dose is 20 mg per kg every two weeks.

TYPE III GLYCOGENOSIS (DEBRANCHING ENZYME DEFICIENCY)

Clinical Features

GSD III, also known as Cori–Forbes disease, accounts for approximately 25% of GSD (Table 26–1, Fig. 26–1).[3,6,42–45] GSD III is caused by the deficiency of debranching enzyme. This enzyme has two separate catalytic functions: (1) oligo-1,4-1,4-glucanotransferase activity and (2) α-1,6 glucosidase activity. Both the transferase and the glucosidase activities are vital in breaking down glycogen into glucose, and a deficiency in either or both enzymatic functions lead to myopathy.

There are two principal and two less common forms of GSD III. In GSD IIIa, debranching enzyme is deficient in both the liver and the muscle. In contrast, enzyme

activity is abnormal only in the liver in GSD IIIb, and a myopathy does not occur in this form of the disease. In rare cases, selective loss of only one of the two debrancher enzyme activities (glucosidase [type IIIc] or transferase [type IIId]) has also been demonstrated.[46]

Deficiency of the debranching enzyme in muscle leads to weakness in patients with GSD IIIa. Onset of muscle weakness may be appreciated in infancy or childhood, although it usually does not manifest until the third to fourth decade of life.[3,6,42–45,47–53] Severe atrophy and weakness of distal extremity muscles, particularly the peroneal and calf muscles, occur in about 50% of patients.[44] Tight heal cords are common, and patients may have the tendency to toe walk. This distal involvement can lead to an initial misdiagnosis of motor neuron disease or a peripheral neuropathy. Some patients do, in fact, have a superimposed mild sensorimotor polyneuropathy. Pseudohypertrophy, particularly of the more proximal muscle groups, may be seen.[50] Generalized muscle weakness can also occur. In addition, some patients develop progressive ventilatory muscle weakness with or without extremity weakness. Respiratory failure can evolve fairly rapidly. Less commonly, some patients develop a cardiomyopathy with or without extremity weakness.[48,54–57] Finally, rare patients manifest with myalgias, cramps, exercise intolerance, or myoglobinuria.[44,49,51,52]

Laboratory Features

Deficiency of debranching enzyme can be demonstrated with biochemical assay of muscle, fibroblasts, or lymphocytes.[58] Serum CK levels are elevated two to 20 times normal. Exercise forearm testing reveals normal increase in serum ammonia but not in lactate levels.[58] EMG demonstrates abnormalities similar to that described with acid maltase deficiency. Pulmonary function tests show reduced forced vital capacity in patients with ventilatory muscle involvement. Echocardiogram reveals findings suggestive of hypertrophic obstructive cardiomyopathy in most patients with GSD IIIa, while conduction defects and arrhythmias are apparent on EKG.[42,54,57,58]

Histopathology

Muscle biopsies demonstrate a vacuolar myopathy with abnormal accumulation of glycogen in the subsarcolemmal and intermyofibrillar regions of muscle fibers.[4,47,49,50] These vacuoles stain intensely with PAS and are digested by diastase. Further, in contrast to acid maltase deficiency, these vacuoles do not stain with acid phosphatase, suggesting that the glycogen does not primarily accumulate in lysosomes. On EM, free pools of glycogen are apparent.[58] Some glycogen appears in lysosymes, but not to the same extent as seen in acid maltase deficiency. Abnormal glycogen accumulation can also be found in skin and peripheral nerves.[59–61]

Molecular Genetics and Pathogenesis

The mutations in the debranching enzyme gene, *AGL*, on chromosome 1p21 cause both GSD IIIa and GSD IIIb.[62–66] Prenatal diagnosis is possible.[67] The *AGL* gene is composed of 35 exons spanning 85 kb of genomic DNA. Alternative splicing and differential RNA transcription result in at least six distinct isoforms and underline the differential expression of the debranching enzyme.[68] Tissue-specific expression of different isoforms results from the presence of at least two promoter regions. Of note, mutations within exon 3 mutations appear to be specific for GSD-IIIb.[65]

Deficiency of the enzyme leads to the accumulation of glycogen in muscle; the exact mechanism of muscle weakness is not known. Similar amounts of glycogen accumulation in muscle can be demonstrated in patients who do not manifest weakness. Accumulation of glycogen in peripheral nerves may account for some degree of weakness and atrophy, particularly of the distal muscles.

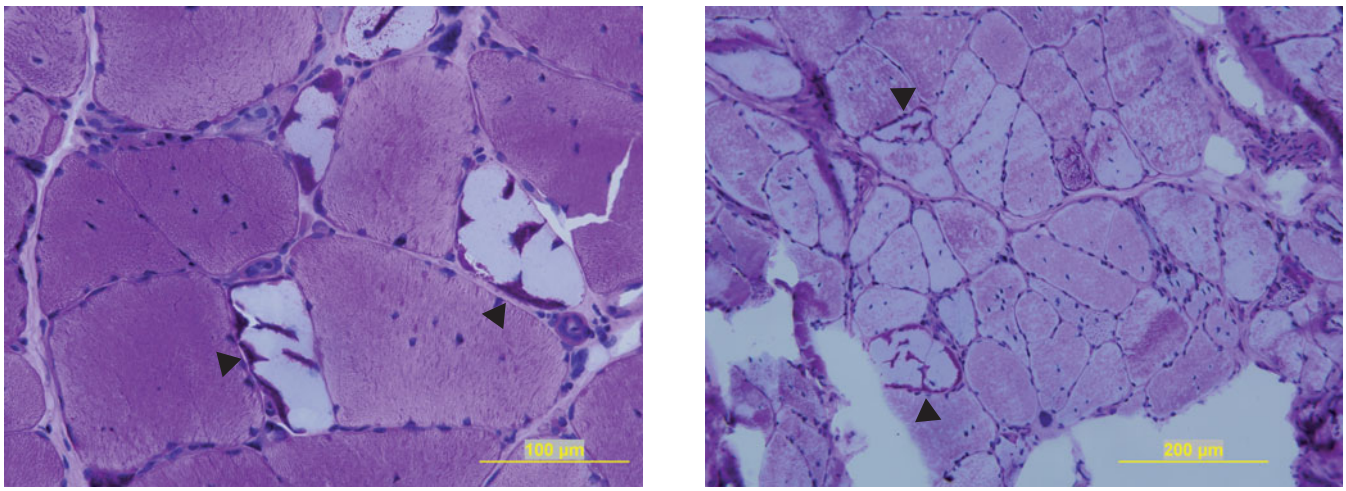
Treatment

Frequent low-carbohydrate meals and maintaining a high protein intake may prevent fasting hypoglycemia. High-protein nocturnal intragastric feedings led to apparent improvement in exercise tolerance, muscle strength and mass, electromyographic findings, and growth in one patient,[53] but this observation has not been subsequently confirmed. Supportive therapy is required for patients with congestive heart failure. Liver transplantation has been done on patients with cirrhosis and hepatocellular carcinoma.[69] However, debranching enzyme activity has remained absent in leukocytes after transplantation and is not likely to normalize in muscle.

TYPE IV GLYCOGENOSIS (BRANCHING ENZYME DEFICIENCY)

Clinical Features

GSD IV is rare and caused by the deficiency of the enzyme that helps make the branched glycogen molecule (Table 26–1, Fig. 26–1).[6,58,68,70–80] There are several forms of branching enzyme deficiency. The classic and most common type of GSD IV, also known as Andersen disease, presents in infancy as progressive liver dysfunction with hepatomegaly, splenomegaly, and failure to thrive. Muscular weakness, atrophy, hypotonia, hyporeflexia, and contractures may occur but are overshadowed by the liver disease.[75,80] Most children succumb to severe liver failure by 5 years of age. There is also a benign hepatic form of GSD IV in which the liver disease does not progress.[68,59,81] Some patients with GSD IV manifests primarily with muscle weakness, atrophy, and cardiomyopathy.[68,70,78,79] Either



A B

Figure 26–3. Type IV glycogenoses/Anderson disease. Muscle biopsy reveals storage of periodic acid-Schiff-positive material (A), which is diastase resistant (B) suggestive of a filamentous polysaccharide that is not glycogen (i.e., polyglucosan).

proximal or distal muscle groups can be preferentially affected. Finally, there is a variant of branching enzyme deficiency, known as polyglucosan body neuropathy, which usually presents in adults as progressive upper and lower motor neuron loss, sensory nerve involvement, cerebellar ataxia, neurogenic bladder, and dementia.[71,73,82,83] Occasionally, polyglucosan body neuropathy manifests in children.[74]

Laboratory Features

Depending on the subtype of GSD IV, deficiency of branching enzyme may be demonstrated in muscle, peripheral nerve, fibroblasts, or leukocytes.[70,71,73,76,82,83] In patients with primary neuromuscular involvement, the deficiency may be noted only in muscle.[70] Branching enzyme activity can be normal in the muscle in patients with adult polyglucosan body neuropathy.[71,73] The serum CK may be normal or slightly elevated. EMG reveals myopathic features and muscle membrane instability similar to that observed with GSDs II and III. In patients with polyglucosan body neuropathy, an axonal sensorimotor neuropathy is apparent while the EMG abnormalities reflect a superimposed polyradiculopathy. EKG can demonstrate progressive conduction defects leading to complete atrio-ventricular (A-V) block.[78] Echocardiogram may reveal a dilated cardiomyopathy.[78]

Histopathology

Routine light and electron microscopy reveals deposition of varying amounts of finely granular and filamentous polysaccharide (polyglucosan bodies) in the central nervous system (CNS), peripheral nerves (axons and Schwann cells), skin, liver, and cardiac and skeletal muscle.[4,70,73,74,77–79] These polyglucosan bodies are PAS positive and diastase resistant, suggesting the accumulation of polysaccharides other than glycogen (Fig. 26–3). This polysaccharide resembles amylopectin in that it has longer than normal peripheral chains and few branch points.[58]

Autopsy studies have demonstrated abnormal polysaccharide material in the liver, heart, skeletal muscle, and in neurons of the brain and the spinal cord. The abnormal polysaccharide material is more abundant in the motor neurons than in other nerve cells and affects all motor neurons of the brainstem and spinal cord.[84]

Molecular Genetics and Pathogenesis

The disease is inherited in an autosomal-recessive manner. Deletions, nonsense, and missense mutations within the *GBE1* (glycogen branching enzyme) gene at chromosome 3p12 have been identified in the severe hepatic, benign hepatic, and the neuromuscular forms of GSD IV, including adult polyglucosan body disease.[68,72,82,83] There are phenotypic variability and differential expression of branching enzyme activity. The mechanism by which the abnormal accumulation of polysaccharide results in muscle damage is not known.

Treatment

Liver transplantation has been performed in some children with GSD IV with beneficial results.[85–87] Apparently, systemic microchimerism occurs after liver allotransplantation and can ameliorate pancellular enzyme deficiencies in this disease. Most of the patients became free of liver, neuromuscular, and cardiac dysfunction, with reduced polysaccharide accumulation in these

tissues on long-term follow-up (mean 42 months). However, at least one child died from cardiomyopathy due to massive deposition of polysaccharide in the heart 2½ years after transplantation.[85] No other medical therapies have been demonstrated to be effective.

TYPE V GLYCOGENOSIS (MYOPHOSPHORYLASE DEFICIENCY)

Clinical Features

The type V glycogenosis (myophosphorylase deficiency), more commonly known as McArdle disease, is the most common disorder of carbohydrate metabolism. McArdle disease is an autosomal-recessive disorder that usually presents with exercise intolerance in childhood or young adults (Table 26–1, Fig. 26–1).[3,6,58,88] Patients complain of exertional muscle pain and cramps induced by brief, but very intense, activities (e.g., weight lifting and sprinting), but these can also occur following prolonged low-intensity exercises (e.g., swimming and jogging). If individuals who are affected ignore these symptoms and continue to exercise at a high level, the muscle pain and cramping can become quite intense and electrically silent contractures may develop. Some patients present with fatigue following exercise without associated cramps or muscle pain. Many patients note a second wind phenomenon in which, after the onset of mild exertional myalgias or cramps (usually after 10 minutes of exercise), the muscle pain and sense of intolerance may dissipate and the individual may continue with the exercise at the previous or a slightly reduced level.[89] The second wind phenomenon is the result of mobilization and use of blood-borne glucose.

Overt myoglobinuria usually does not occur until the second or third decade, although it has developed as early as 8 years of age.[90] Approximately 50% of attacks of myoglobinuria are exertionally related and one-third of cases are complicated by renal insufficiency.

Most patients have normal motor examinations between attacks of muscle cramping. However, fixed proximal weakness develops in as many as one-third of patients perhaps as a result of recurrent bouts of rhabdomyolysis. Rare patients present with progressive proximal muscle atrophy and weakness in late-adult life rather than exercise intolerance.[91] Weakness may involve the arms more than the legs and can be asymmetric. Finally, a few cases have been reported with congenital weakness, some of which were rapidly progressive, leading to ventilatory failure within the first year of life.[92,93]

Laboratory Features

Serum CK levels are invariably elevated. The exercise forearm test reveals a normal rise in serum ammonia but no significant rise in lactic acid.[94] EMG is usually normal in patients with McArdle disease.

Histopathology

Muscle biopsies demonstrate variability in fiber size, scattered necrotic and regenerating fibers, and excessive accumulation of glycogen in the subsarcolemmal and intermyofibrillar areas (see Chapter 3, Figure 3–6).[4,95,96] Staining for myophosphorylase is absent, and biochemical assay for myophosphorylase reveals absent or significantly reduced activity.

Molecular Genetics and Pathogenesis

This disorder is inherited in an autosomal-recessive fashion and is caused by mutations in the *PYGM* gene that encodes myophosphorylase.[93,97,98] This enzyme initiates glycogen breakdown by phosphorylytically lysing α-1,4 glucosyl residues from the outer branches of glycogen, generating glucose-1-phosphate. Mutations result in little detectable protein or enzyme activity. Interestingly, the mutations associated with some of the rare cases of fatal infantile myopathy are the same as evident in the more common clinical presentation of McArdle's disease.[93] A pseudodominant pattern of inheritance may arise secondary to heterozygotes who have low levels of residual myophosphorylase.[99] Another mechanism is the mating of a homozygote (or compound heterozygote) with a heterozygote.[97]

Although exercise intolerance and contractures had been postulated to be due to the inability to generate enough ATP, studies have demonstrated that ATP is not depleted during exercise in McArdle disease, Tauri disease, or in the other disorders of glycogenolysis and glycolysis.[100] Ischemic exercise is associated with (1) an increase in adenosine diphosphate (ADP); (2) intracellular pH that does not acidify in response to exercise; (3) inorganic phosphate levels in muscle, which are 50% lower than normal muscle tissue; and (4) intracellular calcium at the onset of contracture, which is more than 10-fold greater than that found in normal control muscle ischemically exercised.[101] Perhaps the combination of increased intracellular ADP, reduced inorganic phosphate, and lack of acidification with impaired glycolysis increase sensitivity of the muscle fiber contractile apparatus to intracellular calcium. Further, the increased intracellular ADP may inhibit ADP dissociation from actin-myosin cross-bridges, thereby increasing the time spent in contraction.

In addition, patients with McArdle disease have reduced concentrations of the sodium–potassium ATPase pump, higher exercise-induced serum potassium concentrations, and a greater increase in heart rate during exercise.[102] Decreased sodium–potassium ATPase may lead to an exercise-induced increase in extracellular

potassium because of impaired reuptake of potassium released during muscle contraction. Further, exercise intolerance leads to reduced physical activity, which may result in downregulation of the pump, and the increased ADP may decrease the transport rate of the remaining pumps. The increased concentration of extracellular potassium partially depolarizes the muscle membrane, thereby inactivating sodium channels and reducing membrane excitability.[102] Patients with McArdle disease also develop exaggerated tachycardia with exertion that can limit the exercise capacity of individuals who are affected.[102] It is not known why sodium–potassium pump concentrations in skeletal muscle in patients with McArdle disease are reduced. Reduced physical activity may downregulate the number of sodium–potassium ATPase pumps. Alternatively, myophosphorylase deficiency may reduce the pump concentration by disrupting the normal coupling of muscle glycogenolysis and pump activity.[102]

Treatment

A single-blind, placebo-controlled, crossover study of oral sucrose (75 g) in 12 patients with McArdle disease demonstrated marked improvement in exercise tolerance, supported by the subjects' reduced perceived exertion levels and their diminished maximum heart rates.[89] The limitation of oral sucrose loading is that the beneficial effect is short-lived. Repeated dosing may lead to weight gain, which in and of itself can reduce exercise tolerance, and inhibition of fatty acid use, which is an important fuel source with prolonged physical activity. Sucrose loading will also not be helpful in situations of unexpected exertional activity and prolonged physical activity or with static exercise (e.g., weight lifting).

We instruct patients to avoid intense isometric exercises (e.g., weight lifting) and maximum aerobic exercises (e.g., sprinting). However, mild-to-moderate aerobic conditioning may be beneficial, as poor cardiovascular fitness results in a diminished delivery of blood-borne substrates necessary for muscle oxidative metabolism.[89,103] Patients should be instructed on moderating their physical activity and in obtaining a "second wind" response. Any bout of moderate exercise should be preceded by 5–15 minutes of low-level warm-up activity to promote the transition to the second "wind."[103]

A trial of daily creatine monohydrate at a dose of 150 mg/kg/d in McArdle disease actually resulted in worsening of the clinical symptoms of exercise intolerance.[104] The result was surprising, as the same group had previously reported in a placebo-controlled trial that creatine monohydrate doses of 60 mg/kg/d showed an increased exercise capacity.[105]

A high-protein diet might help, but supplementing the diet with branched-chain amino acid supplementation can actually lower exercise capacity.[103] In fact, surplus calories may lead to weight gain and subsequent decline in cardiovascular fitness. Some small studies have suggested that vitamin B6 supplementation (50 mg/d) can reduce exercise intolerance and enhance performance.[97]

TYPE VII GLYCOGENOSIS (PFK DEFICIENCY)

Clinical Features

PFK deficiency or Tauri disease is an autosomal-recessive disease, caused by a deficiency in PFK in muscle and erythrocytes (Table 26–1, Fig. 26–1).[3,6,58] PFK deficiency is much less common than McArdle disease. The clinical features are very similar to McArdle disease with respect to exercise intolerance, muscle pain, contractures, and relief of discomfort by rest, but PFK deficiency is not associated with the warm-up phenomena and there is a lower incidence of myoglobinuria.[106] In addition, some patients develop jaundice (due to mild hemolysis) and gouty arthritis due to PFK deficiency in erythrocytes.

The clinical phenotype can vary, and there are less common presentations. Some individuals who are affected manifest with hemolytic anemia without a myopathy. Others present later in adulthood with fixed weakness, which predominantly affects the proximal or occasionally the scapuloperoneal muscles.[107,108] They may have had only mild exercise intolerance in their younger years but never have a history of cramps or myoglobinuria. In addition, PFK deficiency can present in infancy with severe generalized weakness and cardiomyopathy.[30] Contractures, cortical blindness, and corneal opacifications are evident in some infants, but hemolytic anemia does not occur. Affected children die from cardiorespiratory failure in infancy or early childhood.

Laboratory Features

Serum CK is usually elevated, and mild anemia and increased reticulocyte count are often noted. Exercise forearm testing reveals a normal increase in ammonia production but a blunted increase in lactic acid. EMG is usually normal.

Histopathology

Muscle biopsies demonstrate abnormal accumulation of glycogen.[4,58] In addition, there is also an abnormal accumulation of polysaccharide, which stains intensely with PAS but is diastase resistant, especially in older patients. Muscle biopsies may reveal only nonspecific myopathic features without evidence of abnormal glycogen accumulation in the infantile form of disease. Definitive diagnosis of Tarui disease can be made by biochemical

and histochemical analyses, which reveal the deficiency of PFK activity and staining.

Molecular Genetics and Pathogenesis

PFK catalyzes the ATPase-dependent conversion of fructose 6-phosphate to fructose 1,6-diphosphate. Human PFK is comprised of three distinct isoenzyme subunits (M—muscle, L—liver, and P—platelet). Skeletal muscles contain only the M isoform, while erythrocytes contain a hybrid of M and L subunits. The gene responsible for the M isoform, PFK-M, was initially mapped to 1q32 but was subsequently reassigned to 12q13. The symptoms reflect inactivation of PFK in muscle and partial inactivation in red blood cells. Different molecular defects may explain the different clinical presentations; however, the biochemical and molecular basis for clinical heterogeneity remains unclear.[109]

As in McArdle disease, there is ADP accumulation in exercised muscle, but whether or not there is also reduction in sodium–potassium pumps in Tarui disease is not known. The normal coupling of muscle glycogenolysis and sodium–potassium pump activity may be disrupted by increased ADP or reduction in pump concentration, as we described in the section on McArdle disease.

Treatment

Unlike in McArdle disease, glucose or fructose administration prior to activity does not help rather it may be deleterious. Patients with PFK deficiency rely on free fatty acids as a fuel substrate during exercise. Therefore, they experience more exercise intolerance if given a glucose infusion or if they consume high-carbohydrate meals because glucose reduces the blood levels of free fatty acids.[110] This is just the opposite of the second wind phenomena and is sometime called the *out-of-wind phenomena.* An aerobic conditioning program similar to those given to patients with McArdle deficiency may improve exercise tolerance.

TYPE VIII GLYCOGENOSIS (PBK DEFICIENCY)

Clinical Features

Autosomal-recessive PBK deficiency is associated with heterogeneous clinical manifestations.[111–114] It most commonly manifests as exercise intolerance with cramps and myoglobinuria (Table 26–1, Fig. 26–1). However, PBK deficiency can occasionally present in infancy or childhood with mild weakness and a delay in motor milestones. Rarely, a fatal cardiomyopathy can occur in infancy. Approximately 50% of patients develop proximal or distal weakness in adulthood.

Laboratory Features

Serum CK can be normal or mildly elevated. The exercise forearm test is usually abnormal. EMG is usually normal.

Histopathology

Muscle biopsy may be normal or may demonstrate variability in fiber size, scattered necrotic fibers, and slight subsarcolemmal accumulation of glycogen.[112] Biochemical analysis reveals decreased PBK activity.

Molecular Genetics and Pathogenesis

PBK catalyzes the conversion of inactive myophosphorylase to the active form and converts active glycogen synthetase to an inactive form. PBK is a multimeric enzyme composed of four different subunits. The subunit responsible for the muscle disorder maps to 16q12–q13, and mutations of this gene have been identified.[115]

Treatment

There is no specific medical therapy. Patients should be instructed on a mild-to-moderate exercise program and to avoid vigorous activity.

TYPE IX GLYCOGENOSIS (PGK DEFICIENCY)

Clinical Features

PGK deficiency is an X-linked disorder, which commonly presents in male children as hemolytic anemia and CNS disturbances (e.g., mental retardation and seizures). In addition, some patients present with a myopathy.[116–121] Presentation with hemolytic anemia, CNS disturbances, and myopathy appears to occur in equal frequencies in patients with PGK deficiency.[121] The myopathy is characterized by exercise intolerance, cramps, and recurrent myoglobinuria. Slowly progressive proximal weakness has also been described.

Laboratory Features

Serum CK is two to three times normal. Most patients with the myopathy do not have hemolytic anemia, although it has been described.[119] Exercise forearm test fails to show a normal rise in lactate. EMG is usually normal.

Histopathology

Muscle biopsies are typically normal, but mild and diffuse PAS staining may be noted. Abnormal glycogen accumulation is usually apparent by EM. Enzymatic assays reveal reduced PGK enzyme activity.

Molecular Genetics and Pathogenesis

The disorder is caused by mutations in the PGK gene located on chromosome Xq13.[121] PGK catalyzes the transfer of the acylphosphate group of 1,3-diphosphoglycerate to ADP, with the formation of 3-phosphoglycerate and ATP in the terminal stage of the glycolysis.

Treatment

No specific medical therapy for the myopathy is available.

TYPE X GLYCOGENOSIS (PGAM DEFICIENCY)

Clinical Features

PGAM deficiency presents in childhood or early adult life as exercise intolerance, cramps, and recurrent myoglobinuria (Table 26–1, Fig. 26–1).[109,122]

Laboratory Features

Serum CK is mildly elevated. The exercise forearm test is abnormal. EMG is normal.

Histopathology

Muscle biopsies reveal increased glycogen by PAS staining and on EM. Rarely, these are tubular aggregates in type 2B fibers. Biochemical assay demonstrates normal or only mildly elevated glycogen content and markedly diminished activity of PGAM (<10% of normal).

Molecular Genetics and Pathogenesis

Type X glycogenosis is an autosomal-recessive disorder caused by mutations in the PGAM-M gene encoded on chromosome 7p13–p12.3. PGAM catalyzes the interconversion of 2- and 3-phosphoglycerate. There are two subunits for PGAM: a muscle-specific subunit (PGAM-M) and a non-muscle-specific or brain subunit (PGAM-B). Mature muscle contains the homodimer MM form of PGAM, which has diminished enzymatic activity in type X glycogenosis.

Treatment

There is no definitive medical therapy. Dantrolene improved symptoms in one patient with severe cramps and tubular aggregates on muscle biopsy.[122] Nevertheless, dantrolene is not recommended as routine therapy. Patients should be instructed on avoiding strenuous activity and placed on a mild–moderate aerobic exercise program.

TYPE XI GLYCOGENOSIS (LACTATE DEHYDROGENASE DEFICIENCY)

Clinical Features

This rare autosomal-recessive disorder manifests as exercise intolerance, cramping, and recurrent myoglobinuria (Table 26–1, Fig. 26–1).[123] Muscle strength is normal. Patients may also develop a generalized, scaly, erythematous rash, particularly in the summer. Pregnancies may be complicated by uterine stiffness in early stages of delivery and often requires cesarean section. This complication has not been associated with other glycogenoses. Chronic renal failure can develop secondary to recurrent myoglobinuria.

Laboratory Features

Serum CK level is elevated. Serum LDH, which is usually markedly elevated during attacks of rhabdomyolysis, is normal in patients with LDH deficiency. A reduction in the LDH-M isoform (<5% of normal) in muscle and blood can be demonstrated on electrophoretic studies. On exercise forearm testing, lactate does not rise; however, there is a normal increase in pyruvate levels, because the enzymatic defect lies distal to the formation of pyruvate in the metabolic pathway. EMG is typically unremarkable.

Histopathology

Muscle biopsies can appear normal, but biochemical assay reveals reduced activity of LDH.

Molecular Genetics and Pathogenesis

There are five distinct LDH isoenzymes, each comprised of tetramers composed of combinations of two different subunits, M and H. Thus far, only mutations involving the muscle M subunits encoded by the gene *LDHA* on chromosome 11p15.4 have been associated with muscle disease.[123]

Treatment

There are no specific medical therapy. Obstetricians need to be made aware of potential complications of labor in affected pregnant females.

TYPE XII GLYCOGENOSIS (ALDOLASE A DEFICIENCY)

Clinical Features

This rare disorder has been reported in a single young child (age 4 years) who presented with exercise intolerance and weakness following febrile illnesses.[157] He also had episodes of hemolytic anemia.

Laboratory Features

Serum CK was elevated.

Histopathology

Muscle biopsy appeared histologically normal on routine light microscopy, but EM revealed accumulation of lipid. Biochemical analysis revealed markedly reduced aldolase activity.

Molecular Genetics and Pathogenesis

Homozygous point mutations in the aldolase gene located on chromosome 16q22–24 were reported.[124] Aldolase catalyzes the conversion of fructose 1,6 phosphate to dihydroxyacetone phosphate and glyceraldehyde 3-phosphate.

Treatment

There are no specific medical therapies.

TYPE XIII GLYCOGENOSIS (TRIOESPHOSPHATE ISOMERASE DEFICIENCY)

Clinical Features

There is a report of an 8-year old with history of generalized hypotonia and weakness since infancy, mental retardation, and hemolytic anemia who was found to have trioesphosphate isomerase deficiency.[125]

Laboratory Features

Serum CKs were normal but EMG was reportedly myopathic.

Histopathology

Muscle biopsy demonstrated increased glycogen on routine light microscopy and EM.

Molecular Genetics and Pathogenesis

Trioesphosphate isomerase catalyzes the conversion of dihydroxyacetone phosphate into glyceraldehyde 3-phosphate.

Treatment

There are no specific medical therapies.

TYPE XIV GLYCOGENOSIS (β-ENOLASE DEFICIENCY)

Clinical Features

A 46-year-old man was reported with exercise intolerance, myalgias, and β-enolase or phosphohydratase deficiency.[126]

Laboratory Features

The serum CK levels were episodically elevated. No rise in lactic acid was noted on ischemic forearm testing.

Histopathology

Muscle biopsy revealed abnormal accumulation of glycogen in the sarcoplasm. Selective β-enolase deficiency was demonstrated on immunohistochemistry and immunoblot.

Molecular Genetics and Pathogenesis

Heterozygous mutations were identified within the β-enolase gene. β-Enolase catalyzes the step interconverting 2-phosphoglycerate and phosphoenol pyruvate.

Treatment

There are no specific medical therapies.

▶ OTHER POSSIBLE LYSOSOMAL GLYCOGEN STORAGE MYOPATHIES

DANON DISEASE (X-LINKED VACUOLAR CARDIOMYOPATHY AND MYOPATHY)

Clinical Features

Danon initially described this rare disorder characterized by the triad of hypertrophic or dilated cardiomyopathy, myopathy, and mental retardation.[127–129] Men are more severely affected then women, but women carriers can also manifest with symptoms. Individuals who are affected usually appear normal at birth but develop proximal muscle weakness and a cardiomyopathy in childhood or early adult life. Approximately 70% of males have some degree of mental retardation compared to 6% of women.[129] Patients generally die of heart failure or arrhythmia by the third decade of life.

Laboratory Features

Serum CK levels are moderately elevated. Echocardiograms often demonstrate a hypertrophic or dilated cardiomyopathy. The most frequent EKG abnormality is Wolff–Parkinson–White syndrome, but atrioventricular block, bundle branch blocks, bradycardia and atrial flutter/fibrillation may also be observed. Nerve conduction studies are normal, increased insertional and spontaneous activity in the form of fibrillation potentials, PSWs, complex repetitive discharges, and myotonic discharges are evident on EMG.[127] There is early recruitment of small-amplitude, short-duration, polyphasic MUAPs.

Histopathology

Muscle biopsies demonstrate variability in fiber size with autophagic vacuoles.[127] Excess free glycogen between disorganized myofibrils and within membrane-bound sacs and vacuoles may be seen on EM. On EM, some of the vacuoles are bound by basal lamina. These histological features are similar to Pompe disease, although α-glucosidase activity is normal in Danon disease. The characteristic feature is the absence of, lysosome-associated membrane protein-2 (LAMP-2) on immunostaining. Unlike X-linked myopathy with excessive autophagy (XMEA), which it can resemble, there is no deposition of membrane attack complex on muscle fibers.[130]

Molecular Genetics and Pathogenesis

Danon disease is caused by mutations in the gene that encodes for LAMP-2, which is located on the chromosome Xq24.[128] LAMP-2 is a major lysosomal membrane protein.

Treatment

There is no specific medical therapy at this time for the skeletal muscle weakness. Some patients require pacemakers or cardiac transplantation for the cardiomyopathy.

X-LINKED MYOPATHY WITH EXCESSIVE AUTOPHAGY

Clinical Features

XMEA can present in infancy or early adult life with slowly progressive proximal weakness and atrophy.[130–132] Respiratory weakness can also ensue. Unlike Danon disease, which it can resemble, individuals with XMEA usually do not develop a cardiomyopathy or mental retardation. However, a case resembling XMEA was recently reported with cardiomyopathy.[133]

Laboratory Features

Serum CK levels may be normal or mildly elevated. Routine motor and sensory nerve conduction studies are normal. EMG reveals increased insertional and spontaneous activity with fibrillation potentials, positive sharp waves, complex repetitive discharges, and myotonic discharges.[130–132] There is early recruitment of small-amplitude, short-duration, polyphasic MUAPs.

Histopathology

Muscle biopsies reveal muscle fiber size variation and many fibers with autophagic vacuoles (Figs. 26–4(A) and (B)).[130–132] Unlike Danon disease and acid maltase deficiency, these vacuoles are not PAS positive. Further, LAMP-2 is present in the vacuoles and within the cytoplasm in XMEA (Fig. 26–4(C)). Calcium and membrane attack complex (C5b-9) (Fig. 26–4(D)) deposit along the sarcolemma of abnormal muscle fibers.[130,134] On EM, some of the vacuoles are bound by basal lamina. These are often appreciated in the subsarcolemmal region where they, appear to fuse with the cell membrane allowing expression of their contents into the extracelluar space.[134] Redundant folds of basal lamina surrounding muscle fibers is also characteristic.

Molecular Genetics and Pathogenesis

The XMEA locus has been mapped to chromosome Xq28 but the gene has not as yet been identified.[134]

Treatment

There is no specific medical therapy for XMEA.

▶ DISORDERS OF PURINE NUCLEOTIDE METABOLISM

Disorders of purine metabolism more commonly cause hyperuricemic syndromes (gout and Lesch–Nyhan syndrome) or immunodeficiency disorders rather than a myopathy. A single disorder of nucleotide metabolism, MAD deficiency, has been linked to exercise intolerance and myoglobinuria in the past, but even this association has been questioned.

MYOADENYLATE DEAMINASE (MAD) DEFICIENCY

Clinical Features

Patients with MAD deficiency may develop exertional muscle pain and fatigue[6,76,135–137] and perhaps myoglobinuria[138] in late adolescence to middle age. However, the relationship between MAD deficiency and the exercise intolerance and bouts of myoglobinuria is controversial. The neurological examination is normal. Many individuals with MAD deficiency are asymptomatic, and mild exertional muscle pain and fatigue are extremely common symptoms in the general population. MAD deficiency has been reported in 1–2% of muscle biopsies, making it the most common enzyme deficiency in muscle.[139] In fact, muscle biopsies in patients with other types of neuromuscular disorders such as amyotrophic lateral sclerosis, spinal muscular atrophy, inflammatory myopathies, and various forms of muscular dystrophies have been found to have incidental deficiencies in MAD. Thus, although the frequency of MAD deficiency may be increased in muscle biopsies performed for evaluation of exertional myalgias,[137] the myalgias, a cause and effect relationship between the enzymatic deficiency and symptomatic muscle disease has yet to be established.

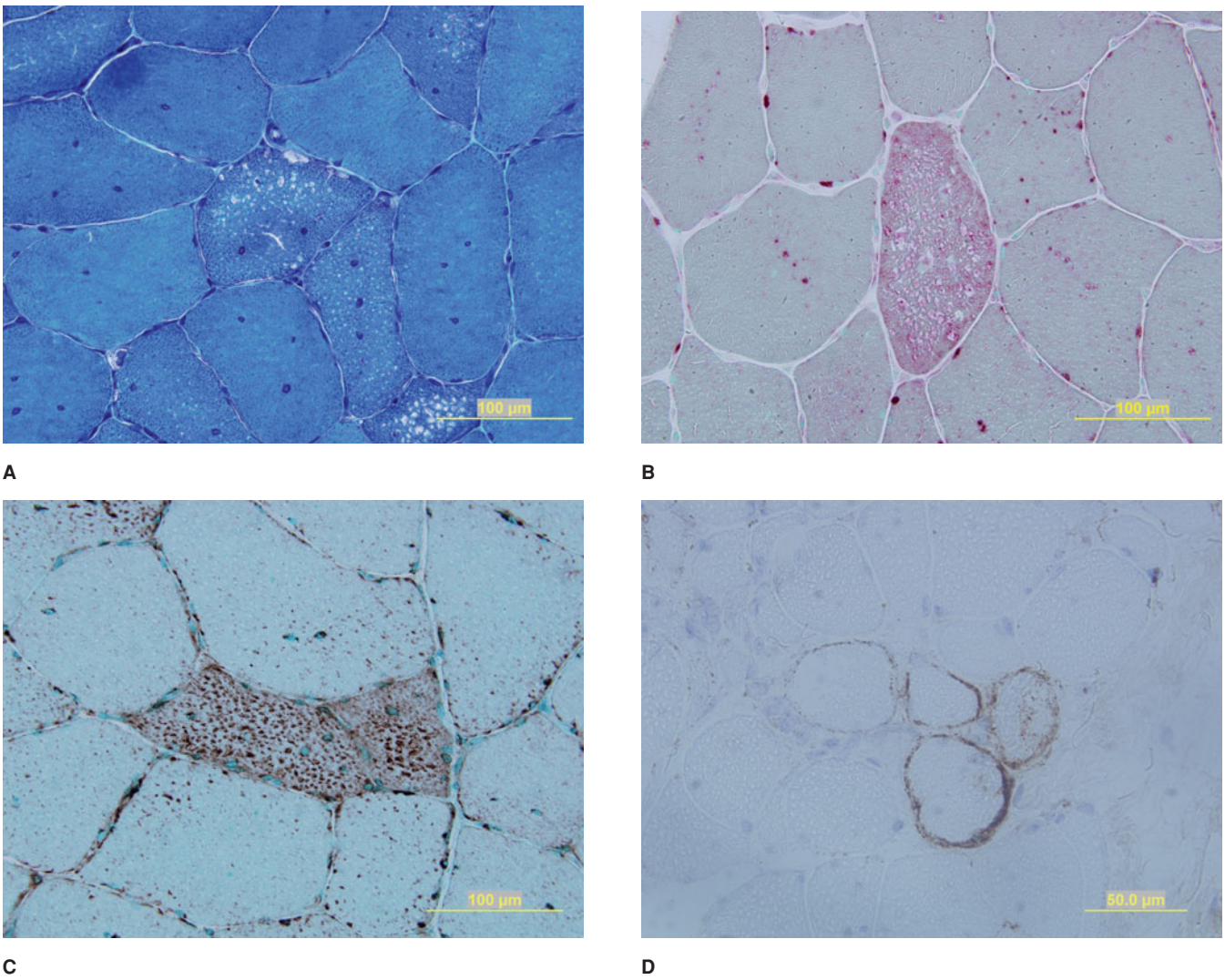


Figure 26–4. X-linked myopathy with excessive autophagia (XMEA). Muscle biopsies reveal fibers with autophagic vacuoles on modified Gomoritrichrome (A), which stain red with acid phosphatase stain (B). Immunoperoxidase stain with antibodies directed against lysosome-associated membrane protein-2 (LAMP-2) demonstrates the presence LAMP-2 in lysosomes (C). Further, immunoperoxidase stain demonstrates membrane attack complex (C5b-9) deposition along the sarcolemma of abnormal muscle fibers (D).

Laboratory Features

Serum CK is normal or only slightly elevated. The exercise forearm test is abnormal: serum lactate levels rise normally with exercise; however, ammonia levels remain relatively stable. EMG is normal.

Histopathology

The routine muscle biopsy is normal.[6,137] Specific biochemical assay or histological stain for MAD is essentially the only abnormality noted.

Molecular Genetics and Pathogenesis

MAD catalyzes the removal of an ammonia group from adenosine monophosphate (AMP) to form inosine monophosphate. AMP combines with ATP to form 2 ADP molecules (2 ADP $\leftrightarrow$ ATP + AMP). By catalyzing the conversion of AMP to inosine monophosphate, thereby reducing available AMP, MAD indirectly tilts the above equation in favor of the formation of ATP, maintaining energy supplies. Also, the production of ammonia by MAD buffers the lactic acid formed during exercise. Further, inosine monophosphate stimulates glycolysis by acting on PFK and aids in making fumarate, a substrate for the Kreb cycle. Thus, MAD deficiency potentially can have wide-reaching metabolic effects in multiple energy production cycles. Reduced phosphocreatine and ADP levels have been demonstrated in MAD deficiency patients compared to normal controls.[140] However, a study of sustained, isometric muscle contraction during ischemia in patients with MAD deficiency and normal controls found no difference in oxygen use, endurance time, resting, and postexercise lactate and phosphocreatine levels, suggesting a normal exercise capacity.[141]

Point mutations have been identified in the gene in primary MAD deficiency, *AMPD1* (AMP deaminase 1), located on chromosome 1p13–21.[139,142] As noted above, MAD deficiency has been associated with a number of neuromuscular disorders. A study in the Dutch population revealed no significant differences in frequencies of the characteristic "mutation" in the MAD gene in patients with exercise intolerance, those with other neuromuscular disorders, and healthy volunteers.[139] It may be that the "mutations" that lead to MAD deficiency are no more than harmless polymorphisms.

Treatment

There is no specific medical treatment available.

▶ LIPID METABOLISM DISORDERS

The major source of fuel for muscles at rest and following prolonged or intense physical activity are free fatty acids, particularly long-chain fatty acids. β-Oxidation of free fatty acids occurs within the inner matrix of mitochondria and generates ATP. Fatty acids are divided into short-, medium-, long-, and very-long-chain fatty acids, depending on their size.[143] Short- and medium-chain fatty acids are readily permeable to either the outer or the inner mitochondrial membranes. However, long-chain fatty acids must interact with various carrier proteins and be actively transported across the mitochondrial membranes (Fig. 26–5). First, the long-chain fatty acids combine with coenzyme A (CoA) in a reaction catalyzed by acyl-CoA-synthetase at the outer mitochondrial membrane, creating a long-chain acyl-CoA. Next, the long-chain acyl-CoA must link with carnitine in a reaction reversibly catalyzed by carnitine palmitoyltransferase 1 (CPT1), an enzyme located on the outer face of the outer mitochondrial membrane, to cross over the outer membrane. The long-chain acyl–carnitine complex within the intermembrane space is then transported across the inner mitochondrial membrane, in a reaction catalyzed by carnitine palmitoyltransferase 2 (CPT2)

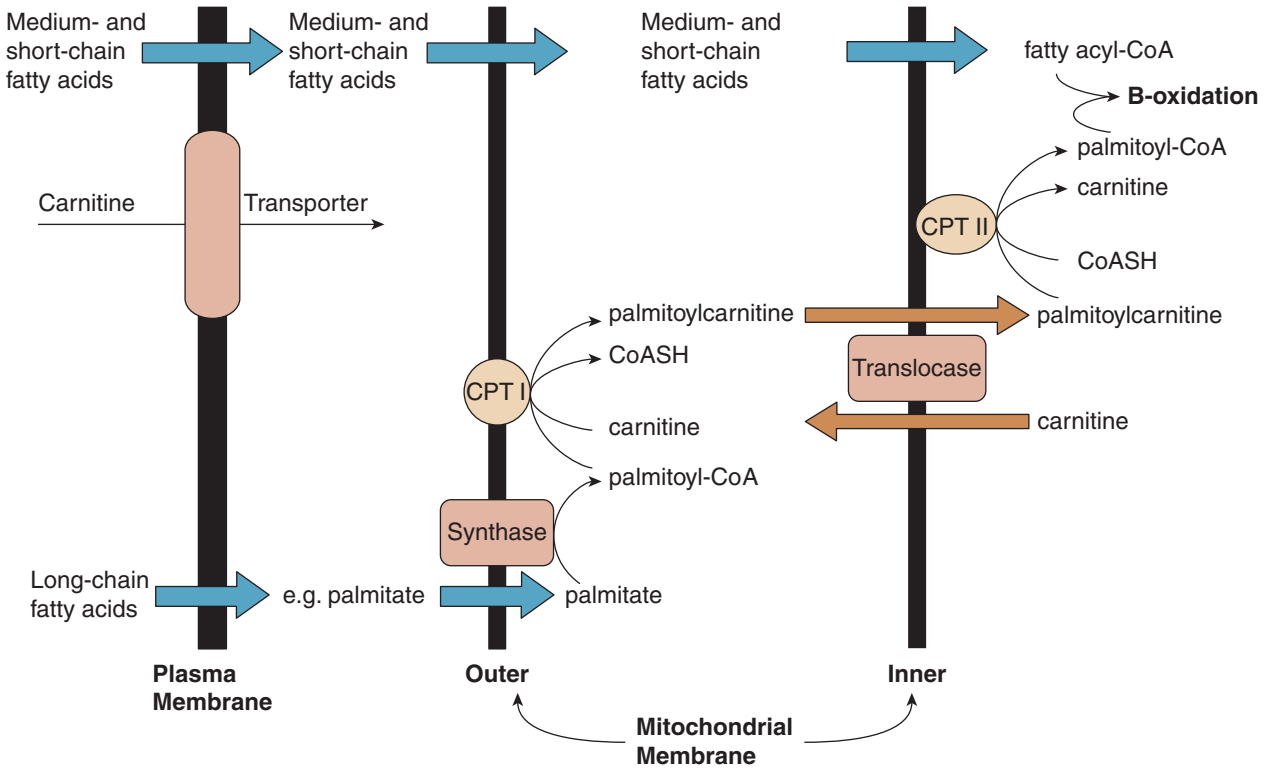


Figure 26–5. Transport of fatty acids across the mitochondrial membrane. Long-chain fatty acids (palmitate is the example here) cross the plasma membrane and the outer mitochondrial membrane. These combine with coenzyme A (CoA) to form a two-carbon fatty-acid-derived fragment (palmitoyl-CoA). This fragment is then joined to carnitine in a reaction reversibly catalyzed by carnitine palmitoyltransferase 1 (CPT1), an enzyme located on the outer mitochondrial membrane. The acylcarnitine complex (e.g. palmitoylcarnitine) traverses the inner mitochondrial membrane in exchange for carnitine in a reaction catalyzed by acylcarnitine translocase. Carnitine palmitoyltransferase 2 (CPT2) located on the inner surface of the inner mitochondrial membrane mediates the formation of acyl-CoA (palmitoyl-CoA) from the acylcarnitine complex and CoASH. The acyl-CoA, now within the mitochondrial matrix, can then undergo β-oxidation. (With permission from Walsh R. Continuum 2006.)

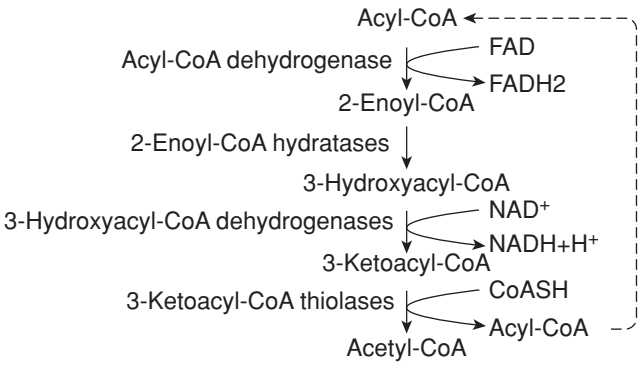


Figure 26–6. β-oxidation of fatty acids pathway. There are four steps involved in the complete oxidation of fatty acids. The main defects in this pathway affecting muscle involve deficiencies of the acyl-CoA dehydrogenases. The details of each reaction are given in the text. (With permission from Walsh R. Continuum 2006.)

located on the inner surface of the inner membrane. This liberates carnitine from the long-chain acyl-CoA. The carnitine is then transported in the opposite direction, in a reaction catalyzed by carnitine/acylcarnitine translocase. The long-chain acyl-CoA, now within the mitochondrial matrix, can be metabolized by β-oxidation into ATP.

Beta-oxidation of the fatty acids within the mitochondria proceeds through repeated cycles consisting of four sequential enzymatic reactions (Fig. 26–6). First, flavin-dependent, length-specific acyl-CoA dehydrogenases (note that there are short-, medium-, long- , and very-long-chain acyl-CoA dehydrogenases [SCADs, MCADs, LCADs, and VLCADs]) convert the acyl-CoA substrates into enoyl-CoAs and reduce flavin adenine dinucleotide (FAD). Second, length-specific enoyl-CoA hydratase catalyze the formation of 3-hydroxyacyl-CoA derivatives. Third, length-specific, NAD-dependent 3-hydroxyacyl-CoA dehydrogenases (HADs) catalyze the formation of 3-ketoacyl-CoA esters by a second dehydrogenation reaction. In the fourth and final step, length-dependent 3-ketothiolase catalyzes the conversion of the 3-ketoacyl-CoA ester to acetyl-CoA and fatty acyl-CoA, which is now two carbon atoms shorter than the acyl-CoA that entered the initial first step. This sequential cycle of four enzymatic reactions is then repeated.

Electrons transferred to $FADH_2$ and NADH are then transferred to the respiratory chain, which is composed of five multimeric protein complexes embedded in the inner mitochondrial membrane. FADH delivers its electrons to coenzyme Q via two flavoproteins: electron-transferring flavoprotein (ETF) and ETF-coenzyme Q oxidoreductase (ETF-QO). NADH delivers its electrons to complex I of the respiratory chain. The electrons are then transported down an energy gradient form one complex to another, generating a proton motive force, which is necessary to produce ATP.

Defects in the transport of long-chain fatty acids and lipid metabolism affect multiple organs, including muscle. Two major muscle manifestations are (1) progressive muscle weakness and hypotonia (e.g., as seen in carnitine transporter and carnitine/acylcarnitine defects) and (2) acute, recurrent rhabdomyolysis (e.g., as seen in deficiencies of CPT2, VLCAD, and trifunctional protein). Some defects result in both fixed weakness and recurrent bouts of rhabdomyolysis (e.g., VLCAD and trifunctional protein deficiencies).

CARNITINE TRANSPORTER DEFICIENCY (PRIMARY CARNITINE DEFICIENCY)

Clinical Features

Carnitine deficiency is the most common disorder of lipid metabolism. Primary systemic carnitine deficiency is a clinically heterogeneous disorder.[144–154] Some patients with primary carnitine deficiency develop symptoms and signs resembling Reye syndrome in early childhood: i.e., acute attacks of vomiting, altered mental status, hypoglycemia, and hepatomegaly.[144,152,154,155] These children may become weak, but the systemic manifestations tend to overshadow the myopathy. More commonly, individuals who are affected present with a hypertrophic or dilated cardiomyopathy and progressive proximal muscle weakness and atrophy in childhood or early adult life.[58,145,146,156–162] Rhabdomyolysis and respiratory weakness can occur.[163] Infantile onset has also been described. A few cases have worsened significantly during pregnancy or in the postpartum period.[164]

Secondary carnitine deficiency may result from a variety of disorders, including respiratory chain defects, organic aciduria, endocrinopathies, dystrophies, and renal and liver failure, malnutrition, and as a toxic effect of certain medications.[11,147,165,166] It is not known if the secondary deficiency of carnitine can in and of itself cause a myopathy.

Laboratory Features

Plasma and tissue (including muscle) carnitine levels are markedly diminished in primary carnitine deficiency, while the levels are only moderately reduced (25–50% normal) in secondary forms of carnitine deficiency.[143,147,155,167,168] Serum CK levels are normal in approximately 50% of patients with the myopathic form of the disease but can be elevated to as much as 15 times normal. In primary systemic carnitine deficiency, liver enzymes are also elevated. Fasting individuals with carnitine deficiency may develop hypoglycemia, acidosis, and elevated CK levels and liver function tests. However, ketones are not elevated in the urine during fasting.

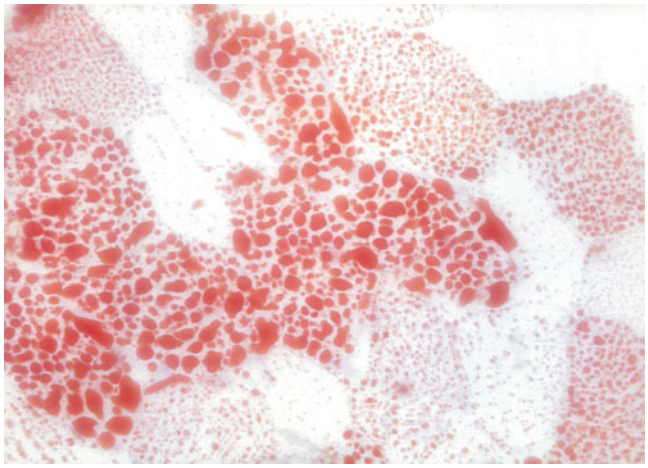


Figure 26–7. Carnitine deficiency. Muscle biopsy demonstrates increase lipid deposition within fibers on oil red O stain.

EMG may reveal increased insertional activity with positive sharp waves, fibrillation potentials, and complex repetitive discharges. Early recruitment of short-duration, small-amplitude, polyphasic MUAPs can be observed. An echocardiogram can demonstrate a dilated or hypertrophic cardiomyopathy.

Histopathology

Muscle biopsies reveal variability in muscle fiber size and abnormal accumulation of lipid in the subsarcolemma and intermyofibrillar regions (Fig. 26–7).[4] Type 1 fibers are preferentially affected as would be expected, given that oxidative metabolism primarily occurs in these fibers. EM also demonstrates increased lipid (Fig. 26–8). Muscle carnitine levels are dramatically decreased (<2–4% of normal) in patients with primary carnitine deficiency (this may serve to distinguish from patients with secondary deficiency).

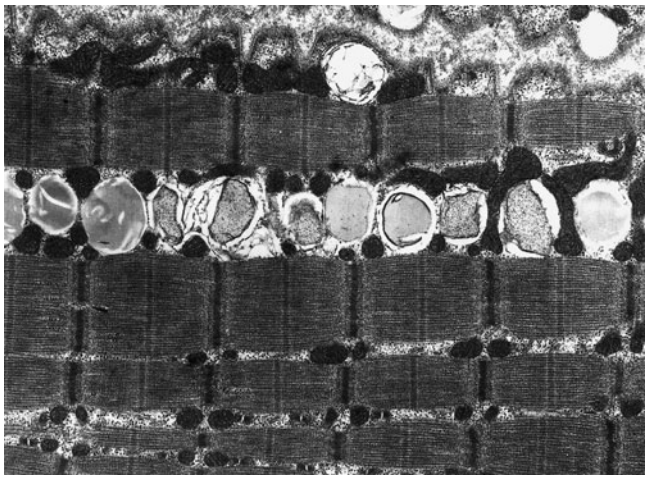


Figure 26–8. Carnitine deficiency. Electron microscopy reveals increased endomysial lipid droplets.

Molecular Genetics and Pathogenesis

Primary carnitine deficiency is caused by mutations in the sodium-dependent carnitine transporter protein, *OCTN2*, gene (also called the *SLC22A5* gene) located on chromosome 5q33.1.[169] Carnitine is supplied to tissues by diet and endogenous synthesis. Intracellular carnitine levels are maintained at 20–50 times the extracellular concentration by this active transport system. The deficiency of carnitine impairs the transport of long-chain fatty acids into the inner mitochondrial matrix, thus severely affecting energy production from these fatty acids.

Treatment

Oral L-carnitine (100–200 mg/kg/d) benefits some, but not all patients, with carnitine deficiency.[149,153,163,170,171] A dramatic clinical response to oral L-carnitine in patients with severe cardiomyopathy and muscle weakness has been reported.[155,161,162] However, only modest increases in muscle carnitine levels have been demonstrated, even in those who improved in muscle strength.[155] Perhaps, intracellular (muscle) concentration of carnitine only needs to be over 2–4% of normal to allow for normal lipid metabolism.

CPT2 DEFICIENCY

Clinical Features

CPT2 deficiency is inherited in an autosomal-recessive manner and typically presents in the second or third decade of life with muscular pain and myoglobinuria following intense or prolonged exertion usually by the second or third decade of life.[150,172–175] Prolonged fasting and infection are other precipitating factors. The neuromuscular examination is usually normal between bouts of rhabdomyolysis. Rare cases of a CPT2 deficiency causing a fatal cardiomyopathy in infancy or early childhood have also been reported.

Laboratory Features

Serum CK levels are usually normal, except when the patient performs intense physical activities or fasts. Exercise forearm test is normal, which can help distinguish CPT2 deficiency from the glycogen storage disorders which can also cause exercise-induced rhabdomyolysis. Muscle and serum carnitine levels are normal. EMG is usually unremarkable, although myopathic units may be seen. EKG is also normal.

Histopathology

There is usually no gross abnormality noted on light microscopic examination of muscle tissue. However, an increase in the lipid content of muscle may be apparent on EM.

Molecular Genetics and Pathogenesis

Mutations in the *CPT2* gene located on chromosome 1p32 have been identified.[174,176,177] The resultant deficiency of CPT2 impairs the transport of acylcarnitine across the inner mitochondrial membrane. Thus, the generation of ATP from fatty acid metabolism is diminished. Interestingly, CPT1 deficiency does not usually cause a myopathy.

Treatment

A high-protein, low-fat diet with frequent meals should be advised. Avoidance of prolonged strenuous activity, cold temperatures, and fasting may prevent episodes of rhabdomyolysis. During febrile illness, patients should be instructed to increase their intake of complex carbohydrates and again avoid fasting.

VLCAD DEFICIENCY

Clinical Features

VLCAD deficiency is a clinically heterogeneous disorder with three major phenotypes.[178–185] The disorder most commonly manifests in childhood with an early onset of hypertrophic cardiomyopathy, recurrent episodes of hypoketotic hypoglycemia and dicarboxylic aciduria, and a high mortality rate (50–75%). There is a milder form characterized by episodes of hypoketotic hypoglycemia and dicarboxylic aciduria but minimal if any cardiac involvement and low mortality. In addition, VLCAD deficiency can rarely present similar to CPT deficiency, with exercise-induced myoglobinuria beginning in early childhood to early adulthood.

Laboratory Features

Serum CK is elevated in cases of myoglobinuria as expected. Between attacks, the CK may be normal. There can be a secondary deficiency of carnitine, in particular with muscle. There is an increase in plasma concentration of tetradecanoic acid ($C_{14:1}$) with normal levels of myristic acid ($C_{14:1}$), consistent with a defect in β-oxidation of long-chain fatty acids.[186] Reduced VLCAD activity can be demonstrated in cultured fibroblasts. EMG may reveal myopathic appearing MUAPs.

Histopathology

Muscle biopsies demonstrate abnormal accumulation of lipid.

Molecular Genetics and Pathogenesis

This myopathy is caused by mutations in the VLCAD gene, which is located on chromosome 17p11.2–p13.1.[178,179,185] Patients with this enzyme deficiency have impaired ability to metabolize very-long-chain fatty acids. Some of the previously described cases of long-chain acyl-CoA deficiency probably in fact had very-long-chain CoA deficiency.[185]

Treatment

A low-fat/high-carbohydrate diet in which long-chain fatty acids are partially replaced by medium-chain triglycerides may be effective in preventing attacks of hypoketotic hypoglycemia, dicarboxylic aciduria, and myoglobinuria in some[182,187] but not all patients.[183] Individuals who are affected should be instructed to avoid fasting.

LCAD DEFICIENCY

Clinical Features

LCAD usually presents in infancy with failure to thrive, hepatomegaly, cardiomegaly, nonketotic hypoglycemia, and an encephalopathy resembling Reye syndrome.[188–190] Individuals who are affected may develop exercise intolerance with attacks of rhabdomyolysis and proximal weakness.

Laboratory Features

Serum CK is elevated during attacks of muscle pain and cramps. Total and free carnitine levels are reduced in the plasma, liver, and muscle, but long-chain acylcarnitine esters are increased. Diagnosis is suggested by demonstrating decreased LCAD activity in cultured fibroblasts.[188]

Histopathology

Muscle biopsies reportedly demonstrate abnormal accumulation of lipid.

Molecular Genetics and Pathogenesis

The *ACADL* gene localizes to 2q34–q35. However, as previously noted, some reported cases of LCAD deficiency were in fact patients with VLCAD deficiency.[185] LCAD acts on fatty acyl-CoA derivatives whose acyl residues contain more than 12 carbon atoms. Patients with LCAD deficiency have an impaired ability to metabolize long-chain fatty acids.

Treatment

Intravenous glucose has led to relief of the myalgias and lowering of the serum CK levels in some patients.[188] Carnitine can improve the cardiomyopathy but does not affect skeletal muscle strength.[188] A gluten-free diet was also suggested to be beneficial.[191]

MCAD DEFICIENCY

Clinical Features

MCAD is the most common form of acyl-CoA deficiency, but unlike defects in long-chain fatty acid metabolism, this deficiency is only rarely associated with cardiac or skeletal muscle involvement.[166,192–197] However, rare episodes of rhabdomyolysis and acute encephalopathy have been reported in infancy and late in life.[166,195,198,199]

Laboratory Features

MCAD activity is diminished to <10% in muscle, fibroblasts, lymphocytes, and liver.[166,192,198] A secondary deficiency of carnitine may be evident in the plasma, liver, and muscle. Dicarboxylic, adipic, and sebacic acids are increased in the urine.

Histopathology

Muscle biopsy is notable only for excess lipid.

Molecular Genetics and Pathogenesis

The disorder is caused by mutations within the MCAD gene located on chromosome 1p31.[198] MCAD acts on fatty acyl-CoA derivatives whose acyl residues contain four to 14 carbon atoms.

Treatment

Carnitine may improve the hepatomegaly and urinary organic acid profile and prevent attacks of rhabdomyolysis and encephalopathy,[196] although there is some concern that carnitine supplementation is ineffective and possibly dangerous.[197] Fasting should be avoided.

SCAD DEFICIENCY

Clinical Features

Patients with SCAD deficiency may present with exercise intolerance, myalgias, or progressive proximal weakness, which may be present in infancy or may develop in early to mid-adulthood.[194,200–202] Facial weakness, ptosis, progressive external ophthalmoplegia, respiratory weakness, and cardiomyopathy have also been described.[201] Some infants present with failure to thrive and nonketotic hypoglycemia.

Laboratory Features

Serum CK is usually normal. There is increased urinary excretion of short-chain metabolites ethylmalonate and methylsuccinate.

Histopathology

The few reports of muscle biopsies have demonstrated excess lipid. Muscle carnitine levels may be secondarily reduced. SCAD deficiency can be demonstrated in muscle tissue. Multicore myopathy has also been reported in the setting of SCAD.[203]

Molecular Genetics and Pathogenesis

Genetic defects have been localized to the SCAD gene at 12q22–qter.[204,205] The gene is 13 kb in length and consists of 10 exons. SCAD acts on fatty acyl-CoA derivatives whose acyl residues contain four to six carbon atoms.

Treatment

No specific medical therapy has been shown to be beneficial, including carnitine supplementation.

▶ MITOCHONDRIAL TRIFUNCTIONAL PROTEIN DEFICIENCY

Mitochondrial trifunctional protein is a complex of eight subunits, which has long-chain HAD, ETF and ETF-QO activities. Mutations in the genes encoding for these enzymes are associated with chronic progressive weakness, cardiomyopathy, or recurrent rhabdomyolysis, as noted below.

LONG-CHAIN HAD DEFICIENCY

Clinical Features

The disorder is clinically heterogeneous. It can present in infancy or early childhood with Reye's-like syndrome, nausea, vomiting, seizures, hypoketotic hypoglycemia, respiratory failure, and cardiomyopathy.[135,206–211] Mortality is high (approximately 50%) due to the cardiomyopathy. Progressive weakness and recurrent episodes of myoglobinuria become more prevalent later in childhood. Some individuals who are affected develop a progressive sensorimotor polyneuropathy and pigmentary retinopathy.[135] Mothers of an affected fetus can develop distinctive complications of pregnancy: HELLP

(hemolysis, elevated liver enzymes, low platelets) and AFLP (acute fatty liver of pregnancy).[209]

Laboratory Features

Serum CK and lactate levels are elevated. An assay of cultured fibroblasts is necessary to demonstrate the deficiency of long-chain HAD deficiency.[135,206–211] Nerve conduction studies may reveal features suggestive of an axonal sensorimotor neuropathy, while myopathic MUAPS are apparent on EMG in weak muscles.

Histopathology

Muscle biopsies reveal an abnormal accumulation of lipids, although this increase is not as prominent as that observed in other disorders of β-oxidation. A nerve biopsy in one patient demonstrated marked loss of myelinated nerve fibers and axonal degeneration.

Molecular Genetics and Pathogenesis

The disorder is inherited in an autosomal-recessive pattern and the gene for HAD maps to 2p23.[212] Long-chain HAD catalyzes the third step in β-oxidation: the conversion of 3-hydroxyacyl-CoA derivatives to 3-ketoacyl-CoA derivatives. Deficiency of the enzyme leads to impairment in metabolism of long-chain fatty acids.

Treatment

Patients may benefit from a high-carbohydrate, low-fat protein diet with or without supplementation with medium-chain triglycerides, riboflavin, and L-carnitine supplementation.[206] Patients should avoid fasting.

ETF AND ETF-QO DEFICIENCIES

Clinical Features

Disorders of ETF and ETF-QO (also known as glutaric aciduria type II) are associated with clinical features similar to HAD deficiency, although these are more severe. The affected children manifest with progressive proximal weakness and atrophy associated with episodes of confusion, ataxia, tremor, nausea, vomiting, hypoketotic hypoglycemia, lethargy, and hepatomegaly in infancy or early childhood.[18,213–215] Some present with recurrent episodes of exercise-induced myoglobinuria later in childhood or adult life similar to CPT2 deficiency. As in patients with HAD deficiency, those with ETF and ETF-QO deficiencies have an associated axonal sensory neuropathy. This feature can distinguish this and HAD deficiency from CPT2 deficiency. Muscle stretch reflexes are reduced, probably due to the neuropathy.

Laboratory Features

Reduced ETF-QO activity can be demonstrated in cultured fibroblasts.[18,213] Secondary carnitine deficiency is evident in the plasma, liver, and muscle. Nerve conduction studies demonstrate an axonal sensory neuropathy, while the EMG may reveal myopathic appearing MUAPs.

Histopathology

Muscle biopsies reveal abnormal accumulation of lipids.

Molecular Genetics and Pathogenesis

The disorder can result from deficiency of any of three subunits of the enzyme complex: the alpha or beta subunits of ETF (ETFA or ETFB) and ETF dehydrogenase (ETF-QO). These genes map as follows: ETFA to 15q23–q25, ETFB to 19q13.3, and ETF-QO to 4q32-qter. ETF transfers electrons from reduced forms of acyl-CoA dehydrogenase to the respiratory chain via ETF-QO.[193] ETF-QO transfers electrons from ETF to ubiquinone. Defects in these enzymes result in the inability to oxidize the reduced forms of various dehydrogenases including VLCAD, LCAD, MCAD, and SCAD.

Treatment

Fasting should be avoided. No specific medical therapy, including carnitine supplementation, has been proven effective, although both low-fat diets[214,216] and riboflavin[215] have been reported to provide benefit.

▶ SUMMARY

The approach to patients with possible metabolic myopathies can be quite daunting. The initial step is to determine if one is dealing with a static or dynamic process. If the patient has fixed or progressive weakness, Pompe disease needs to be considered, particularly if there is early respiratory failure. A good initial screening test is the newly developed dried blood spot analysis. A muscle biopsy may be needed, particularly if less tests are negative. If the patient has exercise intolerance (a dynamic process), then an exercise forearm test can be beneficial in determining if one is dealing with a disturbance in glycogen or fatty acid metabolism. If the exercise forearm test is abnormal (no rise in lactate despite normal rise in ammonia), then genetic testing for McArdle disease can be performed. If this is negative, then we would do a muscle biopsy and metabolic assay to determine which enzyme is deficient. If the patient has a history of myoglobinuria only after excessive exercise, fasting, or infection, then our first step would be genetic

testing for CPT2 deficiency. If this is negative, we proceed with a muscle biopsy and metabolic analysis.

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CHAPTER 27

Mitochondrial Myopathies

Mitochondrial myopathies refer to a heterogeneous group of disorders caused by dysfunction of mitochondrial oxidative phoshorylation.[1–4] Mitochondrial myopathies can be classified according to the associated biochemical, genetic defects, or clinical phenotype (Tables 27–1 to 27–3). One difficulty in classifying patients by any particular scheme is the clinical phenotypic heterogeneity associated with specific mitochondrial mutations and the genetic heterogeneity in well-defined clinical phenotypes that are seen with mitochondrial disorders.

The mitochondria are responsible for converting fuels (carbohydrates, lipids, and proteins) into energy for the cells. Fatty acids are converted into molecules of acetyl-CoA within the mitochondria. Amino acids are converted to pyruvate in the mitochondria. Carbohydrates are metabolized to pyruvate in the cytoplasm and then transported into the mitochondria. Pyruvate is likewise then converted into acetyl-CoA. Acetyl-CoA then enters into the Kreb's cycle from which electrons are generated. Electrons derived from the Kreb's cycle are shuttled to the respiratory chain and processed through complexes I–V to generate ATP molecules. Thus mitochondrial disorders can be classified according to the metabolic defect present: (1) transport, (2) substrate utilization, (3) Kreb's cycle, (4) oxidation/phosphorylation coupling, and (5) respiratory chain (Table 27–1).

Some of the biochemical abnormalities seen in various mitochondrial disorders are nonspecific and the result of primary "upstream" defects in metabolic pathways. For example, cytochrome oxidase (COX) deficiency is seen in many types of mitochondrial myopathy and does not imply that the primary mutation lies in one of the genes encoding for subunits of COX. The rapid advances of molecular genetics may provide a better classification scheme for the mitochondrial myopathies (Table 27–2). However, there is significant phenotypic variability even in patients with the same genetic mutation and therefore a combined classification scheme is currently favored because of phenotypical variability and problems inherent in current genotyping capabilities (Table 27–3). Prior to discussing specific disorders, we will review a few basic principles regarding the mitochondrial genome and different inheritance patterns of mitochondrial disorders.

COMPOSITION OF MITOCHONDRIAL DNA AND PROTEINS

The mitochondrial genome is composed of 16.5 kB circular double-stranded DNA that contains no introns. In fact, contiguous mitochondrial genes overlap in some areas. There is a single promoter site and transcription is polycistronic such that mitochondrial genes are transcribed as two large RNAs. These are subsequently cleaved into 13 respective messenger RNAs (mRNA), 2 ribosomal RNAs (rRNA), and 22 transfer RNAs (tRNA). Interestingly, the genetic code for translation of human mitochondrial genes differs from the standard code which governs the translation of human nuclear genes.

The 13 mRNAs are translated into 13 polypeptides that are subunits of the respiratory chain complexes. Also note that any mutation in a mitochondrial tRNA gene can impair the proper translation of the 13 mitochondrial mRNAs. Importantly, the 13 proteins encoded by the mitochondrial genome account for less than 5% of all mitochondrial proteins. Thus, the majority of mitochondrial proteins are encoded by the nuclear genome that are translated in the cytoplasm and subsequently are transported into the mitochondria. Further, the nucleus appears to regulate replication of the mitochondrial genome.

The respiratory chain is composed of five multienzyme complexes (complexes I–V) (Fig. 27–1). Complex I (NADH-CoQ reductase) contains 41 subunits, seven encoded by mtDNA; complex II (succinate dehydrogenase-CoQ reductase) comprises four subunits, each encoded by nuclear genes; complex III ($CoQH_2$-cytochrome c reductase) is composed of 11 polypeptide units, one of which is encoded by mtDNA; complex IV (cytochrome C oxidase) has 13 subunits, three encoded by mtDNA; and complex V (ATPase synthetase) is composed of 14 subunits, two encoded by mtDNA (Table 27–4).

GENETICS OF MITOCHONDRIAL DISORDERS

Population-based studies in Northern England found that 6.57 per 100,000 adults have a mitochondrial disease and 12.48 per 100,000 of children and adults are at risk for developing a mitochondrial disorder on the

▶ TABLE 27–1. CLASSIFICATION OF THE MITOCHONDRIAL MYOPATHIES BY METABOLIC FUNCTION AFFECTED

Metabolic Function	Defects
Substrate transport	Carnitine palmitoyl transferase (CPT)
	Primary systemic/muscle carnitine deficiency
	Secondary carnitine deficiency
	Combined carnitine and CPT deficiency
Substrate utilization	Pyruvate decarboxylase deficiency
	Pyruvate dehydrogenase deficiency
	Pyruvate carboxylase deficiency
	Fatty acid β-oxidation defects
Kreb's cycle	Fumarase
	α-Ketoglutarate dehydrogenase deficiency
	Dihydrolipoyl dehydrogenase
Oxidation/ phosphorylation coupling	Luft's syndrome: loose coupling with hypermetabolism
Respiratory chain	Complex I
	Complex II
	Complex III
	Complex IV
	Complex V
	Combinations of I–V

With permission from Walsh RJ. Metabolic Myopathies. *Continuum* 2006;12(3):76–120.

▶ TABLE 27–2. CLASSIFICATION OF MITOCHONDRIAL DISORDERS BY GENETIC MUTATIONS

I. Mitochondrial DNA Mutations
  A. Large scale deletions
    1. Kearns-Sayre Syndrome
    2. PEO
  B. Mutations in mtDNA protein coding genes
    1. ATP6: Associated with Leigh syndrome and NARP
    2. Cytochrome b: Associated with exercise intolerance and recurrent myoglobinuria
    3. Cytochrome oxidase: Associated with fatal and benign infantile myopathies, Leigh syndrome, MELAS
  C. Mutations in mitochondrial tRNA and rRNA genes
    1. MERRF is usually associated with mutations in $tRNA^{lys}$ gene. MERRF has also been associated with mutations in $tRNA^{Leu}$ and $tRNA^{Ser}$
    2. MELAS is usually associated with mutations in $tRNA^{leu}$ gene. MELAS also occurs with mutations in $tRNA^{Val}$, $tRNA^{Cys}$, ND5 of complex 1, and in cytochrome b

II. Nuclear Gene Mutations
  A. Nuclear mutations associated with multiple mtDNA deletions
    1. Thymidine phosphorylase gene (chromosome 22q13): Associated with autosomal recessive MNGIE
    2. Autosomal Recessive Cardiomyopathy and Ophthalmoplegia (ARCO): Unknown Gene
  B. Nuclear Mutations Associated with mtDNA Depletion
    1. Adenine nucleotide translocator 1 (chromosome 4q34–35) is associated with autosomal dominant PEO
    2. Twinkle (chromosome 10) is associated with autosomal dominant PEO
    3. Polymerase gamma (chromosome 15q22–q26) is associated with autosomal recessive and dominant PEO
  C. SDH mutations: Associated with exercise intolerance
  D. Leigh syndrome: May be caused by mutations in Surf1 protein (chromosome 9q34) and several different subunits of Complex I, II, IV of the respiratory chain encoded by nuclear genes

basis of identifiable mtDNA mutations.[5] Remember that during fertilization, all the mitochondria are contributed by the mother. Hundreds of mitochondria are present in each cell in the body and every mitochondrion has several copies of mtDNA. Mutations involving mtDNA are more common and more likely to manifest clinically than mutations in nuclear genes because of the lack of introns and decreased DNA repair mechanisms in the mitochondrial genome. Mitochondrial DNA mutations are randomly distributed with generations of somatic cells during mitosis and germ cells during meiosis. Therefore, some cells will have few or no mutant genomes (normal homoplasty), some will have a mixture of mutant and normal or wild-type mitochondrial DNA (heteroplasty), and some will have predominantly mutant genomes (mutant homoplasty). Phenotypic expression depends on the relative proportion of mutant and wild-type mitochondria within each cell. When the number of mitochondria bearing sufficient mutated mtDNA exceed a certain threshold, mitochondrial function becomes impaired and patients manifest clinical symptoms and signs of disease (threshold affect).

During mitosis and meiosis, the proportion of mutant mitochondria in daughter cells can shift, thus changing the genotype and possibly the phenotype (mitotic/meiotic segregation). In addition, mutated mitochondria may utilize the mitochondrial-encoded mRNAs and tRNAs from neighboring normal mitochondria in a process called complementation. Thus, there can be some degree of normal translation of mtDNA-encoded proteins even in mitochondria harboring large DNA deletions.

Different organs have differing susceptibility for mitochondrial abnormalities depending on their energy requirements. Because the central nervous system (CNS)

TABLE 27–3. CLASSIFICATION OF MITOCHONDRIAL MYOPATHIES BY CLINICAL FEATURES AND GENOTYPE

Disease	Mode of Inheritance	Mitochondrial DNA Mutation	Gene Location
Kearns–Sayre syndrome	Sporadic	Single large mtDNA mutation	Large area of mt genome
PEO	Sporadic	Single large mtDNA mutation	Large area of mt genome
PEO	Maternal	Point mutations of mtDNA	$tRNA^{LEU}$, $tRNA^{ILE}$, $tRNA^{ASN}$
PEOA	Autosomal dominant	Multiple mtDNA deletions	POLG, C10ORF2 (twinkle), ANT1
PEOB	Autosomal recessive	Multiple mtDNA deletions	POLG
ARCO	Autosomal recessive	Multiple mtDNA deletions	Unknown nuclear gene
MERRF	Maternal	Point mutations of mtDNA	$tRNA^{LYS}$, $tRNA^{LEU}$, $tRNA^{HIS}$, $tRNA^{PHE}$, $tRNA^{SER}$, MTND5
MERRF	Autosomal recessive	Multiple mtDNA deletions	POLG
MELAS	Maternal	Point mutations of mtDNA	$tRNA^{LEU}$, $tRNA^{VAL}$, $tRNA^{LYS}$, $tRNA^{PHE}$, $tRNA^{SER}$, ND5, ND4, ND1, MTCYB
MNGIE	Autosomal recessive	Multiple mtDNA deletions	ECGG1 (thymidine phosphorylase), POLG
MNGIE	Maternal	Point mutations of mtDNA	$tRNA^{LYS}$
Leigh Syndrome	Maternal	Point mutations of mtDNA	MTND3, MTND5, MTND6, MTCO3, MTATP6, $tRNA^{VAL}$, $tRNA^{LYS}$, $tRNA^{TRP}$, $tRNA^{LEU}$
Leigh Syndrome	Autosomal recessive	None	NDUFV1, NDUFS1, NDUFS3, NDUFS4, NDUFS7, NDUFS8, SDHA BCS1L, COX10, COX15, SCO2, SURF1, LRPPRC
Leigh Syndrome	X-linked	None	PDHA1
Leigh Syndrome	Sporadic	Single large mtDNA mutation	Large area of mt genome
Myoglobinuria	Sporadic	Microdeletions of mtDNA	MTCO3
Myoglobinuria	Sporadic	Point mutations of mtDNA	MTCYB, ND4,
Myoglobinuria	Maternal	Point mutations of mtDNA	$tRNA^{PHE}$
MLASA	Autosomal recessive	None	PUS1
Fatal infantile myopathy	Autosomal recessive	mtDNA depletion	TK2 (thymidine kinase)

Abbreviations: PEO: Progressive external ophthalmoplegia; ARCO: Autosomal recessive cardiopathy and ophthalmoplegia; MELAS: Mitochondrial encephalopathy, lactic acidosis and strokes; MERRF: Myoclonic epilepsy and ragged red fibers; MNGIE: Myo-neuro-gastrointestinal-encephalopathy; MLASA: Mitochondrial myopathy and sideroblastic anemia; mtDNA: Mitochondrial DNA.
With permission from Walsh RJ. Metabolic Myopathies. *Continuum* 2006;12(3):76–120.

is in constant demand for energy, small decreases in energy production can lead to severe abnormalities. In contrast, skeletal muscle has low energy demands at rest, but these demands drastically increase with exercise. Thus, the basis for exercise-intolerance in many patients with mitochondrial myopathies.

Primary mutations of mtDNA can only be inherited from the mother, but unlike X-linked disorders that are also passed on only from the mother, women and men are equally affected in inherited mitochondrial diseases, while men are generally more severely affected in X-lined diseases. Further, based on the degree of mitochondrial segregation and heteroplasty, all the children of an affected mother may be affected to a variable degree, which is different from autosomal dominant and recessive inheritance patterns.

Mitochondrial disorders are not strictly inherited from an affected mother. Because over 95% of mitochondrial proteins are encoded from nuclear genes, mitochondrial disorders can be inherited in an autosomal dominant (e.g., some forms of progressive external ophthalmoplegia—PEO), autosomal recessive (e.g., MNGIE syndrome), and even X-linked (e.g., some forms of Leigh syndrome) fashion. In addition, the presence of mutations involving mtDNA does not imply a

TABLE 27–4. COMPOSITION AND GENETIC CONTROL OF THE MITOCHONDRIAL RESPIRATORY CHAIN

	Respiratory Chain	
Complex	Total Number mtDNA Encoded	Polypeptides
I	41	7
II	4	0
III	11	1
IV	13	3
V	14	2

Modified from Zeviani M, Bonilla E, DeVivo DC, DiMauro S. Mitochondrial Diseases. *Neurol Clin* 1989;7:123–156, with permission.

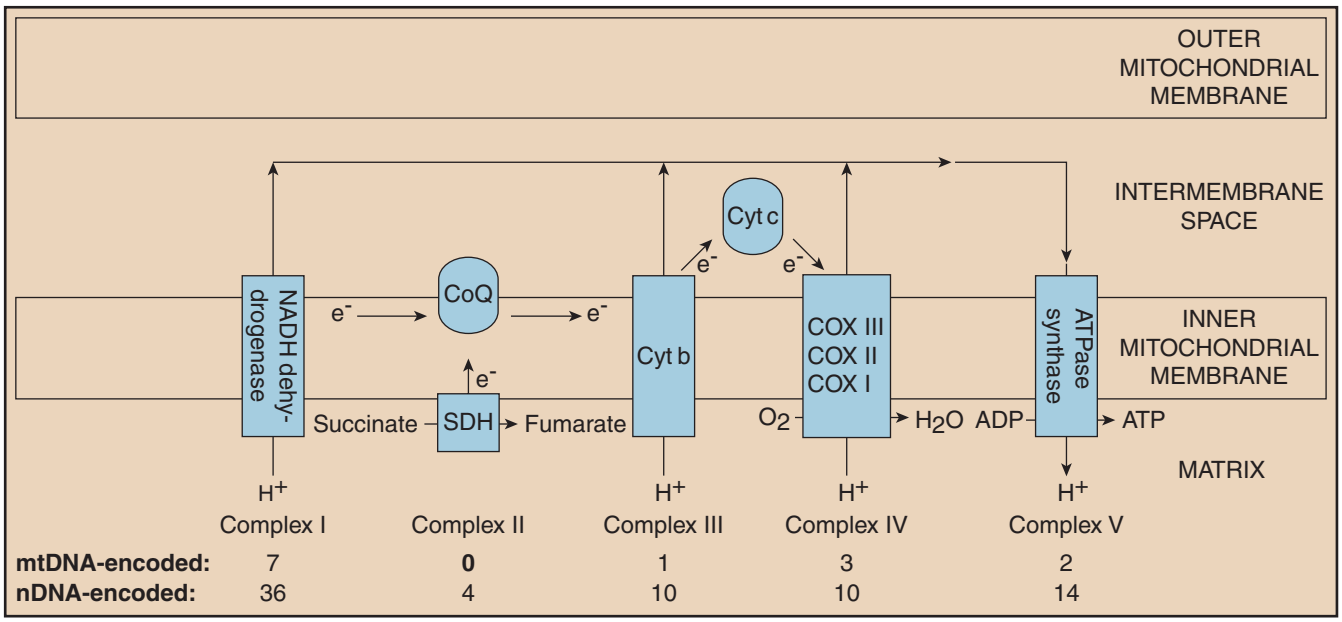

Figure 27–1. Schematic view of the respiratory chain. This diagram shows the number of subunits encoded by mitochondrial DNA (mtDNA) and nuclear DNA (nDNA) for each complex. All of the subunits for complex II are encoded by nDNA. Electrons (e−) flow down the respiratory-chain and protons (H+) are pumped from the matrix to the intermembranous space through complexes I, III, and IV, then back into the matrix through complex V (ATPase synthase). Cytochrome C (Cyt c) and coenzyme Q (CoQ) are electron carriers. This process generates adenosine triphosphate (ATP). (With permission from Walsh RJ. Metabolic Myopathies. *Continuum* 2006;12(3):76–120.)

maternal/ mitochondrial inheritance pattern. In this regard, Kearns–Sayre syndrome (KSS) is associated with large mtDNA deletions but is sporadic in nature. Additionally, as noted earlier there appears to be some nuclear control over the mitochondrial genome; thus mutations in some nuclear genes result in syndromes associated with depletion or multiple deletions of mtDNA. These disorders can demonstrate autosomal recessive or dominant inheritance patterns.

There can be significant genetic heterogeneity even within well-defined clinical syndromes. For example, PEO can be associated with multiple mtDNA deletions, point mutations in various mitochondrial tRNA genes, or have no mitochondrial DNA mutations. In addition, specific mutations of mitochondrial encoded genes can manifest with heterogeneic clinical phenotypes. For example, point mutations in the mitochondrial $tRNA^{Leu}$ can result in MELAS, PEO, encephalomyopathy, or a generalized myopathy with exercise intolerance. Variability in clinical phenotype can also be apparent within families with identical mtDNA mutations. The vast clinical and genetic heterogeneity of the various mitochondrial disorders can be explained by the different segregation patterns of mutant mitochondria, the degree of mutant heteroplasty, tissue-specific thresholds, and the severity of the biochemical impairment related to the specific mutations.

LABORATORY FEATURES

Serum creatine kinase (CK), lactic acid, and pyruvate levels can be normal or elevated. In addition, lactic acid levels may also be elevated in cerebrospinal fluid (CSF). Some mitochondrial disorders (e.g., mtDNA depletion) can be associated with renal tubular defects characterized by glycosuria, proteinuria, and aminoaciduria.

Bicycle ergometry can sometimes be a useful test. Low levels of workload lead to an excessive rise in pulse rate and oxygen consumption. The degree of exercise intolerance correlates directly with the severity of impaired muscle oxidative phosphorylation as indicated by the peak capacity for muscle oxygen extraction and mitochondrial mutation load.[6,7] The diagnostic value of a constant workload protocol may be superior to an incremental cycle test, but that the test is less sensitive for mitochondrial myopathies than simple testing of resting lactate and muscle morphology.[8]

A forearm exercise test can be performed where bicycle ergotmetry testing is not available.[9] The patient is instructed to open and close their hand (about once every 2 seconds at 40% of maximal voluntary contraction for 3 minutes. A butterfly needle can be placed in the antecubital fossa and venous oxygen and lactate levels can be measured at baseline and each minute during and immediately following exercise. Patients with

mitochondrial myopathies and exercise intolerance often demonstrate excessive and prolonged lactate production and paradoxically increased venous oxygen saturation.[9] The range of elevated venous PO_2 during forearm exercise in mitochondrial myopathy patients (32–82 mm Hg) correlates closely with the severity of oxidative impairment as assessed during cycle exercise.[10] Thus, the measurement of venous PO_2 during aerobic forearm exercise provides an easily performed screening test that sensitively detects impaired oxygen use and accurately assesses the severity of oxidative impairment in patients with mitochondrial myopathy and exercise intolerance.

Nerve conduction studies (NCS) may be normal or abnormal. Some mitochondrial myopathies can be associated with an axonal neuropathy (i.e., NARP) or demyelinating neuropathy (MNGIE) but in most cases the NCS are normal. Electromyography (EMG) is usually normal although again some disorders are associated with increased insertional and spontaneous activity as well as early recruitment of small motor unit action potentials (MUAPs) might be evident in weak muscles. Conduction defects may be apparent on electrocardiograms (EKG).

Magnetic resonance imaging (MRI) of the brain and electroencephalography (EEG) are typically abnormal in patients with a mitocochondrial encephalomyopathy. MRI of the skeletal muscle can reveal morphologic changes that resemble muscular dystrophies.[11]

Magnetic resonance spectroscopy (MRS) with ^{31}P and ^{1}H compounds permits the analysis of ATP, creatine phosphate, inorganic phosphate, and pH in muscle and brain.[12,13] In mitochondrial disorders, there is a rapid fall in levels of creatine phosphate and an abnormal accumulation of inorganic phosphates with exercise. In addition, there is a delay in the recovery of phosphocreatine levels to normal after exercise. These techniques may also be potentially valuable in evaluating efficacy of various treatments.[14]

If a mitochondrial myopathy is suspected from the clinical history and laboratory results, a muscle biopsy may be required to confirm the diagnosis. Mutational analysis may be done on white blood cells but in certain syndromes this is not as sensitive as finding mitochondrial mutations in muscle tissue, particularly in those with large mtDNA deletions.

HISTOPATHOLOGY

The histopathological abnormalities in muscle biopsies of the various mitochondrial myopathies are nonspecific. The characteristic histological features are the presence of ragged red fibers on the modified-Gomori trichrome stain (Fig. 27–2) Oxidative enzyme stains: nicotinamide adenine dinucleotide dehydrogenase (NADH), succinate dehydrogenase (SDH), and cytochrome-C oxidase (COX) are also invaluable. The ragged red fibers and small arteries intensely react to NADH and SDH stains, forming ragged blue fibers (Fig. 27–3). An increased number of lipid droplets are also often evident within these abnormal muscle fibers.

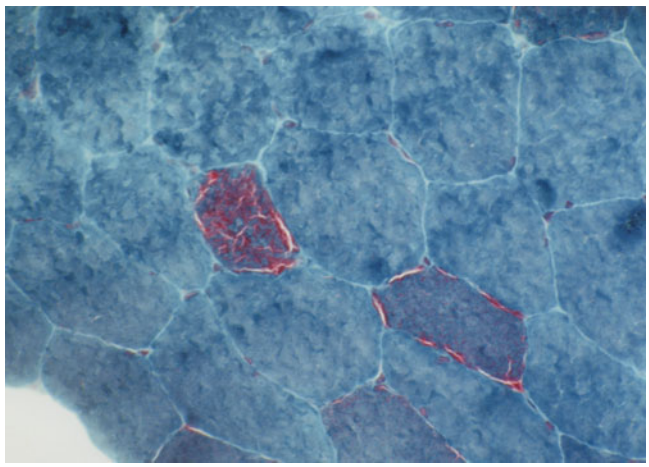

Figure 27–2. Ragged red fibers. Ragged red fibers result from the accumulation of abnormal mitochondrial below the sarcolemma of muscle fibers that are best appreciated on modified Gomori-trichrome stain.

Some patients with mitochondrial myopathies (in particular disorders not associated with mt-tRNA mutations) may have no ragged red fibers and normal NADH and SDH staining. COX stain (directed against one of the subunits encoded by mtDNA)

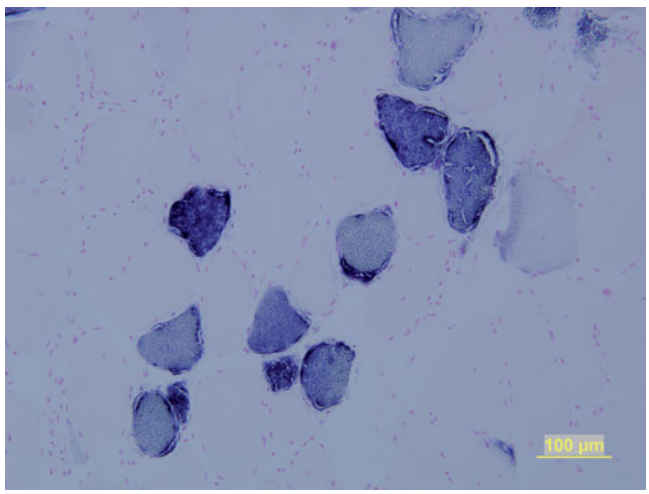

Figure 27–3. Succinic Dehydrogenase (SDH) positive fibers. Mitochondrial myopathies associated with mtDNA mutations often spare SDH which is entirely encoded by the nuclear genome. Therefore, muscle fibers with proliferating mitochondria stain intensely with SDH.

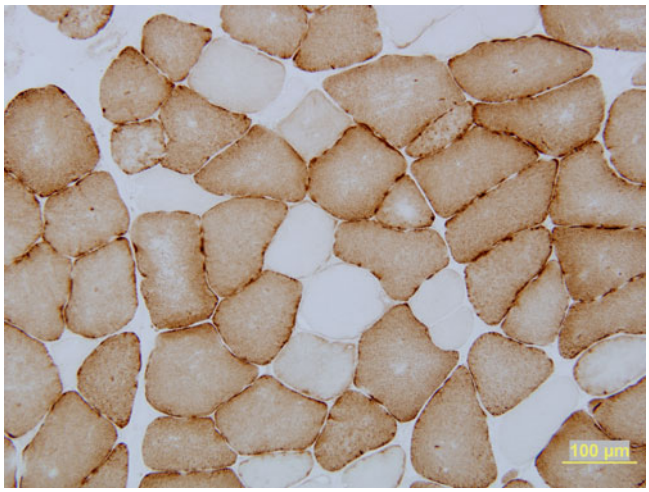

Figure 27–4. Cytrochrome C oxidase (COX) negative fibers. Scattered COX negative fibers are often appreciated in mitochondrial myopathies. The presence of COX negativity in an SDH positive fiber is suggestive of a mtDNA mutation.

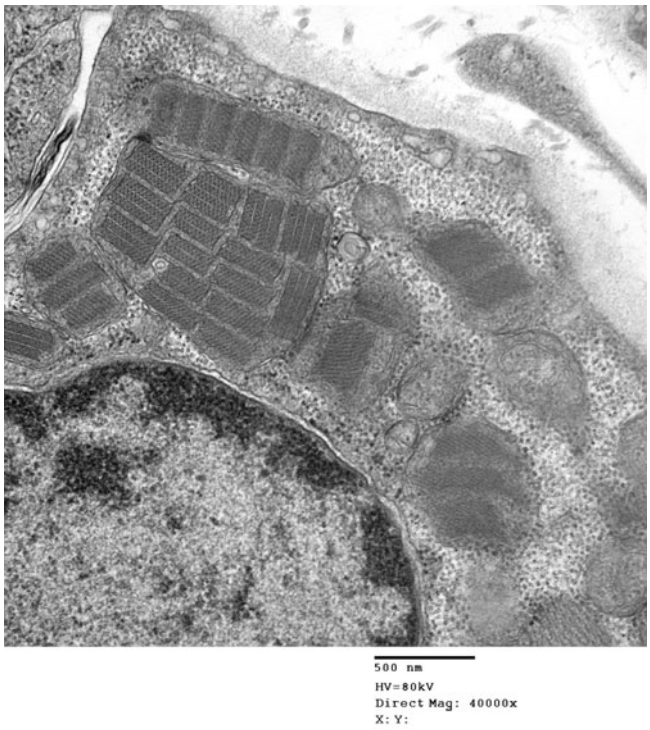

Figure 27–5. Electron Microscopy. EM reveals increased numbers of mitochondria with abnormal paracrystalline inclusions.

appears to be the most sensitive stain and can demonstrate scattered muscle fibers with reduced or absent stain (Fig. 27–4). In addition in some fibers, COX highlights the subsarcolemmal accumulations of mitochondrial. Reduced COX staining can be seen in both ragged red and otherwise normal-appearing muscle fibers. The variability of COX staining in combination with intense SDH staining is characteristic of disorders with mtDNA mutations. Remember, SDH of complex II is entirely encoded by nuclear DNA while three of 13 subunits of complex IV (COX) are encoded by mtDNA. Mutations of mtDNA often lead to a proliferation of mitochondria, perhaps in a compensatory response. Because SDH is encoded by nuclear DNA, its transcription is generally increased in disorders caused by mtDNA mutations. The variability of COX staining reflects the heteroplasmic population of mutant and wild-type mitochondria. COX staining is not always abnormal in mitochondrial myopathies. Some patients with MELAS, point mutations in either ND genes or cytchrome b, or multiple mtDNA deletions due to POLG mutations can have normal muscle histochemistries, including COX staining.[3]

Ultrastructural alterations in mitochondria are usually apparent on EM. These abnormalities include an increased numbers of normal appearing mitochondria, enlarged mitochondria with abnormal cristae, and mitochondria with paracrystalline inclusions (Fig. 27–5). The paracrystalline inclusions are accumulations of dimeric mitochondrial creatine kinase (mtCK). This enzyme exists in both a dimeric and octamer form, but the increased radical generation in patients with mitochondrial disorders favors the production and crystallization of dimeric mtCK.[15]

BIOCHEMICAL ANALYSIS OF MITOCHONDRIAL FUNCTION

Mitochondrial enzyme activities can be assayed in muscle biopsy specimens. This can be useful when the routine muscle histochemistry is unrevealing but the diagnosis of a mitochondrial myopathy is still suspected because of the clinical phenotype. It can also be used to target genes for mutation screening. There is no standard method for performing mitochondrial metabolic analysis. Some centers prefer to assay only fresh muscle biopsy specimens (this is necessary for measurement of substrate oxidation). Rates of flux, substrate oxidation and ATP production can be measured by polarography or using 14C-labeled substrates. More commonly, measurement of enzyme activity of each of the individual respiratory complexes is performed on frozen muscle tissue.

MOLECULAR GENETIC ANALYSIS

Mutation analysis of mtDNA and nuclear genes should be guided by the clinical phenotype, laboratory features, histochemistry, and biochemistry (Fig. 27–6).[3] In

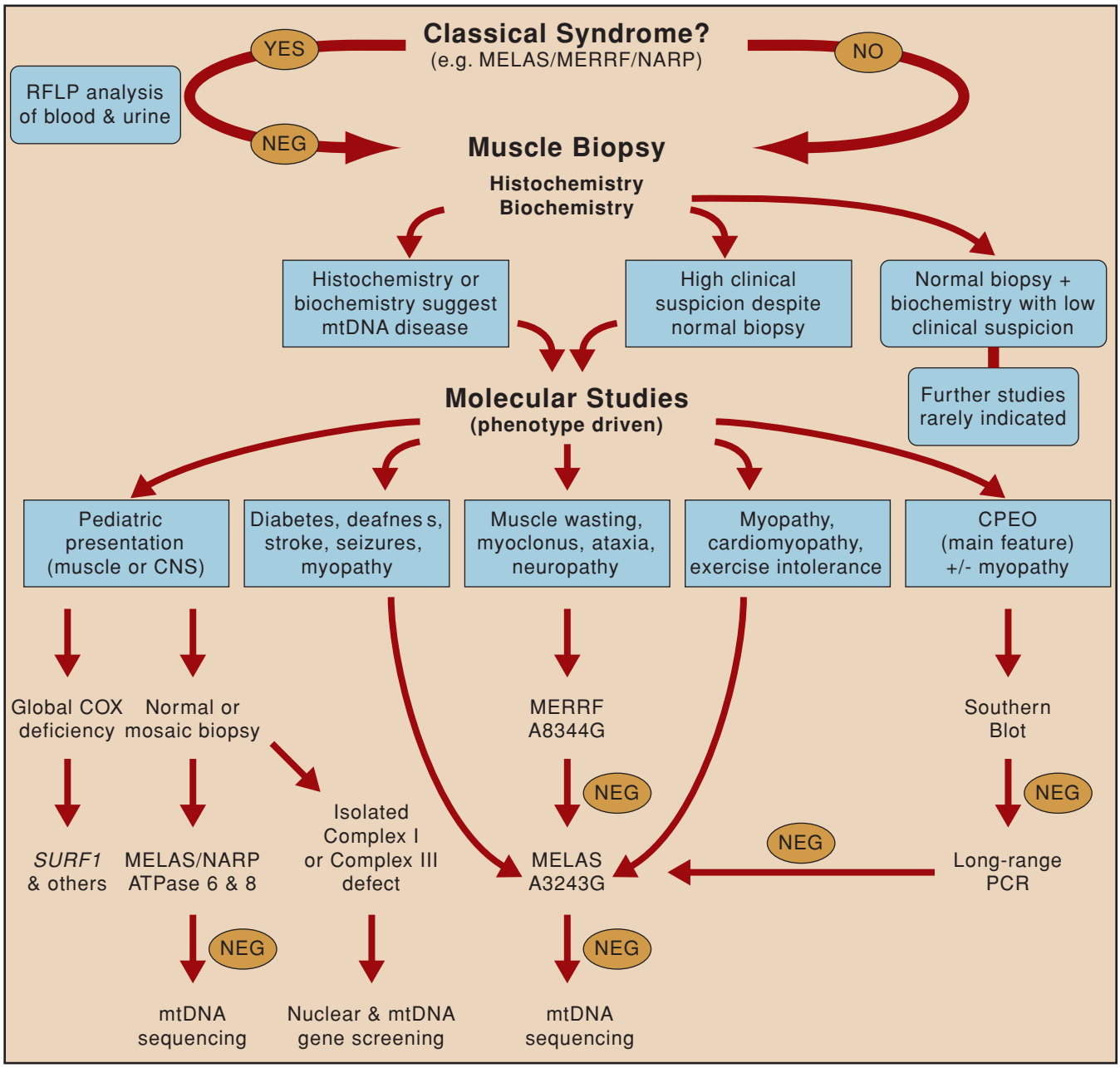

Figure 27–6. Flowchart illustrating routes of investigation in cases of suspected mitochondrial muscle disease. (With permission from Taylor RW, Schaefer AM, Baron MJ, McFarland R, Turnbull DM. The diagnosis of mitochondrial muscle disease. *Neuromusc Dis* 2004;14:237–245.)

patients with classic clinical syndromes (e.g., MERRF, MELAS), one can proceed directly toward mutation screening for the most common mutations associated with these disorders. As will be discussed, however, there is wide genetic heterogeneity even within well-defined clinical phenotypes. If a mutation is not found in blood cells, then a muscle biopsy and screening for mutations based on clinical phenotype aided by histochemical features and biochemical analysis.

▶ SPECIFIC MITICOHONDRIAL MYOPATHIES

MYOCLONIC EPILEPSY AND RAGGED RED FIBERS (MERRF)

Clinical Features

MERRF is characterized by myoclonus, generalized seizures (myoclonic and tonic–clonic), ataxia, dementia, sensorineural hearing loss, optic atrophy, and

progressive muscular weakness developing in childhood or adult life.[16–25] The clinical spectrum is variable, which may be a reflection of the percentage of abnormal mitochondria that segregate into the respective tissues. Age of onset, spectrum and severity of involvement, and the course can vary, even within families. Muscle weakness and atrophy can be generalized but there is a predilection for involvement of proximal arm and leg muscles. In addition, a generalized sensorimotor polyneuropathy and pes cavus deformities may be appreciated. The myoclonus is stimulus-sensitive but can be present at rest. The seizures may be photosensitive. Patients are often misdiagnosed as juvenile myoclonic epilepsy,[26] until other signs or symptoms (e.g., weakness, ataxia) manifest. Unlike KSS and PEO, ptosis, ophthalmoparesis, and pigmentary retinopathy are not seen with MERRF. However, cardiomyopathy with conduction block or heart failure may also be seen in MERRF, particularly those cases presenting early.[22] MERRF can also be complicated by respiratory weakness and associated with life-threatening hypoventilation in the setting of surgery, sedation, or intercurrent infection.[22,27] Some patients also manifest with multiple symmetric lipomatosis.[28,29]

Laboratory Features

Serum CK can be normal or mildly elevated. Serum lactate can be normal or elevated as well. Generalized slowing of the background activity and bursts of spikes and slow waves may be apparent on EEG. MRI or CT scan of the brain often reveal cerebral and cerebellar atrophy. NCS may demonstrate reduced decreased amplitudes of sensory nerve action potentials consistent with a superimposed axonopathy in some patients.[17,30,31] EMG is usually normal, although early recruitment of small MUAPs might be evident in weak muscles.

Histopathology

Muscle histopathology is abnormal as noted previously. Many ragged red fibers and COX negative fibers are evident that demonstrate increased SDH staining. Neuronal loss and gliosis of the dentate nuclei, globus pallidus, red nuclei, substantia nigra, inferior olivary nuclei, optic nerves, and cerebellar cortex are apparent on autopsy.[18] In addition, demyelination and gliosis are evident in the spinothalamic tracts, posterior columns, and cortical spinal tracts.

Molecular Genetics and Pathogenesis

There is non-Mendelian maternal inheritance of MERRF. Approximately 80% of MERRF causes are caused by a point mutation at nucleotide position 8344 of the mitochondrial genome that results in an A to G transition in the $tRNA^{Lys}$ gene (*MTTK*).[24,32,33] Of note, there is clinical heterogeneity in patients with this specific mutation as some can present with PEO, Leigh syndrome, or multiple symmetric lipomatosis.[18,29] MERRF has also been described with mutations at other locations in the $tRNA^{Lys}$ gene (positions 8356 and 8366) and with mutations in the $tRNA^{Leu}$ (*MTTL1*) that is most commonly mutated in MELAS. Other tRNA mutations associated with MERRF include $tRNA^{His}$ (*MTTH*), $tRNA^{Phe}$ (*MTTF*) and $tRNA^{Ser}$ (*MTTS1*). In addition, a MERRF clinical phenotype can also be found in patients with multiple mitochondrial DNA deletions[16] caused by mutations in the polymerase gamma gene (*POLG*) and in patients with mutations in ND5 (*MTND5*). Mutations can be demonstrated by polymerase chain reaction of mtDNA in leukocytes or muscle specimens, but the frequency of abnormal mtDNA is greater in muscle.

As described previously, the mitochondrial tRNA gene mutations impair the translation of mitochondrial-DNA-encoded respiratory chain proteins. Assays of mitochondrial enzyme activity in biopsied muscle tissue reveals diminished activity of complex I and IV. At least 90% of the mitochondria must harbor mutations in order for clinical abnormalities to appear.[34]

Treatment

There is no specific therapy for MERRF other than treating the myoclonus (e.g. clonazepam) and the seizures with antiepileptic medications. A slight benefit was reported in a few patients with MERRF treated with creatine monohydrate (5–10 gm/day).[35,36] Special care must be taken as patients with mitochondrial myopathies can develop marked alveolar hypoventilation in response to sedating medications and anesthetic agents.[27,37]

MITOCHONDRIAL MYOPATHY LACTIC ACIDOSIS AND STROKES (MELAS)

Clinical Features

MELAS is characterized by muscle weakness, high lactate levels in the serum or CSF, and stroke-like episodes.[38–42] Onset occurs in the first year of life in fewer than 10% with 60–80% developing symptoms and signs of the illness by the age of 15 years.[38,41] Rarely, MELAS can present as late as the eighth decade.[39] Most affected individuals patients have recurrent stroke-like episodes manifesting as migraine-type headaches with nausea and vomiting, hemiparesis, hemianopsia, or cortical blindness. These stroke-like attacks may be provoked by exercise or intercurrent infection. Progressive dementia may ensue. Most patients exhibit proximal muscle weakness and complain of easy fatigue and myalgias with exercise.

As with other mitochondrial disorders, many patients with MELAS are short-statured. Some affected individuals develop myoclonus, seizures, or ataxia and thus overlap clinically with MERRF. Ptosis, ophthalmoparesis, pigmentary retinopathy and/or cardiomyopathy

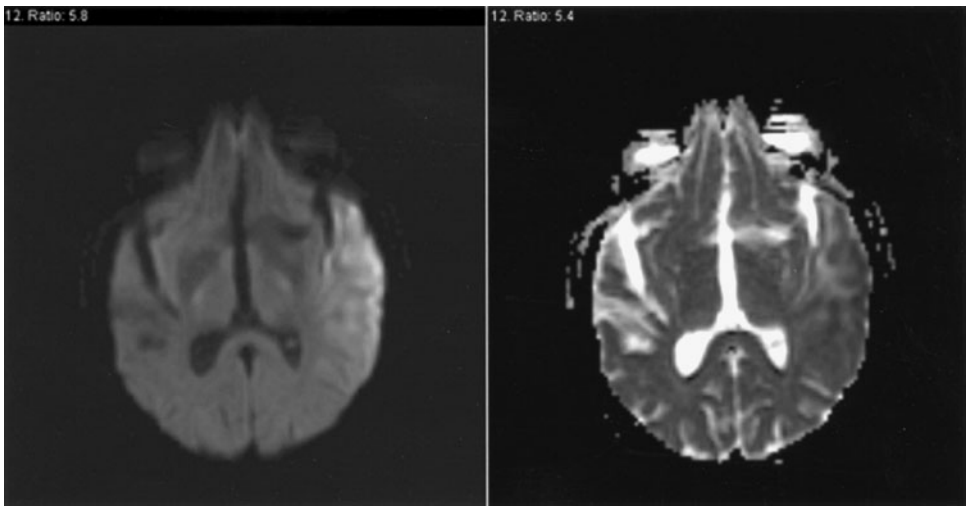

Figure 27–7. MRI in MELAS. The MRI brain imaging, during a stroke-like episode in a 61-year-old patient with genetically proven MELAS, shows a DWI high intensity lesion in the left temporal lobe in the first image and absence of corresponding hypointensity on the corresponding ADC image. (With permission from Walsh RJ. Metabolic Myopathies. *Continuum* 2006;12(3):76–120.)

occur in less than 10% of patients. Rare individuals manifest with only diabetes mellitus and/or deafness.

Laboratory Features

Serum CK can be normal or elevated. Lactate levels are elevated in the serum and CSF in the majority of patients. EEG may demonstrate epileptiform activity. NCS are normal but EMG may reveal early recruitment of myopathic appearing MUAPs.

MRI scans of the brain reveal cortical atrophy and high T(2) signal and FLAIR abnormalities in the cerebral cortex, basal ganglia, and thalamus (Fig. 27–7). The apparent diffusion coefficient (ADC) of the lesions have been reported as being increased [Kolb 2003], but other reported the ADC as being decreased.[43]

Magnetic resonance spectroscopy (MRS) of acute cortical lesions reveal severely elevated lactate levels and reduced concentrations of *N*-acetylaspartyl compounds, glutamate, and myo-inositol.[13] In addition, MRS of skeletal muscle may demonstrate a reduced phosphocreatine level, elevated concentrations of inorganic phosphate and free adenosine 5′-diphosphate, and an abnormally low phosphorylation potential.[13]

Histopathology

Muscle biopsies are indistinguishable from other mitochondrial myopathies as described previously. There are many ragged red fibers that have variable COX staining, ranging from increased reactivity to absent staining. This variability in COX staining is more prominent than that seen in MERRF. The COX-negative fibers intensely stain with SDH. Arterioles are also strongly SDH-reactive and an increase number of mitochondria are evident in muscular walls of small blood vessels. Mitochondrial enzyme analysis of muscle tissue reveals reduced activities of complexes I, III, IV, and V.

Molecular Genetics and Pathogenesis

MELAS is inherited maternally in a non-Mendelian pattern. Over 70% of cases are caused by a mtDNA mutation, an A to G substitution, at nucleotide position 3243 in the gene (*MTTL1*) encoding for $tRNA^{Leu}$.[40] There is genetic heterogeneity of MELAS as mutations have also been identified at positions 3252, 3260, 3271, 3291 in the $tRNA^{Leu}$ gene as well as in the genes for $tRNA^{Val}$ (*MTTV*), $tRNA^{Lys}$ (*MTTK*), $tRNA^{Phe}$ (*MTTF*), $tRNA^{Ser}$ (*MTTS1*), the dehydrogenase-ubiquinone oxidoreductase (ND) subunits of complex I: ND1 (*MTND1),* ND4 (*MTND4*), ND5 (*MTND5*), and cytochrome B of complex III (*MTCYB*).[44] In addition there is phenotypic heterogeneity even in patients and within families who carry the common 3243 mutation within the $tRNA^{Leu}$ gene. Mutant mtDNA in cerebral blood vessels or the neurons themselves may be responsible for the stroke-like episodes secondary to impaired energy production in metabolically active regions of the brain.

Treatment

No specific medical therapy is available other than treating the seizures and myoclonus. Coenzyme Q does not appear to be of any significant benefit. A small study reported some improvement with dichloroacetate (DCA),[45] but a double-blind, placebo-controlled, randomized, 3-year crossover trial of DCA (25 mg/kg/day)

in 30 patients demonstrated no efficacy and peripheral nerve toxicity.[46] Creatine monohydrate (5–10 gm/day) modestly improved strength if a few patients with MELAS,[47,35,36] but again, blinded controlled studies are lacking.

KEARNS–SAYRE SYNDROME (KSS)

Clinical Features

KSS is characterized by the clinical triad of PEO, pigmentary retinopthy, and cardiomyopathy with onset usually before the age of 20 years.[48–54] Other clinical features include short stature, proximal muscle weakness, sensorineural hearing loss, dementia, ataxia, depressed ventilatory drive, and multiple endocrinopathies (e.g., diabetes mellitus, hypothyroidism, hypoparathyroidism, delayed secondary sexual characteristics). Affected individuals are very sensitive to sedatives and anesthetic agents can provoke respiratory failure.[55,56]

Laboratory Features

Serum CK level is typically normal, however, lactate and pyruvate levels may be elevated. CSF protein is usually increased. The EKG often reveals conduction defects. NCS are usually normal, although diminished amplitudes suggestive of an axonal sensory or sensorimotor polyneuropathy may be seen. EMG usually demonstrates normal insertional and spontaneous activity, but early recruitment of small polyphasic MUAPs in weak muscles.

Histopathology

Muscle biopsies demonstrate ragged red fibers, however unlike MERRF and MELAS, there is little variability of COX staining with most of the ragged red fibers lacking COX reactivity.[40,57] The number of ragged red fibers and COX negative fibers correlate with the percentage of mitochondria harboring large deletions. Autopsy may reveal spongy degeneration of the cerebral white matter.

Molecular Genetics and Pathogenesis

Single large mtDNA deletions (ranging from 1.3 to 8.8 kB) can be demonstrated in most patients with KSS.[50,52,54,57] As many as 43% of patients have a characteristic 4.9 kB deletion, suggesting there may be "hot spots" in the mitochondrial genome for these large deletions. One is more likely to find mtDNA mutations in muscle tissue than in peripheral white blood cells with the percentage of affected mitochondrial genomes in muscle biopsies ranging from 20 to 90%.[52] These large deletions most likely arise during oogenesis.[2] Mitochondrial disorders with single large deletions need to be differentiated from disorders with multiple deletions—see later). The large deletions usually involve several tRNA genes, thus impairing the adequate translation of mtDNA-encoded proteins. The single deletion mutations are usually sporadic in nature, although rare cases with familial occurrences have been reported.[22,50]

The clinical phenotype of individuals harboring single large mtDNA is again heterogeneous. Some patients develop migraines and stroke-like episodes with or without PEO, some have PEO with or without limb weakness, retinopathy, or deafness, others have an encephalopathy without PEO (including Leigh syndrome), while rare patients manifest only with diabetes mellitus, deafness, or Pearson's syndrome.

Treatment

Some patients with KSS treated with creatine supplementation (0.08–0.35 g/kg body weight/day) have improved exercise capacity measured with bicycle ergometry.[47] Patients with cardiac conduction defects may require pacemaker insertion. Ptosis may be treated with eyelid surgery provided there is sufficient facial strength to allow full eye closure. However, there is risk for injuries to the corneal due to exposure/trauma if the eyelids cannot completely close and the ptosis may recur. Patients and their physicians need to be made aware of the extreme sensitivity to CNS depressants and potential for decreased respiratory drive.[55,56]

PROGRESSIVE EXTERNAL OPHTHALMOPLEGIA (PEO)

Clinical Features

Patients with PEO have ptosis and ophthalmoparesis (Fig. 27–8) with or without extremity weakness, but they

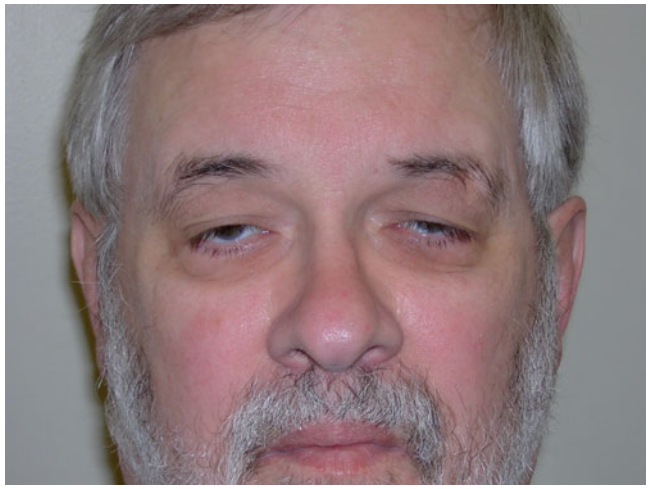

Figure 27–8. Progressive external ophthalmoplegia. A patient has ptosis and inability to move the eyes.

lack pigmentary retinopathy, cardiac conduction defects, or other systemic manifestations (e.g., endocrinopathies).[50–52,57] Some cases that are sporadic in nature and associated with single large deletions of mtDNA probably represent a partial clinical expression KSS. There are autosomal dominant and recessive forms as well as maternally inherited forms of PEO.

Laboratory Features

Serum CK, serum lactate and CSF lactate can be normal or elevated. CSF protein may be increased. In contrast to classic KSS, the EKG does not demonstrate cardiac conduction defects. NCS are normal. EMG is also usually normal, although myopathic MUAPs may be found in weak extremity muscles.

Histopathology

Muscle pathology is indistinguishable from KSS.

Molecular Genetics and Pathogenesis

Approximately 40–70% of patients with PEO have single large mtDNA deletions similar to KSS.[50,51,52,54,57] Such cases are generally sporadic in nature and PEO is not passed on to subsequent generations. Point mutations have been identified within various mitochondrial tRNAs (Leu, Ile, Asn, Trp) genes in several kinships with maternal inheritance of PEO.[58]

Autosomal dominant PEO is usually associated with multiple mtDNA deletions and is genetically heterogeneic.[49,51,58,59] Three distinct genes have been identified in autosomal dominant PEO (PEOA): PEOA1 due to mutations in the polymerase-gamma gene (*POLG*) on chromosome 15q25; PEOA2 at chromosome 10q24, is caused by mutations in the *ANT1* gene located on 4q34-q35 that encodes for adenine nucleotide translocator (ANT) gene (*ANT1*); and PEOA3 caused by mutation in the twinkle gene (*C10ORF2*) on 10q24.[60,61] In addition, some kinships have been localized to a fourth locus at chromosome 3q14.1–21.4.[62] ANT1 is the most abundant mitochondrial protein and is responsible for transporting adenosine triphosphate across the inner mitochondrial membrane, while *twinkle* and polymerase gamma are involved in mitochondrial DNA replication.

Autosomal recessive progressive external ophthalmoplegia (PEOB) is also caused by mutations in the *POLG* gene. Mutations in this gene also have been implicated in Alpers syndrome, which causes a clinical triad of psychomotor retardation, intractable epilepsy, and liver failure in infants and young children.

Treatment

Surgery to correct ptosis may help. As with other mitochondrial disorders, individuals with PEO can develop hypoventilation in with infections and in response to sedatives or anesthetic agents.[55,56] Improvement in ventilatory muscle weakness has been reported with vitamin E treatment.[55,56,63]

AUTOSOMAL RECESSIVE CARDIOMYOPATHY AND OPHTHALMOPLEGIA (ARCO)

Clinical Features

Only a few patients have been reported with this rare syndrome characterized by childhood-onset PEO, facial and proximal limb weakness, and a severe cardiomyopathy.[64,65] Affected individuals frequently complained of chest pain, dyspnea, and palpitations secondary to severe dilated cardiomyopathy and some require heart transplantation. The severe cardiomyopathy and autosomal recessive inheritance pattern help to distinguish this myopathy from autosomal dominant and maternally inherited PEO. The reported patients had no evidence of pigmentary retinopathy, hearing loss, ataxia, or peripheral neuropathy, although deep tendon reflexes were reduced.

Laboratory Features

Serum CK levels are mildly elevated. Serum lactate can be normal at rest but increases excessively during exercise. The EKG reveals cardiac conduction defects, while echocardiogram usually demonstrates dilated ventricles and reduced ejection fractions. NCS are normal but EMG may reveal myopathic appearing MUAPs.

Histopathology

Muscle biopsies reveal ragged red fibers which are strongly reactive to SDH but COX-negative.[64,65] However, there are also many COX-negative fibers which do not colocalize to ragged red and SDH positive fibers. Biochemical assay have demonstrated decreased activity of respiratory chain enzymes containing mtDNA-encoded subunits, sparing the entirely nuclear-encoded SDH and citrate synthetase.

Molecular Genetics

Multiple mtDNA deletions may be found and the genetic defect is suspected to lie in nuclear genes involved in regulating the mitochondrial genome.

Treatment

Many patients will die from the severe cardiomyopathy within the first two decades of life, unless they receive cardiac transplantation.

MITOCHONDRIAL DNA DEPLETION SYNDROMES

Clinical Features

The mtDNA depletion syndrome is an autosomal recessive disorder characterized by decreased mtDNA copy number in affected tissues. Onset is usually in infancy or early childhood and the spectrum of severity can vary. A severe fatal form presents during infancy with generalized hypotonia and weakness.[66–70] Some infants may appear normal during the first year of life.[71,72] There is a predilection for proximal muscle involvement but ptosis and ophthalmoplegia are also common. Some affected infants also have a superimposed polneuropathy. Muscle stretch reflexes are diminished or absent. Besides the myopathy, affected infants can develop a cardiomyopathy, De Toni-Fanconi-Debré syndrome (a renal tubular defect), seizures, or liver failure. The muscle weakness is severe and progressive leading to feeding difficulties, respiratory failure, and death usually within the first year of life.

There is also a more benign form that can resemble the fatal form of myopathy initially.[4,54,70,73,74] It can present shortly after birth or later in childhood. Affected infants can have severe hypotonia, weakness, respiratory and feeding difficulties. Although ventilatory assistance may be required for a period of time, muscle strength gradually improves. Motor milestones may be delayed but are usually attained, and by age two or three years children appear to be normal. Some children die in the first two decades of life but other have normal life expectancy. In contrast to the fatal infantile form, patients with the benign infantile myopathy usually do not have a renal tubular defect.

Laboratory Features

Serum CK can be normal or elevated as can serum lactate levels. The associated renal tubular defect results in glycosuria, proteinuria, and aminoaciduria. Cerebral atrophy and patchy areas of hypomyelination of subcortical white matter may be apparent on MRI scans.[74] Unlike most other mitochondrial myopathies, EMG may demonstrate numerous fibrillation potentials and positive sharp waves in those myopathies with mtDNA depletion.[67] Motor units can have a mixed myopathic and neuropathic appearance.[67,74] NCS can be normal or reveal features of an axonal or demyelinating sensorimotor neuropathy.[74]

Histopathology

Muscle biopsies demonstrate many COX-negative fibers, although ragged red fibers may not be apparent.[67,73,74] EM shows enlarged mitochondria, some with concentric or whorled cristae, dense bodies, or paracrystalline inclusions. Biochemical assay of COX activity in skeletal muscle tissue of affected patients is greatly diminished or absent.

Molecular Genetics and Pathogenesis

At least half the cases are sporadic in nature but some are inherited in an autosomal recessive fashion. A depletion of mtDNA was first reported by Moraes et al. in 1991[75] and subsequently confirmed by others.[67,73,74,76–79] The quantity of mtDNA indirectly correlates with the clinical severity of the disorder. As much as a 99% reduction in mtDNA is present in the fatal infantile myopathy form of the disease, while the more benign myopathy has been demonstrated to have lesser depletions (36–88%) of mtDNA.

Nuclear genes important in regulating the mitochondrial genome are responsible for mitochondrial DNA depletion. Mutations in thymidine kinase 2 (TK2) and deoxyguanosine kinase gene (DGK), both important in mitochondrial deoxynucleotide metabolism, have been associated with this syndrome.[71,72,80–82,83] Mitochondrial deoxyribonucleoside triphosphate (dNTP) pools measured in patients' fibroblasts reveals an imbalance in dNTP pools.[80,81] Specifically, deoxythymidine triphosphate (dTTP) content was markedly decreased, resulting in reduced dTTP:deoxycytidine triphosphate ratio.

Not all cases of fatal and benign infantile myopathy are associated with mtDNA depletion. Some cases are related to mutations in one of the genes encoding for subunits of COX or assessory proteins necessary for complex IV assembly (e.g, *SURF1*).[3] However, most of these infants have other neurological deficits (Leigh syndrome).

Treatment

No specific medical therapy has been demonstrated to be effective.

FOCAL MITOCHONDRIAL DEPLETION

Clinical Features

This disorder has been described in only a few patients.[84–85] A sister and brother presented in the second decade of life with exertional muscle pain and fatigue, myoglobinuria, and mild proximal weakness.[84] Their father of this pair was asymptomatic but had an elevated serum CK. Congenital weakness, hypotonia, delayed motor milestones, and mental retardation has also been reported.[85]

Laboratory Features

Serum CK levels are mild to moderately elevated and serum lactate levels are normal. A decreased selenium

level has been described in one patient.[85] NCS are normal but EMG may reveal myopathic MUAPs.

Histopathology

The most striking histologic feature, for which this disorder is named, is focal depletion of mitochondria in the center of the sarcoplasm in type 2 muscle fibers. At the periphery of muscle fibers, the mitochondria are enlarged. Scattered degenerating and regenerating fibers can be appreciated.

Molecular Genetics and Pathogenesis

This myopathy is presumably autosomal dominant. No molecular or quantitative defects of mtDNA have been reported in patients with this syndrome. Similar histological findings have been demonstrated in patients with myopathy felt to be related to selenium deficiency.[86]

Treatment

There is no specific medical therapy. A trial of selenium replacement should be considered in patients who are deficient in selenium.

MITOCHONDRIAL NEUROGASTOINTESTINAL-ENCEPHALOMYOPATHY (MNGIE)

Clinical Features

MNGIE, also referred to as POLIP syndrome, (*P*olyneuropathy, *O*phthalmoplegia, *L*eukoencephalopathy, and *I*ntestinal *P*seudo-obstruction) is an autosomal recessive mitochondrial disorder.[59,87–89] As the acronyms imply, the disorder is associated with a sensorimotor polyneuropathy, leukoencephalopathy on MRI of the brain, ragged red fibers on muscle biopsy, and chronic intestinal pseudo-obstruction. Affected individuals develop distal greater than proximal muscle weakness and atrophy, a stocking–glove distribution of sensory loss, and reduced muscle stretch reflexes throughout. Most patients have ptosis and extraocular muscle weakness. Despite the leukoencephalopathy apparent on MRI and on autopsies, most affected patients little in the way of CNS symptoms or signs. However, rare patients have mental retardation. Other clinical features include pigmentary retinopathy, sensorineural hearing loss, facial weakness, hoarseness, or dysarthria. The earliest symptoms are often caused by gastrointestinal dysmotility (i.e., dyspepsia, bloating, eructations, cramps, intolerance of large meals, and episodic nausea, vomiting, and diarrhea). The disorder usually manifests before the age of 20 years (mean 13.9 years, range 2.5–32 years).[59] The course is progressive with severe disability or death by the third or fourth decade of life.

Laboratory Features

Serum CK can be normal or mildly elevated. Lactate, pyruvate, and CSF protein levels are typically elevated. Leukoencephalopathy of the cerebral and cerebellar white matter is apparent on MRI scans. Radiological studies also demonstrate dilatation and dysmotility of the esophagus, stomach, and small intestine. EKG has shown conduction defects in some patients although they remained asymptomatic from a cardiac standpoint. Motor and sensory nerve conduction velocities are typically slowed to within the demyelinating range and F-wave latencies are markedly prolonged.[59,89] Sensory nerve action potentials and occasionally compound muscle action potentials have reduced amplitudes. EMG may reveal a fibrillation potentials and positive sharp waves.[59] Recruitment of MUAPs can be decreased, suggestive of denervation in distal muscles. However, quantitative electromyography of proximal muscles reveals small duration MUAPs suggesting a superimposed myopathic process. The generalized weakness coupled with the demyelinating polyneuropathy can lead to misdiagnosis as chronic inflammatory demyelinating polyneuropathy.[90]

Histopathology

Muscle biopsies may demonstrate ragged red fibers, ragged blue fibers with NADH and SDH staining, and COX-negative fibers.[59] Neurogenic atrophy may be apparent biopsies of distal muscles. Nerve biopsies have shown loss of myelinated nerve fibers, demyelination/remyelination, and rare onion bulb formation, in addition to features of axonal degeneration. Abnormal mitochondria with paracrystalline inclusions occur in both muscle fibers and Schwann cells. Diminished COX and other respiratory complex activities can be demonstrated on enzymatic assays of muscle tissue.[59]

Autopsies have revealed widespread endoneurial fibrosis and demyelination in the peripheral nervous system and poorly defined white matter changes in the cerebral and cerebellar white matter.[89] Cranial nerves and spinal roots are less severely involved. Neurons of the brainstem and spinal cord appeared relatively intact. Interestingly, a loss of neurons and fibrotic changes of the autonomic ganglia and of the celiac and myenteric plexuses has been noted, which likely explains the associated gastrointestinal dysmotility.[89]

Molecular Genetics and Pathogenesis

Multiple mtDNA deletions similar to those found in some cases of autosomal dominant PEO have been demonstrated in some patients with autosomal recessive

MNGIE.[59,88,91] Some cases of MNGIE are caused by mutations in the thymidine phosphorylase (*ECGG1*) gene located on chromosome 22q13.32-qter.[4,88,89,92] Thymidine phosphorylase converts thymidine to 2-deoxy D-ribose 1-phosphate and may regulate thymidine availability for DNA synthesis. Interestingly, thymidine phosphorylase is not normally expressed in muscle tissue so how it leads to multiple mtDNA deletions is unclear. It may lead to a reduction in the pools of nucleotides within the mitochondria. Rare cases of MNGIE have been shown to be caused by mutations in the polymerase gamma (*POLG*) gene and the $tRNA^{Lys}$ (*MTTK*) gene.

Treatment

No specific medical therapy is available. PEG tube or parenteral feedings for nutritional support are required in the majority of cases. Ankle foot orthotics may be beneficial in patients with foot drop.

LEIGH SYNDROME

Clinical Features

Leigh syndrome, or subacute necrotizing encephalomyopathy, usually presents in infancy or early childhood, but can rarely develop in adult life.[93,94] Affected individuals can manifest with recurrent vomiting, psychomotor retardation, hypotonia, generalized weakness and atrophy, ptosis, ophthalmoplegia, poor suck, respiratory failure, nystagmus, optic atrophy, hearing loss, involuntary movements, seizures, spasticity, ataxia, and peripheral neuropathy. The rate of progression varies but is generally fatal.

Laboratory Features

Serum and CSF lactate levels are elevated as can be the lactate:pyruvate ratio. The syndrome is biochemically heterogeneous. Defects in activity of the pyruvate dehydrogenase (PDH), pyruvate decarboxylase (PDC), COX, and complex I have been described in some patients with Leigh syndrome. MRI demonstrates symmetric lesions in the thalamus, brainstem, cerebellum, and spinal cord reflecting the underlying pathology.

Histopathology

Muscle biopsy can demonstrate reduced or absent COX staining (mitochondrial and nuclear-encoded COX subunits) of muscle fibers, although ragged red fibers are usually not seen.[94] Unlike fatal infantile myopathy, COX staining is also deficient in muscle spindles and in the smooth muscle of intramuscular blood vessels. Autopsy studies of the brain and spinal cord demonstrate symmetric cystic necrosis, spongioform changes, demyelination, and vascular proliferation in the thalamus, basal ganglia, brainstem, cerebellar white matter, dentate nuclei, and posterior columns.

Molecular Genetics and Pathogenesis

Leigh syndrome is genetically heterogeneous. Mutations have been identified in both nuclear- and mitochondrial-encoded genes. These genes are all involved in energy metabolism, including the generation of ATP, components of the pyruvate dehydrogenase complex and mitochondrial respiratory chain complexes I, II, III, IV, and V, which are involved in oxidative phosphorylation.

Complex I is composed of at least 41 subunits, of which seven are encoded by the mitochondrial genome (ND1–6, ND4L) and the other 39 are encoded by nuclear genes. Multiple complex I genes have been implicated in Leigh syndrome including mitochondrial-encoded *MTND3*, *MTND5*, and *MTND6*, and nuclear-encoded *NDUFV1*, *NDUFS1*, *NDUFS3*, *NDUFS4*, *NDUFS7*, and *NDUFS8* genes.[95,96]

From complex II, a mutation has been found in the nDNA gene flavoprotein subunit A (*SDHA*).[97] In complex III a mutation has been found in the nDNA gene BCS1L, which is involved in the assembly of complex III.

Complex IV mutated genes include mitochondrial-encoded cytochrome c oxidase subunit 3 (MTCO3) and nuclear-encoded cytochrome c oxidase assembly proteins 10 (*COX10*), and 15 (*COX15*). Two other nuclear-encoded genes with mutations are: synthesis of cytochrome c oxidase 2 (*SCO2*), and surfeit 1(*SURF1*). SURF1 is involved in the assembly of complex IV.[98] A mutation has also been found in a complex V gene: The mitochondrial-encoded ATPase 6 (*MTATP6*).[44,99] Of note, mutations in this gene are also responsible for the mitochondrial disorder termed NARP (neuropathy, ataxia, and retinitis pigmentosa). When the proportion of mutated mitochondrial DNA is high (>90%), Leigh syndrome occurs; but NARP develops when the burden of mitochondrial DNA mutations is lower.

Mutations in multiple genes encoding mitochondrial tRNA proteins have also been identified in patients with maternally inherited Leigh syndrome: $TRNA^{Val}$ (*MTTV*),$tRNA^{Lys}$ (*MTTK*), $tRNA^{Trp}$ (*MTTW*), and $tRNA^{Leu}$ (*MTTL1*).[93,100] Single large deletions of mtDNA have also been demonstrated.[101]

Leigh syndrome may also be caused by mutations in components of the pyruvate dehydrogenase complex. The gene *DLD* encodes for dihydrolipoamide dehydrogenase, which is a component not only of the pyruvate dehydrogenase complex, but also of the alpha-ketoglutarate dehydrogenase complex, and the branched-chain alpha-keto acid dehydrogenase complex. Compound heterozygous mutations in DLD have been implicated in Leigh syndrome. X-linked Leigh syndrome is caused by mutation in the gene encoding the

E1-alpha subunit of the pyruvate dehydrogenase complex (*PDHA1*).[102–104]

The French-Canadian (or Saguenay-Lac Saint Jean) type of Leigh syndrome with COX deficiency (LSFC) is caused by mutation in the leucine-rich PPR motif-containing protein gene (*LRPPRC*). This gene encodes for an mRNA-binding protein involved in the processing and trafficking of mtDNA-encoded transcripts, but how this causes COX deficiency is not yet clear.

Treatment

There is no specific medical therapy available.

MITOCHONDRIAL MYOPATHIES ASSOCIATED WITH EXERCISE INTOLERANCE/RECURRENT MYOGLOBINURIA

Clinical Features

Some patients with mitochondrial myopathy manifest only with exercise induced myalgias beginning in infancy or early adulthood. They are typically short-statured and have generalized reduction in muscle bulk. Muscle strength may be normal or there can be mild proximal weakness. Recurrent episodes of myoglobinuria can also occur and be provoked by exercise and alcohol intake. However, provocative factors often are not present. We have seen patients with progressive deafness as well.

Laboratory Features

Serum lactate and pyruvate may be normal or slightly at rest but become significantly elevated with aerobic exercise. Serum CK can be normal or mildly elevated between episodes of myoglobinuria. EMG and NCS are typically normal.

Histopathology

Muscle biopsies may reveal scattered ragged red fibers, increased SDH and NADH stains (ragged blue fibers), as well as COX-negative fibers. However, COX stain can be normal, particularly in patients with mutations in MTCO3, ND4, and MTCYB (see below). Decreased COX activity has been found on enzyme analysis of muscle tissue in some,[105] but not all cases.[106] Abnormal mitochondria with paracrystalline inclusions can be detected on EM.

Molecular Genetics and Pathogenesis

This is a genetically heterogeneous group of disorders. Multiple mtDNA deletions were demonstrated in two brothers with presumed autosomal recessive inheritance.[105] In addition, point mutations in $tRNA^{Phe}$ have been found in kinships with and without recurrent myoglobinuria,[107,108] and microdeletions within the gene encoding for COX III (*MTCO3*) have been reported in sporadic cases.[109] Other cases of exercise intolerance and recurrent myoglobinuria have be ascribed to mutations in the mtDNA genes encoding for $tRNA^{Gly}$,[110] subunit 4 of NADH dehydrogenase (*ND4*),[111] and cytochrome *b* (*MTCYB*).[71,72,112,113] Mutations within this same gene, ND4, may also produce Leber hereditary optic neuropathy[114] or Wolfram syndrome.[115] In addition, mutations in nuclear encoded subunits of SDH have been associated with exercise intolerance and myoglobinuria.[116]

Treatment

Attenuation of free-radical production and paracrystalline inclusions in muscle biopsies has been reported following a 5-week trial of creatine supplementation in a patient with a novel cytochrome *b* mutation.[15] However, the patient did not feel any subjective improvement and there was no effect on his maximal oxygen consumption. There is no specific medical therapy other than treatment of myoglobinuria and avoidance of strenuous activity and alcohol.

▶ SUMMARY

There is a wide range of phenotypic and genotypic variability in patients with mitochondrial disorders. This makes definitive diagnosis (i.e., identifying specific genetic mutation) an often long and expensive process. Although there is a greater understanding regarding the molecular pathogenesis of the different forms of mitochondrial encephalomyopathies, these advances have not as yet led to medical treatments, other than supportive measures.

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CHAPTER 28

Myotonic Dystrophies

Myotonic dystrophy is the most common myotonic disorder (Table 28–1). There are at least two genetically distinct forms of myotonic dystrophy: Dystrophica myotonia type 1 (DM1) and dystrophica myotonia type 2 (DM2) which is also known as proximal myotonic myopathy (PROMM).

MYOTONIC DYSTROPHY (DM1)

Clinical Features

DM1 in an autosomal dominant manner with an incidence of approximately 13.5 per 100,000 live births and a prevalence of 3–5 per 100,000.[1–4] DM1 can present at any age, including infancy. Limb weakness begins distally in the extremities and can progress slowly to affect proximal muscles. The neck flexors are affected early as well. Atrophy and weakness of facial and jaw muscles give rise to the characteristic "hatchet face" appearance (Fig. 28–1). Some patients develop dysarthria and dysphagia due to involvement of the pharyngeal and lingual muscles involvement.

Many patients do not complain or are not aware of their myotonia, although it is usually readily apparent on examination, particularly in the hands. Delayed relaxation of the fingers is seen following a forceful hand grip (action myotonia). The myotonia is lessened with repeated muscle contractions, a so-called warm-up phenomenon. Percussion of muscle groups, in particular of the thenar eminence also gives rise to delayed relaxation (percussion myotonia). Muscle reflexes are diminished, but sensory testing is normal.[5] Adult patients with DM1 may have a mild reduction in cognitive abilities, while severe mental retardation is associated with congenital myotonic dystrophy.[6,7]

Congenital myotonic dystrophy is much more severe than adult-onset DM1. Affected infants are invariably born to mothers with myotonic dystrophy.[8,9] It is important to examine mothers of floppy infants as they may not even be aware that they have the disorder. Pregnancy may have been complicated by polyhydramnios and diminished fetal movements. Infants with congenital myotonic dystrophy have severe generalized weakness and hypotonia and may also have arthrogryposis. Clinical myotonia is not apparent in the neonatal period and may not be noticeable until about five years of age. However, myotonic discharges can be appreciated on electromyography before the appearance of clinical myotonia. Many infants require ventilatory assistance due to ventilatory insufficiency. The mortality rate in infancy is approximately 25%. Severe psychomotor abnormalities affect 75% of surviving children. Most will have some degree of mental retardation. Life expectancy is greatly reduced in DM1 patients, particularly those with early onset of the disease and significant proximal addition to distal weakness.[10,11]

Associated Manifestations

DM1 is a systemic disorder affecting the gastrointestinal tract, ventilatory muscles, cardiac muscle, the eyes, and the endocrine system.[12] In addition to dysphagia, reduced gastrointestinal motility can lead to chronic pseudo-obstructions.[13,14] Alveolar hypoventilation can arise due to involvement of the diaphragm and intercostal muscles. It is more severe in congenital myotonic dystrophy and may lead to ventilatory failure.[9] It is unclear if decreased central drive contributes to hypoventilation.[15,16] Nonetheless, many patients develop symptoms suggestive of sleep apnea: Frequent nocturnal arousals, excessive daytime hypersomnolence, and morning headaches. Pulmonary hypertension can develop and may lead to cor pulmonale.

Cardiac abnormalities are common with approximately 90% of patients having conduction defects on electrocardiograms.[17] Sudden cardiac death secondary to arrhythmia is well documented. However, the severity of the cardiomyopathy does not necessarily correlate with the severity of skeletal muscle weakness. The size of the mutation (discussed in Pathogenesis section) and the severity of the skeletal muscle weakness does not correlate with the occurrence cardiac conduction abnormalities or sudden death.[18] It seems that risk of sudden death increases with duration of disease and age, and that risk is higher in male patients.[18]

Neurobehavioral abnormalities are common in patients with DM1.[19,20] Neuropsychological testing demonstrates elements of obsessive–compulsive, passive–aggressive, dependent, and avoidant personality traits in many patients. Apathy and depression are also frequent. Cognitive impairment, particularly in memory and spatial orientation, may be demonstrated. The neuropsychological deficits appear to correlate with brain single photon emission computed tomography that show frontal and parieto-occipital hypoperfusion.[20]

▶ **TABLE 28–1. MYOTONIC DISORDERS**

Myotonic dystrophy type 1
Myotonic dystrophy type 2/proximal myotonic myopathy
Myotonia congenita
Paramyotonia congenita
Hyperkalemic periodic paralysis
Chondrodystrophic myotonia (Schwartz–Jampel syndrome)
Drug-induced
Cholesterol lowering agents (statin medications, fibrates)
Cyclosporine
Chloroquine

Other systemic manifestations include posterior subscapular cataracts, frontal balding, testicular atrophy and impotence in males, and a high rate of fetal loss and complications of pregnancy in women. Hyperinsulinemia is common following glucose tolerance tests, however, the frequency of overt diabetes mellitus is not increased.[21]

Laboratory Features

Serum creatine kinase (CK) may be normal or mildly increased. Motor and sensory nerve conduction studies (NCS) are usually normal. Electromyography (EMG) demonstrates myotonic discharges (Fig. 28–2). It is important to sample multiple muscles as myotonic discharges are not necessarily appreciated in every muscle studied.[22] In congenital myotonic dystrophy, electrical myotonia may be observed as early as 5 days to 3 weeks following birth and increases with age.[23,24] Fibrillation potentials, positive sharp waves, and myopathic motor unit action potentials (MUAPs) may also be seen but the can be obscured by the myotonic discharges.

Figure 28–1. Myotonic dystrophy type 1. Note the typical myotonic facies of a DM 1 patient with frontal balding and temporal, jaw, and facial muscle atrophy, and weakness.

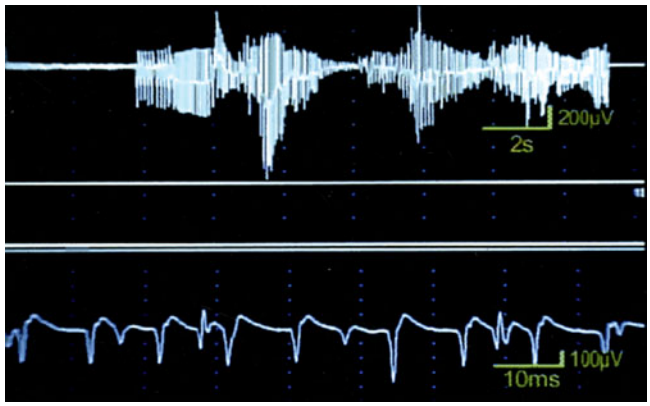

Figure 28–2. Myotonic dystrophy. Electromyography reveals myotonic discharges which wax and wane in frequency and amplitude.

Histopathology

Muscle biopsies demonstrate an increased number of internal nuclei in the muscle fibers (Fig. 28–3). Type 1 predominance and atrophy are very common. In addition, hypertrophic type 2 fibers, ring fibers, small angulated fibers, atrophic fibers with pyknotic nuclear clumps, and sarcoplasmic masses are also frequently observed. In contrast to other muscular dystrophies, necrotic fibers and increased connective tissue are less conspicuous. Autopsy studies of the brain demonstrate neurofibrillary degeneration with abnormal tau expression.[25]

Molecular Genetics and Pathogenesis

DM1 is caused by an expansion of unstable polymorphic cytosine–thymine–guanine (CTG) trinucleotide repeats

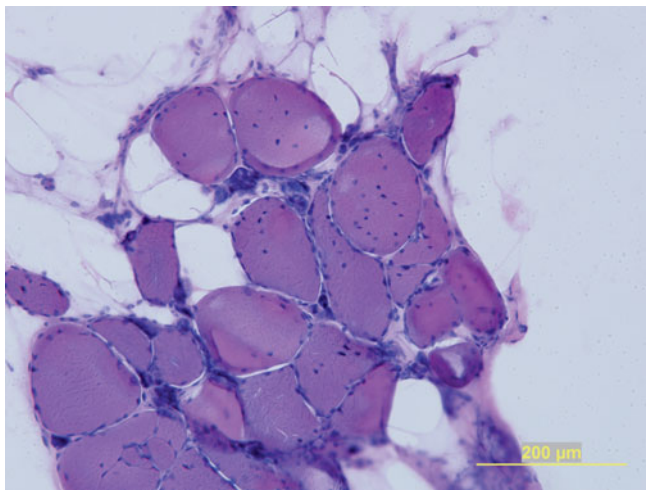

Figure 28–3. Myotonic dystrophy type 1. Muscle biopsies reveals adipose tissue and remaining muscle fibers with numerous internalized nuclei and atrophic fibers with pychnotic nuclear clumps.

in the 3′ untranslated region of the myotonin protein kinase (*DMPK*) gene on chromosome 19q13.2.[12,26,27–33] This CTG repeat is copied in the gene up to 27 times in normals, but 50 to more than 4000 copies are found in DM1 patients. The severity of the myopathy directly correlates with the size of the CTG repeat, which is unstable. The mutation size usually expands from one generation to the next, which accounts for the anticipation phenomena (i.e. the earlier presentation and/or more severe disease in each generation). More marked expansion of the CTG repeat usually occurs in children of mothers with DM1, which explains the severe phenotype of congenital myotonic dystrophy.

It is not the abnormal expression of myotonin protein kinase itself that is responsible for the disorder. Rather, DM1 seems to be a consequence of nuclear retention of mutant mRNA containing expanded CTG repeats rather than a specific lack or gain of function of the DMPK protein. Indeed, the myopathy and other systemic features appear to be due to a toxic gain of function of the mutant mRNA.[34]

The transcribed mRNA with expanded CTG (DM1) accumulates as abnormal focal collections in the nucleus that cannot be transported to the cytoplasm, where RNA translation into protein takes place.[35–38] Aggregates of mutated mRNA are directly toxic to cells by sequestering RNA binding proteins (such as muscleblind proteins), which in-turn, lead to abnormal splicing of pre-mRNA from various target genes (e.g., chloride ion channel, insulin receptor, tau protein, cardiac troponin, ryanodine receptor and sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase).[35–37,39–43] Therefore, there is abnormal translation of the RNAs into functional proteins and this explains the multiple organ/systemic manifestations of DM1. Other studies have shown that mutant RNA binds and sequesters transcription factors with up to 90% depletion of selected transcription factors from active chromatin.[44] This leads to reduced expression of a variety of genes, including the chloride ion channel (CIC-1), which is mutated in myotonia congenita.

Treatment

There are no medical therapies that clearly improve muscle strength. A small pilot study of dehydroepiandrosterone sulfate (DHEAS) in 11 patients with DM1 seemed to be beneficial in a few patients but larger controlled trials are necessary before commenting on the possible efficacy. Small trials of creatine monohydrate in DM1 failed to demonstrate efficacy.[45]

Patients are usually not so bothered by the myotonia that it warrant treatment. Further, some drugs that may improve myotonia such as quinine, procainamide, and tocainide can potentiate cardiac arrhythmias and should be avoided. We usually prescribe phenytoin or mexiletine only if the myotonia is severe, painful, or bothersome for the patient.[12] In addition, aerobic training is safe and may improve fitness effectively in patients with myotonic dystrophy.[46]

We obtain yearly electrocardiograms (EKGs) to monitor for evidence of conduction defects/arrhythmias. If abnormalities are detected we obtain a cardiology consultation, 24-hour Holter monitoring and echocardiograms because some patients may require antiarrhythmic medication or pacemaker insertion. Pulmonary function tests are routinely performed. Patients with DM1 are at risk for pulmonary and cardiac complications from general anesthesia and neuromuscular blocking medications.[47–50] These agents should be used with extreme caution.

We obtain overnight polysomnography in patients with symptoms and signs of sleep apnea. Patients with significant hypoventilation or sleep apnea may benefit from noninvasive ventilatory assistance with BiPAP. Modafinil 200–400 mg per day is also effective in reducing the excessive daytime somnolence that is commonly associated with DM1.[51–53]

Some patients require excision of their cataracts. Physical and occupational therapy are important. Orthotic devices such as ankle braces are indicated in patients with foot drop to assist their gait.

Genetic counseling is of utmost importance. Patients need to know that the risk of passing the disease on to their children is 50% with each pregnancy. Further, the disease severity is generally worse from one generation to the next particularly when the mother has DM1. Prenatal diagnosis is possible via amniocentesis or chorionic villous sampling.

MYOTONIC DYSTROPHY TYPE 2 (DM2) OR PROXIMAL MYOTONIC MYOPATHY (PROMM)

Clinical Features

DM2 is a multisystem, autosomal dominant disorder that resembles DM1 with myotonia, weakness, cataracts, testicular failure, glucose intolerance, hypogammaglobulinemia, and cardiac conduction defects.[2–4,12,21,54–62,64] In a study of 234 individuals with DM2, 90% had electrical myotonia, 82% weakness, 61% cataracts, 23% diabetes, and 19% cardiac involvement.[54] Most patients with DM2 become symptomatic between the ages of 20 and 60 years, although onset can occur in childhood. The initial symptoms are usually intermittent stiffness and pain of the thigh muscles in one or both legs. Myotonia may be evident in proximal and distal extremity muscles as well as facial muscles, however it is variable and not always present. Myotonia can initially manifest or worsen during pregnancy.[65,66] There is an associated "warm-up" phenomenon with decreased myotonia following repeated muscle contractions. The

myotonia does not exacerbate with cold temperature, although a few patients have described worsening of symptoms with warm temperatures.[67]

Patients often describe pain that is episodic and disabling, with burning, tearing or jabbing characteristics. This pain typically affects the thighs, shoulders and upper arms and is not necessarily related to the myotonic stiffness of the muscles. They may complain of peculiar chest pains as well leading to cardiac evaluations to rule out coronary artery disease.

Slowly progressive proximal and distal weakness develops in the majority of patients. The characteristic pattern of muscle weakness involves the neck flexors, elbow extensors, thumb and deep finger flexors, and hip flexors and extensors in the legs.[54] Some patients describe fluctuations of their weakness with episodes of increased weakness lasting hours or weeks.[59] During these periods of increased weakness, repeated activity can lead to transient improvement in strength. Significant loss of muscle bulk is not apparent early, however, approximately 9% of patients develop considerable atrophy of proximal muscles late in life.[54] Calf hypertrophy occurs in some patients, which can be asymmetric. Rarely, patients myoglobinuria can occur as a complication of DM2.

Symptoms and severity can vary within families. Studies have demonstrated an earlier onset of symptoms among offspring of affected individuals suggesting that anticipation phenomena is also a feature of DM2.[54,59,62] However, in contrast to DM1, anticipation in DM2 is much milder and a congenital form has never been described.[54,62]

Associated Manifestations

Cataracts that are indistinguishable from those seen in DM1 are common in DM2.[12,54] These cataracts usually appear before the age of 50 years and have even developed in patients in their late childhood. Cardiac abnormalities may also develop.[12,54,68] Syncope, near-syncopal spells, or symptomatic tachycardia occur in 8%, cardiac conduction defects in 20%, and a potentially life-threatening cardiomyopathy occur in as many as 7% of individuals who are affected.[54] Unlike DM1, most series have not reported an increased incidence of alveolar hypoventilation in patients with DM2, however, some patients develop sleep apnea and excessive daytime somnolence.[67]

Also, in contrast to DM1, mental retardation is not a prominent feature. However, white matter abnormalities may be appreciated on magnetic resonance imaging (MRI) of the brain.[13] In addition, some of the affected individuals have stroke-like symptoms, seizures, parkinsonian features, and hypersomnia. Further, neuropsychological testing reveal lower scores on tests of frontal lobe function compared to normals, avoidant personality traits, while brain single photon emission and computed tomography can show frontal and parieto-occipital hypoperfusion similar to DM1.[20] Frontal balding has been reported in as many as 20–50% of men aged 21–34 years.[day 2003] Testicular atrophy with gonadal insufficiency can occur. Gastrointestinal hypomotility has not been described. Late-onset deafness was reported in one kinship with atypical DM2.

Laboratory Features

Serum CK levels are often mildly elevated. Low testosterone levels may be seen in as many as 29% of affected males and insulin insensitivity in 75% of patients.[54] A high GGT was demonstrated in 64%, low IgG in 65%, and low IgM in 11%.[54] Abnormalities are common in EKG as described earlier.

Motor and sensory nerve conduction studies are normal. Electromyography reveals myotonic discharges even in patients without clinical myotonia, although these discharges can be difficult to detect in some patients. Despite the prominent proximal muscle involvement clinically, electrical myotonia is often more easily detected in distal muscles.

Histopathology

Muscle biopsy reveals nonspecific myopathic features including a mild to moderate increase in internalized nuclei, variability of fiber size with atrophy of type 2 fibers, small angular fibers, and atrophic fibers with pyknotic nuclear clumps.[54,69,70] In contrast DM1, selective type 1 fiber atrophy, sarcoplasmic masses, and ringed fibers are not usually appreciated. Autopsy studies demonstrate neurofibrillary degeneration with abnormal tau expression as in DM1.[25]

Molecular Genetics and Pathogenesis

DM2 and PROMM are allelic disorders caused by CCTG repeat expansions in intron 1 of the zinc finger protein 9 *(ZNF 9)* gene on chromosome 3.[38,54] The transcribed mRNA with expanded CCTG repeats accumulates as abnormal focal collections in the nucleus similar to expanded CTG repeats seen in DM1.[35–38] As with DM1, the aggregates of mutated mRNA appear to exert their toxic effect on cells by sequestering RNA binding proteins that leads to abnormal splicing of pre-mRNA from various target genes (e.g., chloride ion channel, insulin receptor, tau protein, cardiac troponin).[35–37,40,43] The subsequent abnormal translation of the RNAs into functional proteins explains the multiple organ/systemic manifestations of both DM1 and DM2.

Treatment

There is no specific treatment for DM2. A small randomized controlled trial of creatine monohydrate in

DM2 was ineffective.[71] There is insufficient information regarding the efficacy of various antimyotonia agents, but mexilitine or carbamezepine, or phenytoin can be tried if the myotonia or muscle pain is bothersome to the patient.[67,72] Cataracts may need surgical excision. It seems prudent to carefully monitor patients during surgery and the postoperative period. One patient with PROMM developed increased muscle pain, myoglobinuria, and transient renal insufficiency after minor surgery.[59]

▶ SUMMARY

DM1 and DM2 are systemic disorders caused by expanded repeats in the noncoding regions of the *DMPK* and *ZNF9* genes, respectively. The novel pathogenic consequence of these mutations is not due to a loss of function created by loss of *DMPK* and *ZNF9* protein products but to a toxic effect on the cell of the abnormal mRNA. The mutant mRNA sequesters necessary RNA binding proteins and this results in abnormal splicing of pre-mRNA from various target genes (e.g., chloride ion channel, insulin receptor, tau protein, cardiac troponin), thus explaining the multisystemic manifestations of DM1 and DM2. There may be additional forms of myotonic dystrophy not localized to the DM1 and DM2 loci. Treatment of these disorders at this time is largely symptomatic.

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CHAPTER 29

Nondystrophic Myotonias and Periodic Paralysis

In this chapter we describe the pathophysiology, clinical presentation, laboratory findings, and treatment of the nondystrophic myotonias and periodic paralyses (Table 29–1).

There are several inherited myopathic disorders associated with clinical or electrical myotonia in which muscle tissues are not dystrophic. These disorders are caused by mutations in various ion channels and are thus referred to here as muscle channelopathies. Mutations in the chloride channel cause myotonia congenita (MC). The sodium channelopathies include potassium-sensitive (hyperkalemic) periodic paralysis (HyperKPP), paramyotonia congenita (PMC), potassium-aggravated myotonias (PAM) (e.g., myotonia fluctuans, myotonia permanens, and acetazolamide-responsive myotonia), and familial hypokalemic periodic paralysis type 2 (HypoKPP2). HyperKPP and PMC are usually associated with episodes of transient generalized or focal weakness. Hypokalemic periodic paralysis type 1 (HypoKPP1) is not associated with myotonia clinically or electrically and is caused by mutations in the dihydropyridine receptor (a type of calcium channel) of muscle cells. Andersen–Tawil syndrome (ATS) is another rare form of hereditary periodic paralysis of which some forms are due to mutations in a potassium channel.

Electrophysiological studies, in particular the short and long exercise tests, can be useful in distinguishing subtypes of muscle channelopathy and thus deserve special comment (Table 29–1).[1,2,3] The short exercise test is performed by having the patient isometrically exercise a muscle (e.g., adductor digiti minimi) for 10 seconds, followed by measurement of compound muscle action potential (CMAP) amplitudes immediately after exercise and every 10 seconds thereafter up to 50 seconds. Fornier and colleagues modified the test by having the short exercise study repeated twice more with a rest period of 60 seconds between trials. In addition, the short exercise test should be done at room temperature and then with cooling of the muscle. In normal individuals, immediately after short exercise there is a mild increase in the CMAP amplitudes compared to baseline (mean 5%, range –6%–+14%) and the amplitudes return to baseline within 10 seconds (Fig. 29–1).[2] If the short exercise test is performed after cooling the limb (e.g., with an ice pack) the CMAP amplitudes decrease (−25%), but the durations of the CMAPs increase (+140%).[3]

The long exercise test is performed by having the patient isometrically exercise a muscle (e.g., adductor digiti minimi) for five minutes (with 3–4 seconds of rest every 30–45 seconds), while CMAP amplitudes are recorded every minute during the exercise period, immediately after cessation of exercise, then every minute for 5 minutes, and finally every 5 minutes for 40–45 minutes. In normal people, CMAP amplitudes only slightly decrease after the exercise period (mean −6%, range −16–+5%) and the amplitudes then return to normal within the next 30–60 seconds and remain so during the next 40–50 minutes.[2]

Changes in CMAP amplitudes with the short exercise test separates muscle channelopathies into five patterns (Table 29–1).[2] The first three patterns help distinguish the nondystrophic myotonias, particularly when performed at room temperature and then with cold, while patterns IV and V are useful in diagnosing periodic paralysis in combination with the long exercise test.[3]

▶ CHLORIDE CHANNELOPATHIES

MYOTONIA CONGENITA

Clinical Features

The autosomal dominant form of MC, or Thomsen disease, often presents in the first few years of life.[4–10] Affected infants may have difficulty opening their eyes after crying. Stiffness in the legs upon arising and taking the first few steps may lead to tripping and falling. As patients become older, their muscle stiffness may become more noticeable in the arms. Myotonia of muscles of mastication may result in difficulties in chewing and swallowing. As with most forms of myotonia, the stiffness in the muscles eases with repeated contractions, the so-called warm-up phenomena. Thus, although an affected individual may have initial stiffness in their legs when they begin to walk within a short time ambulation becomes easier. After rest, the same stereotypical

▶ **TABLE 29–1. NONDYSTROPHIC MYOTONIAS AND HEREDITARY PERIODIC PARALYSIS**

Disorder	Inheritance	Gene (location)	Clinical or EMG Myotonia	Short Exercise Test	Long Exercise Test	Fornier Electro-physiologic Pattern
Myotonia Congenita (MC) Thomsen's Disease Becker Disease	AD AR	*CLCN-1* (7q35)	Yes	±PEMPs; Transient decrease in CMAP amplitudes after first trial in AR-MC but not with AD MC; Reduction in amplitudes is less in second and third trials. No change with cold with AR-MC but reduction in amplitudes occurs after 1st trial in AD-MC that improves with subsequent trials	Slight or no decrease in amplitudes immediately after exercise with no change over time	Pattern II
Hyperkalemic Periodic Paralysis Type (HyperKPP)	AD	*SCNA4A* (17q13.1–13.3)	Maybe	No PEMPs; Increase in amplitudes after 1st trial with further increase after second and third trials.	Transient increase in amplitudes immediately after exercise with subsequent gradual decrease in amplitudes over a prolonged period of time (as much as 40 minutes or more)	Pattern IV
Paramyotonia Congenita (PMC)	AD	*SCNA4A* (17q13.1–13.3)	Yes	PEMPs are common; Amplitudes may increase or decrease with initial trial but gradually decline after second and third trials; Reduction in amplitudes is more prominent in cold	Decrease in amplitudes during and following exercise that may persist for hours.	Pattern I
Potassium-aggravated Myotonias Myotonia Permanens Myotonia Fluctuans Acetazolamide-responsive MC	AD	*SCNA4A* (17q13.1–13.3)	Yes	No PEMPs; usually no change even with cooling	No change	Pattern III

(*continued*)

▶ **TABLE 29–1. (CONTINUED)**

Disorder	Inheritance	Gene (location)	Clinical or EMG Myotonia	Short Exercise Test	Long Exercise Test	Fornier Electrophysiologic Pattern
Hypokalemic Periodic Paralysis Type (HypoKPP1)	AD	*CACL1A3* (1q31–32)	No	No PEMPs; usually no change even with cooling	Slight increase or no immediate change with exercise but gradually decline of amplitudes over time is seen in most	Pattern V
Hypokalemic Periodic Paralysis Type (HypoKPP2)	AD	*SCNA4A* (17q13.1–13.3)	No	No PEMPs; usually no change even with cooling	A slight increase in amplitudes may be seen during and immediately after exercise followed by a delayed reduction in amplitudes after 10–20 minutes	Pattern V
Andersen-Tawil Syndrome (ATS)	AD	*KCNJ2* (17q23.1–q24.2)	No	Unknown	Unknown	Unknown
Schwartz-Jampel Syndrome	AR	*HSPG2* (1p34.1–36.1)	Yes	Unknown	Unknown	Unknown

AD = autosomal dominant.
AR = autosomal recessive.
PEMPs = post-exercise myotonic potentials on the motor conduction studies.
Data modified from: Fournier E, et al. Ann Neurol 2006;60:356–365 and Salajegheh MK, Amato AA. Channelopathies: Paroxysmal Paralysis. In Squire LR, Albright TD, Bloom FE (eds). New Encyclopedia of Neuroscience. Oxford: Elsevier (in press).

pattern of stiffness returns on initiation of physical activity. The myotonia can worsen with cold similar to that seen in PMC.[11] The severity of the myotonia can fluctuate and is variable even within affected family members. The stiffness may worsen during pregnancy. Of note, people with MC usually do not typically complain of muscle pain with their stiffness. In contrast to the myotonic dystrophies, there are no systemic disorders (e.g., cataracts, endocrinopathies, cardiopathy, ventilatory muscle weakness) associated with MC or increased mortality. However, some individuals present later in life with stiffness and proximal weakness and resemble myotonic dystrophy type 2 (DM2) or proximal myotonic myopathy (PROMM).[11] There may be an increased risk of malignant hyperthermia with anesthetic agents.

On examination, affected individuals usually appear extremely muscular (e.g., Herculian). Muscle strength is usually normal but some patients do develop mild proximal weakness. Action myotonia can be elicited by having the patient make a strong grip and then try to relax their fingers or by having patients forcefully close their eyes and then try to open them. One sees delayed relaxation, which improves with repeated activity due to the warm-up phenomena discussed above. In addition, myotonia can be demonstrated by percussing a muscle (e.g., the thenar eminence) with a reflex hammer (percussion myotonia).

Becker described the features of the autosomal recessive form of MC which bears his name.[12] The clinical features of the autosomal recessive and dominant forms of MC are similar but there are some differences. The autosomal recessive or Becker type of MC usually presents between 4 and 12 years of age, somewhat later than that seen in the autosomal dominant form, however, the severity of weakness is typically worse.[7] Furthermore affected individuals are more likely to complain of weakness. Transient muscle weakness, particularly in the distal arms, may occur following a severe bout of myotonia. On examination, muscle is usually increased. Mild fixed weakness is apparent in proximal muscles of the arms and legs as well as in the neck. Systemic complications are not seen though there is an increased risk of malignant hyperthermia.

Laboratory Features

Serum creatine kinase (CK) is normal or only slightly elevated.[5] Routine motor and sensory nerve conduction

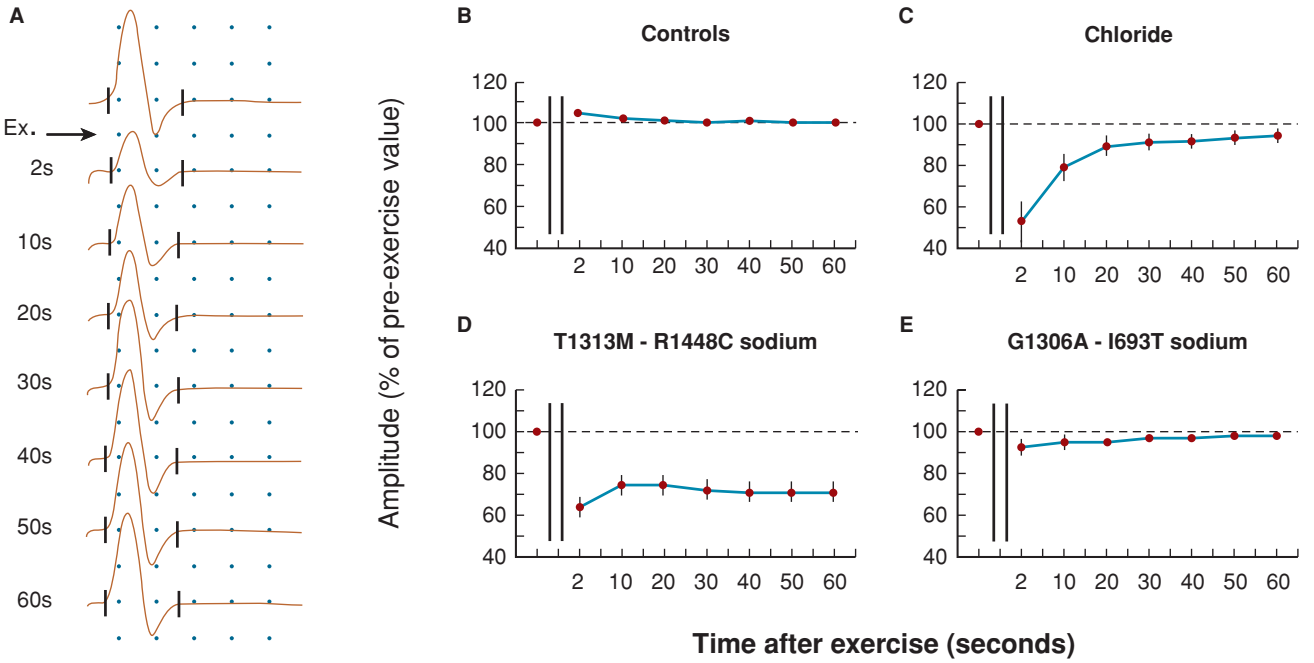

Figure 29–1. Short exercise test in myotonic syndromes. (A) Transient decrease of compound muscle action potential (CMAP) amplitude (−55%) after short exercise in a myotonia congenita (MC) patient with the F167L-C277R chloride channel mutation. Preexercise *(top trace)* and postexercise recordings *(bottom traces)* at different times after the trial (Ex.) as indicated to the left of the tracings. Scale between two dots: 5 milliseconds, 5 mV. (B–E) Changes in CMAP amplitude of abductor digiti minimi (ADM) muscle following short exercise *(double bars)* in 41 unaffected controls (B), 6 MC patients with chloride channel mutations (C), 16 paramyotonia congenita (PC) patients with T1313M or R1448C sodium channel mutations (D), and 8 patients with G1306A or I693T sodium channel mutations (E). The amplitude of the CMAP expressed as a percentage of its preexercise value is plotted against the time elapsed after the exercise trial. (*symbols* and *vertical bars*) Means ± standard errors of the means. (Reproduced with permission from Fournier E., Arzel M, Sternberg D, et al. Electromyography guides toward subgroups of mutations in muscle channelopathies. *Ann Neurol* 2004;56(5):650–661.) (Figure 3, page 655.)

studies (NCS) are normal. On repetitive nerve stimulation a decrement may be appreciated when a prolonged train of stimuli are delivered at 10 Hz or more. In such cases, the CMAP amplitudes may decrease to 65% of normal and even large degrees of decrement can occur with stimulation at higher rates.[3,13]

In over 80% of individuals with MC, the short exercise test is associated with a decrease in CMAP amplitudes immediately after exercise (mean –47%, range –17–90%) that returns to baseline after 20–40 seconds (Fig. 29–1).[1] The reduction in the CMAP amplitudes decreases with repeated trials of short exercise (–11 ±4% after the third trial) corresponding to the clinical warm-up phenomena (Fig. 29–2). Fornier and colleagues called this Pattern II (Table 29–1).[1] If one looks at the effects of the short exercise test by pattern of inheritance, it is the autosomal recessive cases that have the reduction in CMAP amplitudes while the autosomal dominant cases are not associated with significant change in amplitude.[2] However, performing the short exercise after the limb is cooled in patients with autosomal dominant MC results in a drop in amplitude that improves with repeated short exercise (e.g. a conversion from normal to Pattern II with cold). In contrast, there is no significant difference in the results of the short exercise performed in room temperature in comparison to cold in individuals with autosomal recessive MC (they remain with Pattern II) (Fig. 29–3).[2] In addition, post-exercise repetitive discharges or myotonic potentials (PEMPs) are seen in about one third of MC patients after short exercise.[1] These PEMPs disappear within 10–30 seconds after exercise.

On the long exercise test, a slight increase in CMAP amplitudes during exercise followed by a mild reduction of the CMAP amplitudes (–13 ± 4%) after exercise of the muscle. This pattern is similar to the responses in normal individuals (Fig. 29–4).[1,14] However, about one-third of patients with MC have decreases in amplitude outside the normal range.[1]

On needle electromyography (EMG), myotonic discharges are evident at rest and during volitional activity. Cooling a limb does not lead to an exacerbation of the clinical or electrical myotonia or development of weakness, unlike that seen in PMC.[15] It may be difficult to appreciate motor unit action potential (MUAP) as the myotonic discharges obscure the voluntary MUAPs, but morphology and recruitment are usually normal.[1,9,12]

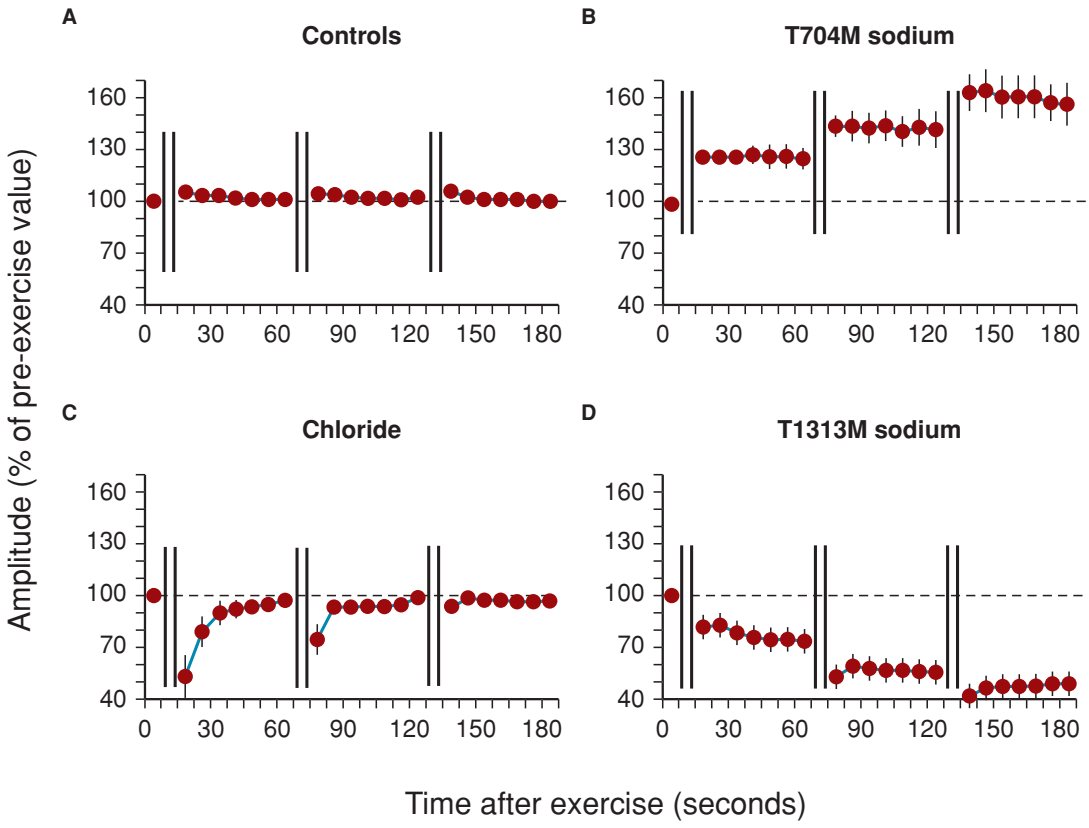

Figure 29–2. Effects of short exercise repetition in myotonic syndromes and periodic paralysis. Short exercise of the abductor digiti minimi (ADM) muscle was repeated three times successively at 1-minute intervals. *(double bars)* Successive trials. Compound muscle action potentials (CMAPs) were recorded during the 50-second resting periods. The amplitude of the CMAP, expressed as a percentage of its value before the trials, is plotted against the time elapsed after the first exercise trial in unaffected controls (A), 6 hyperPP patients with T704M sodium channel mutations (B), 6 myotonia congenita (MC) patients with chloride channel mutations (C), and 11 paramyotonia congenita (PC) patients with T1313M sodium channel mutation (D). *(symbols* and *vertical bars)* Means ± standard errors of the means. (Reproduced with permission from Fournier E., Arzel M, Sternberg D, et al. Electromyography guides toward subgroups of mutations in muscle channelopathies. *Ann Neurol* 2004;56(5):650–661.) (Figure 4, page 656.)

However, short duration, small amplitude MUAPs may occasionally be appreciated in weak muscles. Single fiber EMG reveals normal fiber density but slightly increased jitter.

Molecular Genetics and Pathogenesis

Both the autosomal dominant form (Thomsen) and recessive form (Becker) of MC are caused by mutations in the muscle chloride channel gene (*CLCN1*) on chromosome 7q35 (Fig. 29–5).[16,17,18] Of note, there is a so-called painful variant of MC that resembles the Thomsen and Becker forms except patients with this disorder more frequently complain of myalgias. This painful variant of MC is usually caused by a mutations in the muscle sodium channel, *SCN4A* (discussed later). Structurally, the chloride ion channel is a homotetramer with each subunit encoded by the *CLCN1* gene.[17] The function of the chloride ion channel is to maintain the high resting membrane conductance in muscle fibers.[19] Mutations of the *CLCN1* gene are associated with reduced chloride conductance. Because chloride ions are responsible for 70% of the skeletal muscle resting membrane potential, reduced chloride conductance leads to a decrease in the rate of muscle membrane repolarization. Thus, sodium channels are able to recover from inactivation. Despite the muscle membrane still being in a state of depolarization, recurrent firings of action potentials or myotonia discharges occurs.[19]

Treatment

Many individuals with MC do not require medical treatment. However, when the myotonia is severe and impairs function, treatment with antiarrhythmic or antiepileptic medications (e.g., mexilitine, phenytoin,

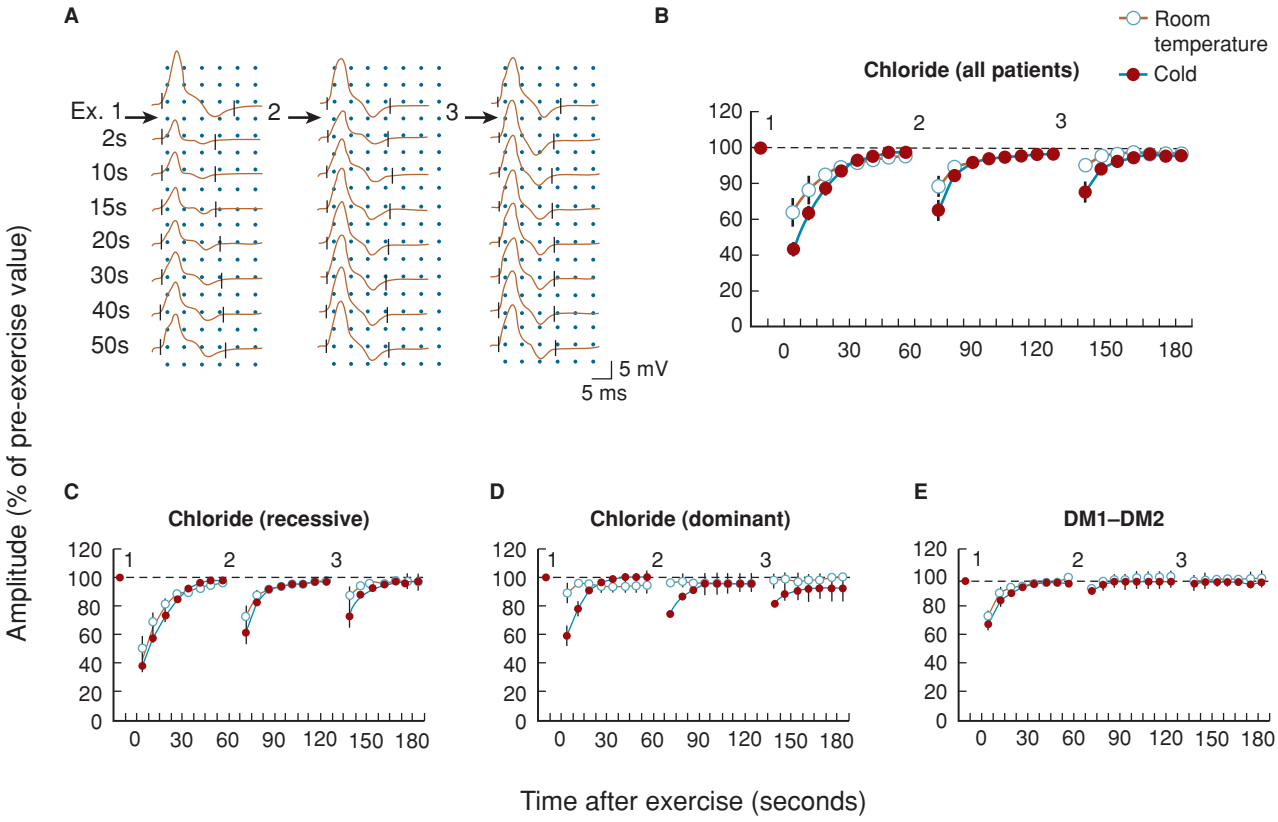

Figure 29–3. Repeated short exercise test in myotonia congenita (MC) patients with chloride channel mutations and in myotonic dystrophy (DM) patients. (A) Three successive short exercises (Ex. 1, 2, 3) performed at room temperature in a MC patient carrying the Q807X homozygous chloride channel mutation. Top traces are preexercise recordings. Subsequent traces are postexercise recordings at different times during the 50-second resting periods, as indicated left to the tracings. Note that the decrease in compound muscle action potential (CMAP) amplitude is gradually relieved with exercise repetition (−81%, −37%, −19%). Scale between two dots: 5 milliseconds, 5 mV. (B–E) Changes in CMAP amplitude after the three exercise trials (noted as *1, 2, 3*) in all 18 MC patients with CLCN1 mutations (B), in the 11 MC patients with recessive CLCN1 mutations (C), in the 7 MC patients with dominant CLCN1 mutations (D), and in the seven patients with DM1 or DM2 mutations (E), at room temperature (*open circles*) and at cold (*solid circles*). The amplitude of the CMAP, expressed as a percentage of its value before the trials, is plotted against the time elapsed after the first exercise trial. *Symbols* and *vertical bars* represent mean ± standard error of the mean. (Reproduced with permission from Fournier E, Viala K, Gervais H, et al. Cold extends electromyography distinction between ion channel mutations causing myotonia. *Ann Neurol* 2006;60:356–365.) (Figure 3, page 360.)

carbamezapine) that interfere with the muscle sodium channel can be beneficial. In this regard, we have found that mexilitine is very helpful, not only in easing muscle stiffness, but also in diminishing the transient exacerbations of weakness that can accompany the myotonia. Prior to starting mexilitine, it is important to obtain a baseline electrocardiogram (EKG) as the drug can prolong the QT interval. If the EKG is abnormal, we obtain a cardiology consultation before beginning mexilitine. In patients with severe muscle stiffness, we initiate treatment with mexilitine 150 mg daily and gradually increase as tolerated and as necessary to control the myotonia to a maximum of 300 mg thrice daily. Lightheadedness, diarrhea, and dyspepsia are dose limiting side effects of mexilitine. Dantrolene, which blocks the release of calcium from the sarcoplasmic reticulum, may reduce myotonia as well, but is not used much because of side effects.

▶ SODIUM CHANNELOPATHIES

The sodium channelopathies include potassium-sensitive (hyperkalemic) periodic paralysis (HyperKPP), paramyotonia congenita (PMC), the potassium-aggravated myotonias (PAM) (e.g., myotonia fluctuans, myotonia permanens, and acetazolamide responsive myotonia)[20,21,22] and familial hypokalemic periodic paralysis type 2 (HypoKPP2)[23,24,25] are myopathies that share some similar clinical and laboratory features but have

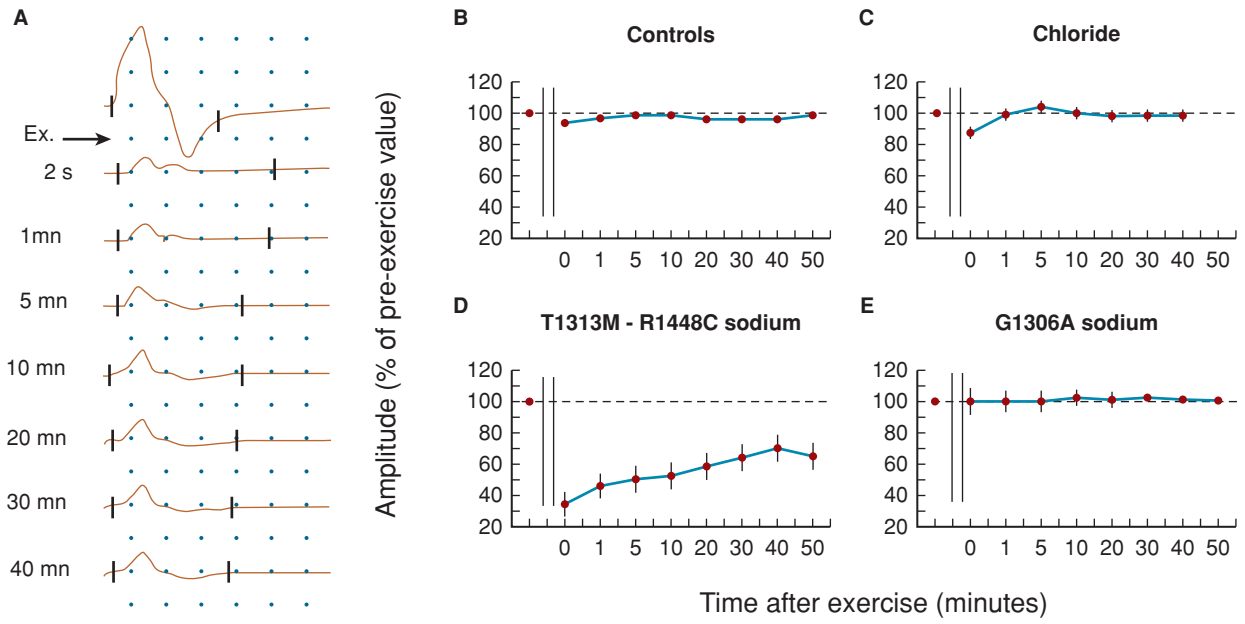

Figure 29–4. Long exercise test in myotonic syndromes. (A) Immediate and persistent decrease of compound muscle action potential (CMAP) amplitude (−85%) after long exercise in a paramyotonia congenita (PC) patient with the T1313M sodium channel mutation. Preexercise *(top trace)* and postexercise recordings *(bottom trace)* at various times following the trial (Ex.) as indicated to the left of the tracings. Scale between two dots: 5 milliseconds, 5 mV. (B-E) Changes in CMAP amplitude of the abductor digiti minimi (ADM) muscle after long exercise *(double bars)* in 41 unaffected controls (B), 6 myotonia congenita (MC) patients with chloride channel mutations (C), 16 PC patients with T1313M or R1448C sodium channel mutations (D), and 2 patients with G1306A sodium channel mutations (E). The amplitude of the CMAP, expressed as a percentage of its preexercise value, is plotted against the time elapsed after the exercise trial. *(symbols* and *vertical bars*) Means ± standard errors of the means. (Reproduced with permission from Fournier E., Arzel M, Sternberg D, et al. Electromyography guides toward subgroups of mutations in muscle channelopathies. *Ann Neurol* 2004;56(5):650–661.) (Figure 5, page 657.)

differences (Table 29–1). These disorders are inherited in an autosomal dominant fashion. They are all caused by missense mutations in the pore-forming α subunit of the voltage-gated skeletal-muscle sodium channel NaV1.4 (encoded by the gene *SCN4A* located on chromosome 17q23–25) (Fig. 29–6).[7,20,22–24,27–35] For the most part, each missense mutation of *SCN4A* is consistently associated with one of the four allelic sodium channel disorders, suggesting the presence of separate classes of functional defects. However, some variability exists and the distinction is often blurred between PMC and HyperKPP, even in affected members of the same family.

POTASSIUM-SENSITIVE OR HYPERKALEMIC PERIODIC PARALYSIS (ADYNAMIA EPISODICA HEREDITARIA)

Clinical Features

Potassium-sensitive periodic paralysis or hyperkalemic periodic paralysis (hyperKPP) is an autosomal dominant disorder with a high degree of penetrance.[6,22,35–42] HyperKPP manifests in three forms: (1) without myotonia, (2) with clinical or electrical myotonia, or (3) associated with paramyotonia congenita (PMC). The course of the attacks of weakness is similar in each form, except that cooling triggers weakness in PMC. Clinical myotonia is often mild, and can be elicited in the face (e.g., eyelids), tongue, forearms (e.g., finger extensors), and the thenar eminence with percussion or activity. The myotonia eases with repetitive activity except in individuals with PMC who exhibit paradoxical myotonia in which muscle stiffness is induced or worsened by exercise and cold temperature.

Most affected individuals become initially symptomatic with attacks of weakness in the first decade of life. These attacks usually develop in the morning, although can occur at any time, and are often precipitated by rest following exercise, intake of potassium rich food, fasting, and even by stress. The weakness can be mild or severe, with the latter more commonly occurring after strenuous physical activity. People may note paresthesiae and achiness in the muscles prior to the development of weakness. The thigh and calf muscles are often affected and weakness may progress to other

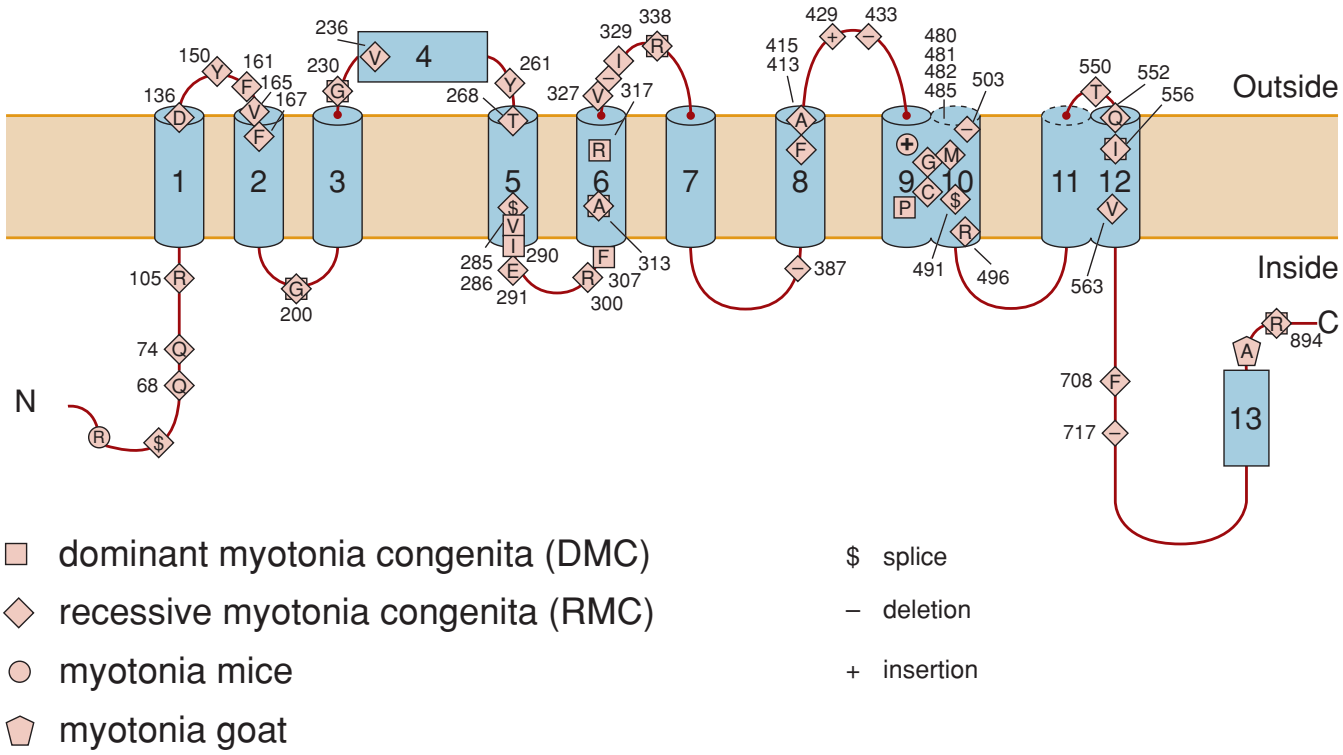

Figure 29–5. The chloride channel monomer, ClC-1, is functional as homodimeric channel complex. Different symbols used for known mutations leading to dominant Thomsen-type myotonia, recessive Becker-type myotonia, recessive myotonic mice, and dominant myotonic goat are explained on *bottom left*. Conventional one-letter abbreviations were used for replaced amino acids located at positions given by respective numbers of human protein. (Reproduced with permission from Lehmann-Horn F, Jurkat-Rott K. Voltage-gated ion channels and hereditary disease. *Physiol Rev* 1999;79(4):1317–1372.) (Figure 10, page 1335.)

muscle groups. However, the weakness can also be focal. In contrast to hypoKPP, generalized flaccid paralysis is uncommon. Rarely, the bulbar and respiratory muscles are affected. The sphincter muscles are well preserved during attacks.

The duration of weakness is usually less than 2 hours, although mild weakness can persist for a few days. The frequency of attacks is highly variable, and ranging from several times a day to less than once a year. In addition, there is great variation of attack severity and frequency within and between families, and the frequency of paretic attacks often decreases with age. Sustained mild exercise after a period of strenuous activity may postpone or prevent weakness from developing in the exercising muscles while resting muscle groups become weak. Following a bout of weakness, it is not uncommon for pain to be experienced in the affected muscles up to several days. During attacks, the reflexes are diminished or absent, while sensation remains normal. Between the attacks, sensation and muscle stretch reflexes are normal and lid lag or eyelid myotonia may be the only clinical signs present. Not infrequently, affected individuals develop fixed or slowly progressive weakness, independent of the episodic attacks, usually involving the more proximal muscles.

Laboratory Features

Serum CK levels are usually mildly elevated. In between the attacks, serum potassium levels are within normal limits. Increase in serum potassium levels (usually 5–6 mEq/L) are associated with attacks of weakness, though serum levels may remain within normal limits. Serum sodium levels can fall during episodes of weakness. During attacks, there is increased urinary excretion of potassium that can actually result in transient hypokalemia at the end of an attack. On EKG, the hyperkalemia can result in increased amplitudes of the precordial T waves.

Secondary causes of hyperkalemia can cause generalized weakness and must be excluded particularly in individuals with no family history (Table 29–2). Usually the serum potassium levels are greater than 7 $mEqL^{-1}$. Patients with secondary causes of hyperkalemic do not exhibit clinical or electrical myotonia.

While provocative testing such as potassium challenge can be performed when the diagnosis is unclear, there are obvious risks of such testing. The availability of

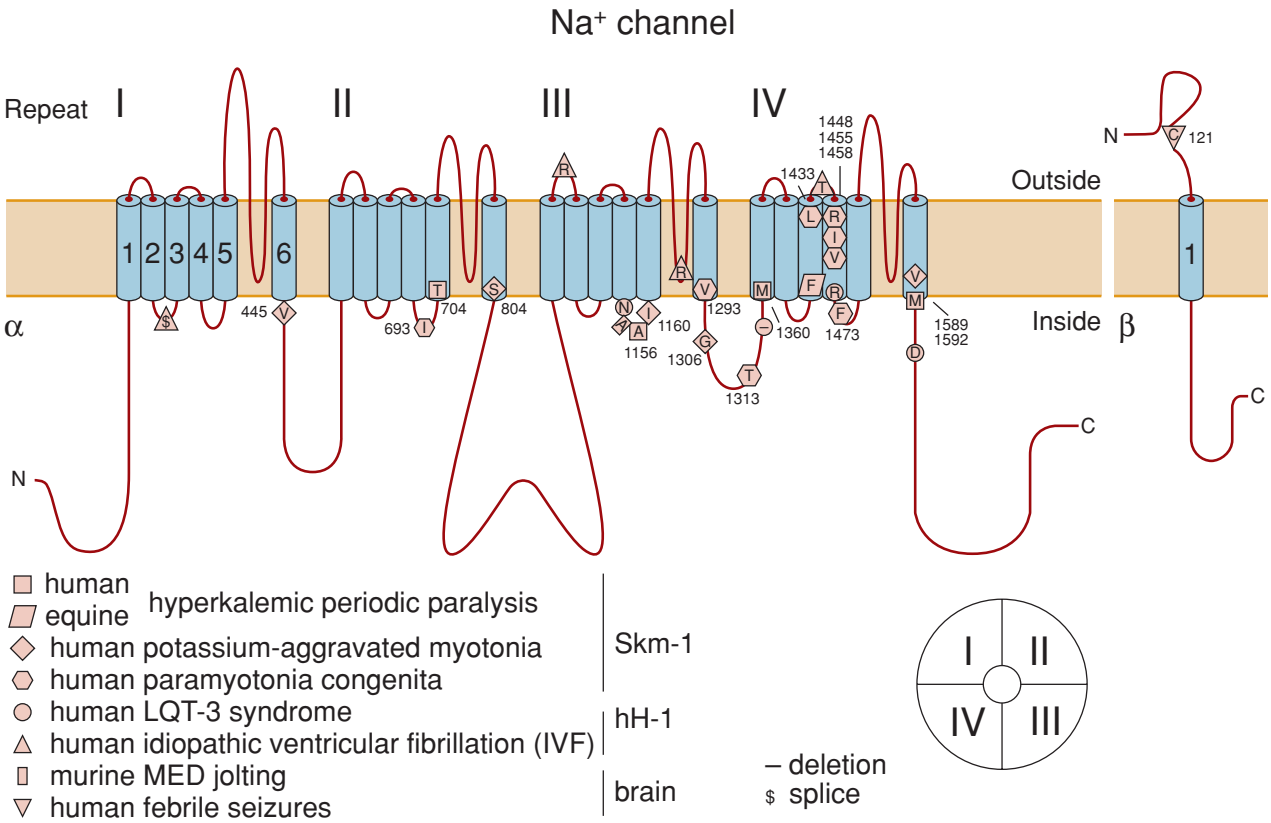

Figure 29–6. Subunits of voltage-gated sodium channel. α-Subunit consists of four highly homologous domains (repeats I–IV) containing two transmembrane segments each (S1–S6). S5–S6 loops form ion-selective pores, and S4 segments contain positively charged residues conferring voltage dependence to the protein. Repeats are connected by intracellular loops; one of them, III–IV linker, contains supposed inactivation particle of channel. β_1 and β_2 are auxilliary subunits. When inserted in membrane, four repeats of protein fold to generate a central pore as schematically indicated on *bottom right*. Mutations have been described for α-subunits of various species and tissues: human and equine adult skeletal muscle (Skm-1), human heart (hH-1), and murine brain. So far, only one mutation has been reported for a sodium channel subunit, i.e., one of human brain. Conventional one-letter abbreviations are used for replaced amino acids whose positions are given by respective numbers of human skeletal muscle channel. Different symbols used for point mutations indicate resulting diseases as explained at *bottom left*. (Reproduced with permission from Lehmann-Horn F, Jurkat-Rott K. Voltage-gated ion channels and hereditary disease. *Physiol Rev* 1999;79(4):1317–1372.) (Figure 3, page 1320.)

commercial genetic testing and features on electrophysiologic testing obviates the need for such provocative testing in most cases. Provided the patient has no significant underlying cardiac or renal disease, a potassium load can be administered to increase the serum potassium levels, and to see whether an attack of weakness can be provoked. The patient's strength, electrolytes, and cardiac function (EKG) need to be closely monitored during the study.

Routine motor and sensory NCS are normal between and during attacks of weakness.[43–46] However, during an attack of weakness the CMAP amplitudes may be reduced in affected muscles. The short and long exercise tests are often abnormal and may demonstrate abnormalities that can be useful in distinguishing subtypes of channelopathies.[1,2]

With the short exercise test, patients with potassium-sensitive periodic paralysis have abnormal increased CMAPs amplitudes that persist for a longer period of time than normal individuals (Fig. 29–2).[1] Further, repetition of short exercise amplifies the increase in CMAP amplitudes. With the long exercise test, during the exercise period and immediately afterwards, there is an initial increase in CMAP amplitudes from baseline that is followed by a progressive decline in the amplitudes over the next 40–50 minutes. Brief exercise (e.g., 10 seconds) during this paretic phase may induce an increment in the CMAP amplitudes (Fig. 29–7).

Needle EMG reveals variable findings. Myotonic discharges are found in 50–75% of affected individuals, though clinical myotonia is apparent in less than 20%.[1,47] In patients with myotonia, examination of the muscle

TABLE 29–2. ETIOLOGIES OF SECONDARY HYPOKALEMIC AND HYPERKALEMIC PARALYSES

Hypokalemic Paralysis
Thyrotoxic periodic paralysis
Renal tubular acidosis
Gitelman syndrome
Villous adenoma
Bartter syndrome
Hyperaldosteronism
Chronic or excessive use of diuretics, corticosteroids, licorice
Amphotericin B toxicity
Alcoholism
Toluene toxicity
Barium poisoning
Hyperkalemic Paralysis
Addison disease
Hypoaldosteronism (hyporenemic)
Isolated aldosterone deficiency
Excessive potassium supplementation
Potassium-sparing diuretics (e.g., spironolactone, triamterene)
Chronic renal failure
Rhabdomyolysis

Modified from Amato AA, Dumitru D. Hereditary myopathies. In Dumitru D, Amato AA, Swartz MJ (eds). Electrodiagnostic Medicine, 2nd edn. Philadelphia: Hanley & Belfus, Inc., 2002, pp. 1265–1370.

between attacks of weakness reveals an increase in insertional activity, in the form of fibrillation potentials and positive sharp waves, in addition to mild to moderate amounts of spontaneous runs of myotonic discharges. These abnormal discharges reflect the hyperexcitability or instability of the muscle membrane and are not due to denervation. Reducing the limb temperature may exacerbate the runs of myotonic discharges. Analysis of MUAP parameters may reveal a slight increase in small amplitude, short duration, polyphasic potentials. In people with hyperKPP without myotonia, the insertional and spontaneous activity is normal between attacks of weakness. During an attack of weakness the MUAPs decrease in duration and amplitude and may disappear altogether in plegic muscles.

Histopathology

Muscle biopsy in patients with hyperkalemic periodic paralysis frequently reveals vacuoles.[6,48,49]

Molecular Genetics and Pathogenesis

Potassium sensitive periodic paralysis is caused by mutations in the α subunit of the voltage-dependent sodium channel (*SCN4A*) (Fig. 29–6).[7,26,29,50–52]

Treatment

Attack frequency may be reduced with a low-potassium, high-carbohydrate diet and avoidance of fasting, strenuous activity, and cold. Mild, short-lasting attacks of weakness usually do not require treatment. Sometimes a simple ingestion of simple carbohydrates (e.g., fruit juices, glucose-containing candies) decreases the serum potassium level by increasing insulin secretion and this can improve strength. Beta-adrenergic agonists (e.g., metaproterenol, albuterol, salbutamol) also may increase strength but one needs to take care in regarding to associated cardiac arrhythmias. Beta-adrenergic medications may have their effect through the sodium–potassium pump. Only in severe attacks of weakness is treatment with intravenous glucose, insulin, or calcium carbonate warranted. Prophylactic use of acetazolamide (125–1000 mg per day), chlorothiazide (250–1000 mg per day), or dichlorphenamide (50–150 mg per day) may be beneficial in reducing the frequency of attacks and perhaps the myotonia.[10,21] Mexilitine is useful in managing myotonia when it is bothersome.

PARAMYOTONIA CONGENITA (EULENBURG DISEASE)

Clinical Features

Paramyotonia congenita (PMC) is an autosomal dominant disorder with high penetrance that is allelic to potassium-sensitive periodic paralysis, which probably explains why many patients have clinical features of both disorders (paralysis periodica paramyotonica).[6,21,22,39,53,54] The name derives from the "para"-doxical reaction to exercise. In contrast to the warm up phenomena observed in the other myotonic syndromes, repeated exercise worsens the muscle stiffness in patients with PMC. Myotonia is also exacerbated by exercise or cold. Further, some affected individuals develop either focal or generalized attacks of weakness.

Symptoms and signs of PMC usually manifest within the first decade of life. During a crying spell, infants may be noted to have difficulty opening their eyes secondary to the "exercise" induced myotonia of the orbicularis oculi muscles. A cold-induced attack of weakness can last for several hours even after return to a warm environment. Weakness can also be induced in some cases by potassium intake. Paramyotonia, particularly of the eyelids, is typically evident in most patients. While percussion myotonia may be demonstrated, it is usually not prominent. Some people complain of mild muscle pain, but myalgias are usually not as prominent as that seen in patients with DM2/PROMM which PMC can resemble. In addition, fixed, progressive weakness muscle weakness of proximal or distal muscles can develop over time.

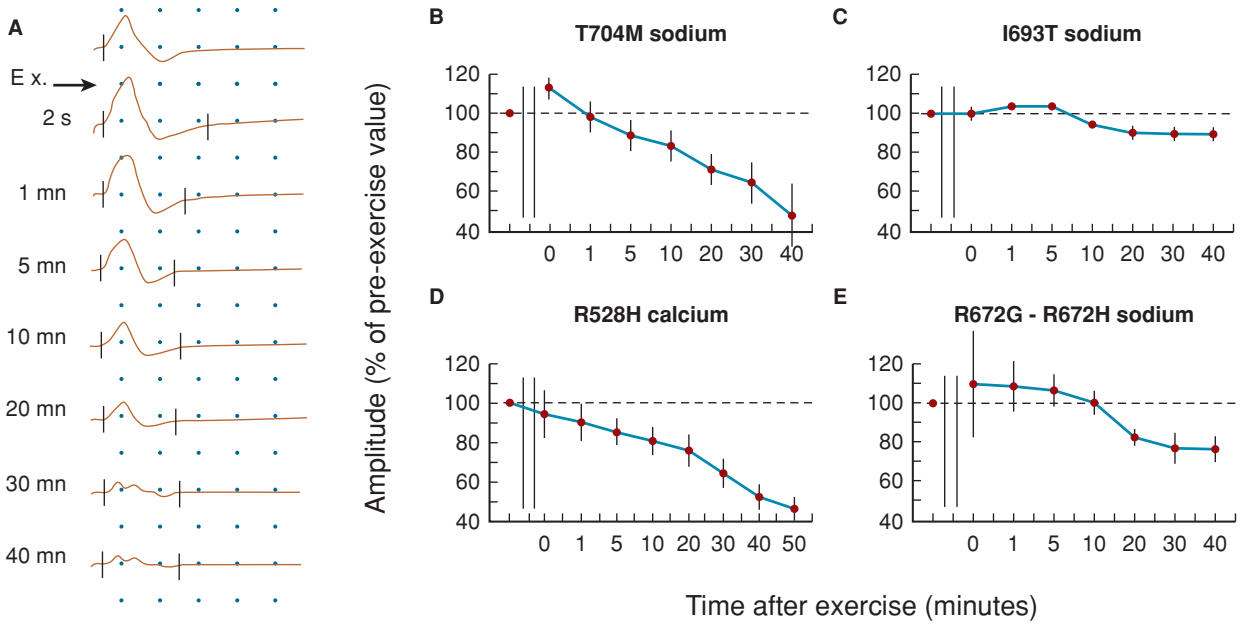

Figure 29–7. Long exercise test in periodic paralyses. (A) Early increase (+38%) and delayed decrease (−74%) of compound muscle action potential (CMAP) amplitude after long exercise in hyperPP patient with the T704M sodium channel mutation. Preexercise *(top trace)* and postexercise recordings *(bottom trace)* at different times following the trial (Ex.) as indicated left of the traces. Scale between 2 dots: 5 milliseconds, 5 mV. (B–E) Changes in CMAP amplitude of the abductor digiti minimi (ADM) muscle after long exercise *(double bars)* in six hyperPP patients with T704M sodium channel mutations (B), 6 Myotonia-hyperPP patients with the I693T mutation of the sodium channel (C), 13 hypoPP-1 patients with the R528H calcium channel mutation (D), and two hypoPP-2 patients with R672G or R672G sodium channel mutations (E). The amplitude of the CMAP, expressed as a percentage of its preexercise value, is plotted against the time elapsed after the exercise trial. *(symbols* and *vertical bars)* Means ± standard errors of the means. (Reproduced with permission from Fournier E., Arzel M, Sternberg D, et al. Electromyography guides toward subgroups of mutations in muscle channelopathies. *Ann Neurol* 2004;56(5):650–661.) (Figure 6, page 658.)

Laboratory Features

Serum CK levels are usually mildly to moderately elevated. Serum potassium levels may be normal or elevated in some patients during an attack of paralysis.

Routine sensory and motor NCS are normal between attacks of weakness.[53] Prolonged repetitive stimulation at rates exceeding 5 Hz or repetitive stimulation following a minute or more of exercise can induce a decrement in the CMAP in some patients.[13,53] The short exercise test may demonstrate several distinctive abnormalities (Table 29–1).[1,2] Immediately after 10 seconds of exercise, repetitive after-discharges may be seen on recorded CMAPs evoked by a single supramaximal stimulus (post-exercise myotonic potentials or PEMPs) (Fig. 29–8). Subsequent stimulations are associated with reduction of these PEMPs. Also, there is decrement in the amplitudes of the main CMAP wave forms compared to baseline with repeated stimulations following the short exercise in some patients. We repeat the short exercise test with 10 second break in between epochs to increase the yield of finding abnormalities. Upon repetition of the short exercise, even in those patients who do not show any CMAP decline after the first trial, one may see marked reduction of CMAP amplitudes by the third trial (Fig. 29–2). In some patients, there is also a gradual decrease in PEMPs. This so-called Fornier Pattern 1 is seen in 95% of patients with PMC caused by T131M, R1448C, or R1448H mutations in the *SCN4A* gene (Table 29–1).[1] The pattern is for the most part distinct from that seen in MC and myotonic dystrophy type 2 which PMC may clinical resemble (Fig. 29–9). However, patients with PMC mutations caused by Q270K mutations in the *SCN4A* gene may have short exercise tests that resemble those seen in MC (e.g. reduced amplitudes that improve with repetition of short exercise (Fig. 29-10).[2] To further increase the yield, the short exercise test should be repeated after the extremity has been cooled).[2] Cooling may bring out further abnormalities (even more marked reduction in amplitudes that worsen with repetition of short exercises than seen when the short exercise test is performed at room temperature). Upon cooling, the short exercise test in patients with Q270M mutations

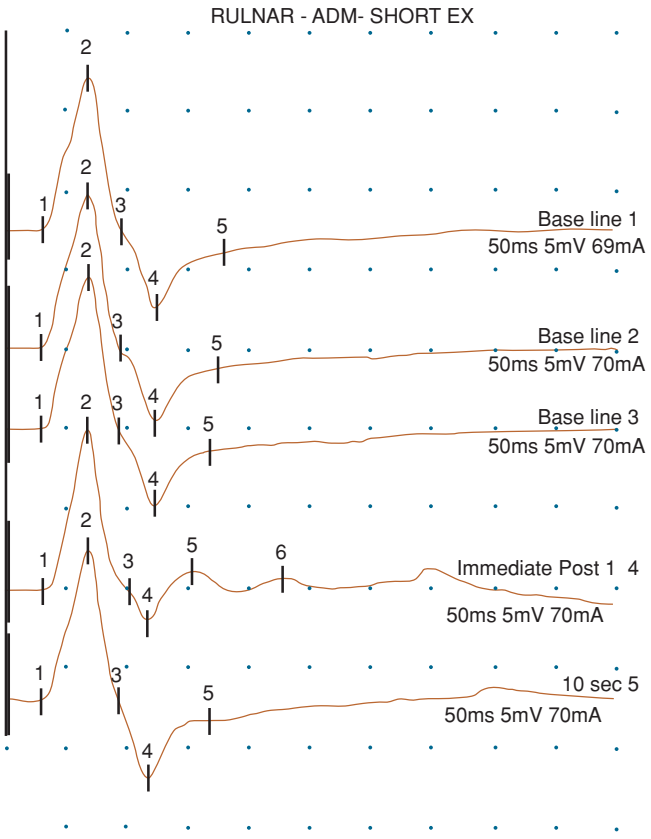

Figure 29–8. Postexercise myotonic potentials (PEMPs). PEMPs are seen following short exercise test in a patient with paramyotonia congenital. The top three tracings are baseline compound muscle action potentials (CMAPs). Following short exercise of 10 seconds, the fourth trace from the top demonstrates PEMPs following the CMAP (labeled as 5 and 6 with tracer). The fifth CMAP 10 seconds no longer demonstrates any PEMPs.

converts to the pattern 1 that is more typical of PMC. With the long exercise test, the CMAP amplitudes are markedly reduced during and following the exercise compared to baseline.[1,3,15,53,53a] The amplitudes remain reduced for prolonged periods, sometimes exceeding an hour.

EMG reveals normal MUAPs though they are often difficult to appreciate with the background of diffuse myotonic potentials.[1,55] In patients with PMC and periodic paralysis, local cooling of the muscle results in dense fibrillation potentials and the gradual reduction in MUAP activity. As the muscle becomes flaccid, the myotonic discharges abate and complete electrical silence is observed. In contrast, in patients with pure PMC without periodic paralysis, local cooling of the muscle results in increased myotonic discharges, but MUAP morphology and recruitment remain normal and the muscle strength remains normal. Single fiber EMG reveals a slight increase in jitter and fiber density.[56]

Histopathology

Muscle biopsy reveals nonspecific myopathic features mild fiber size variation with a mixture of normal, atrophic and hypertrophic fibers.[57] Intracytoplasmic vacuoles may be appreciated, particularly those with superimposed periodic paralysis. Electron microscopy may show myofibrillar disarray and tubular aggregates.

Molecular Genetics and Pathogenesis

PMC with and without episodes of periodic paralysis are caused by mutations in *SCN4A* (Fig. 29–6).[23,27,29,58]

Treatment

Mexilitine is often helpful in alleviating the muscle stiffness and weakness associated with cold.[59] Cold induced decrements of baseline CMAP amplitudes following exercise or repetitive stimulation are improved with mexilitine.[59] Hydrochlorothiazide is also helpful in some patients with myotonia.[60]

POTASSIUM AGGRAVATED MYOTONIAS (MYOTONIA FLUCTUANS, MYOTONIA PERMANENS, AND ACETAZOLAMIDE-RESPONSIVE MYOTONIA)

The potassium-aggravated myotonias (PAM) are also caused by mutations in the muscle sodium channel gene and are allelic to the above described HyperKPP1 and PMC (Table 29–1).[61] Patients with these disorders have myotonia without episodes of weakness. The electrophysiology of these disorders is more variable. Short exercise test in subjects with G1306A or G1306V or –1693T may be normal or show mild reduction in amplitude that improves with repetitive activity (i.e., Fornier Pattern 2) that is similar to what is seen in MC and there is no change with cooling (Fig. 29–10).[1,2] Most PAM patients with A715T or I1310N mutations have a normal short exercise test at room temperature (Fig. 29-10). However, short exercise test performed with cooling in these individuals is associated with a reduction in amplitude that worsens with repeated short exercises similar to what is seen in PMC (conversion to Fornier Pattern 1).[2] Long exercise test in patients with G1306A mutations is usually normal.

MYOTONIA FLUCTUANS

Clinical Features

Myotonia fluctuans is characterized by (1) fluctuating myotonia of varying severity, (2) increased myotonia of delayed onset (several minutes) following exercise, (3) paramyotonia of eyelids, (4) warm-up phenomena

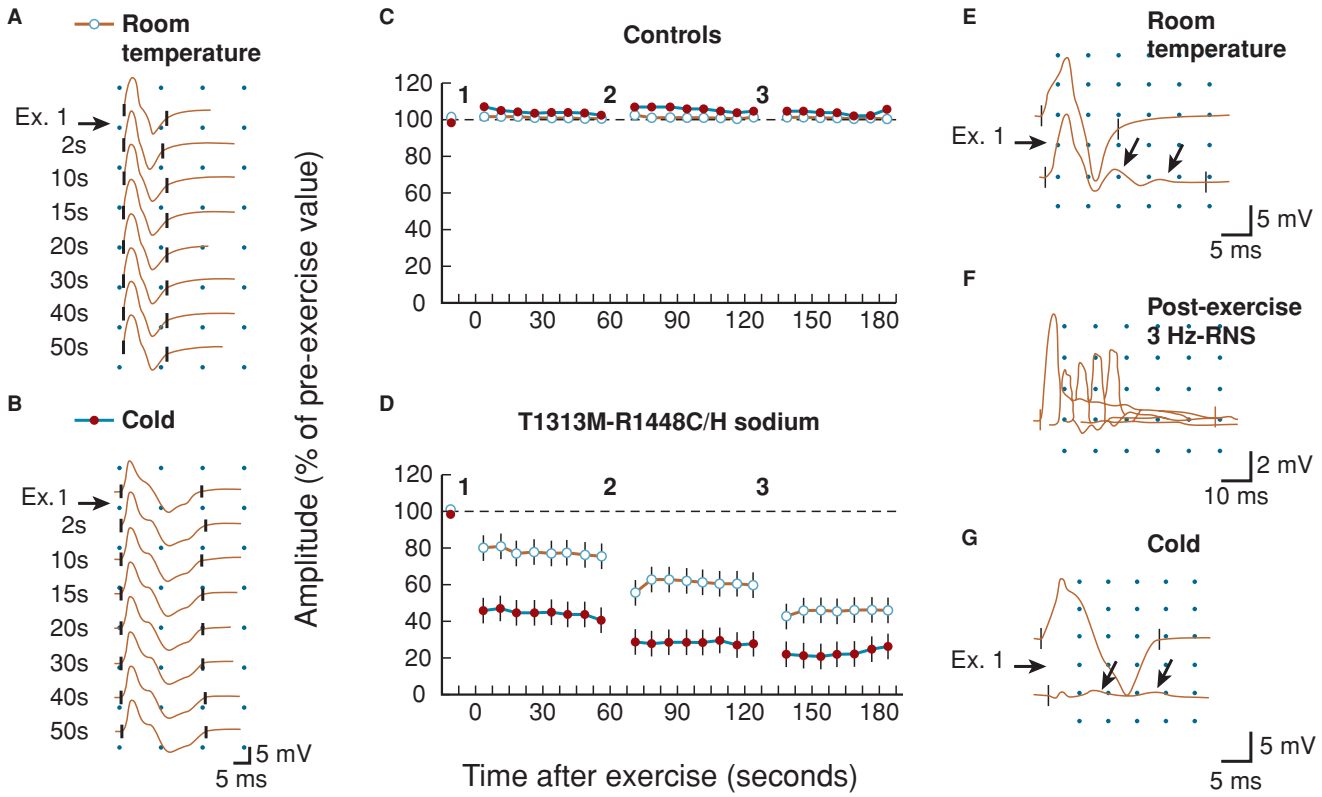

Figure 29–9. Repeated short exercise test in unaffected control subjects and paramyotonia congenita (PC) patients with T1313M, R1448C, or R1448H sodium channel mutations. (A, B) Recordings of the abductor digiti minimi compound muscle action potential (CMAP) in a control subject during the first of three successive short exercises performed at room temperature on the right hand (A) and after 7 minutes of cold exposure on the left hand (B). Top traces are preexercise recordings. Subsequent traces are postexercise recordings at different times during the 50-second resting period, as indicated left to the tracings. Scale between two dots: 5 milliseconds, 5 mV. (C, D) Changes in CMAP amplitude after each of the three exercises (noted as *1, 2, 3*) in 31 unaffected control subjects (C) and in 18 PC patients with T1313M, R1448C, or R1448H sodium channel mutations (D), at room temperature (*open circles*) and at cold (*solid circles*). The amplitude of the CMAP, expressed as a percentage of its value before the trials, is plotted against the time elapsed after the first exercise trial. *Symbols* and *vertical bars* represent mean ± standard error of the mean. (E, G) CMAP responses in a T1313M patient before and 2 seconds after the first exercise performed at room temperature (E) and at cold (G). Note the appearance of postexercise myotonic potentials (PEMPs) (*arrows* indicate extra potentials). Scale between two dots: 5 milliseconds, 5mV. (F) Repetitive stimulation of the ulnar nerve (RNS; 5 stimuli at 3Hz) 2 seconds after the first exercise performed at room temperature in another T1313M patient. Note the decrease in CMAP amplitude response during the train, with a 61% decrement between the first and the second response. Note also that the PEMPs, elicited by the first stimulation, did not reappear after the stimulations. Scale between two dots: 10 milliseconds, 2 mV. (Reproduced with permission from Fournier E, Viala K, Gervais H, et al. Cold extends electromyography distinction between ion channel mutations causing myotonia. *Ann Neurol* 2006;60:356–365.) (Figure 2, page 359.)

of myotonia in the limbs, (5) no episodes of weakness nor weakness following potassium loading, exercise, or cold, and (6) increased myotonia with potassium but not with exposure to cold.[22,31–33,62] The fluctuating severity of the myotonia is unlike that seen in MC, PMC, and hyperKPP associated with myotonia. The severity of the myotonia can range from absolutely no stiffness to severe myotonia affecting the extraocular muscles, the muscles of mastication and swallowing, and the extremities. Myotonia fluctuans is also dissimilar from other myotonic disorders in that exercise induces myotonia, which is delayed in onset. The stiffness is not worse in the cold.

Laboratory Features

Serum CK levels are usually slightly elevated. The short exercise test may be normal or show mild reduction in amplitude that improves with repetitive activity (i.e., Fornier Pattern 2) that is similar to what is seen in MC and there is no change with cooling.[1,2] The long exercise test is normal.

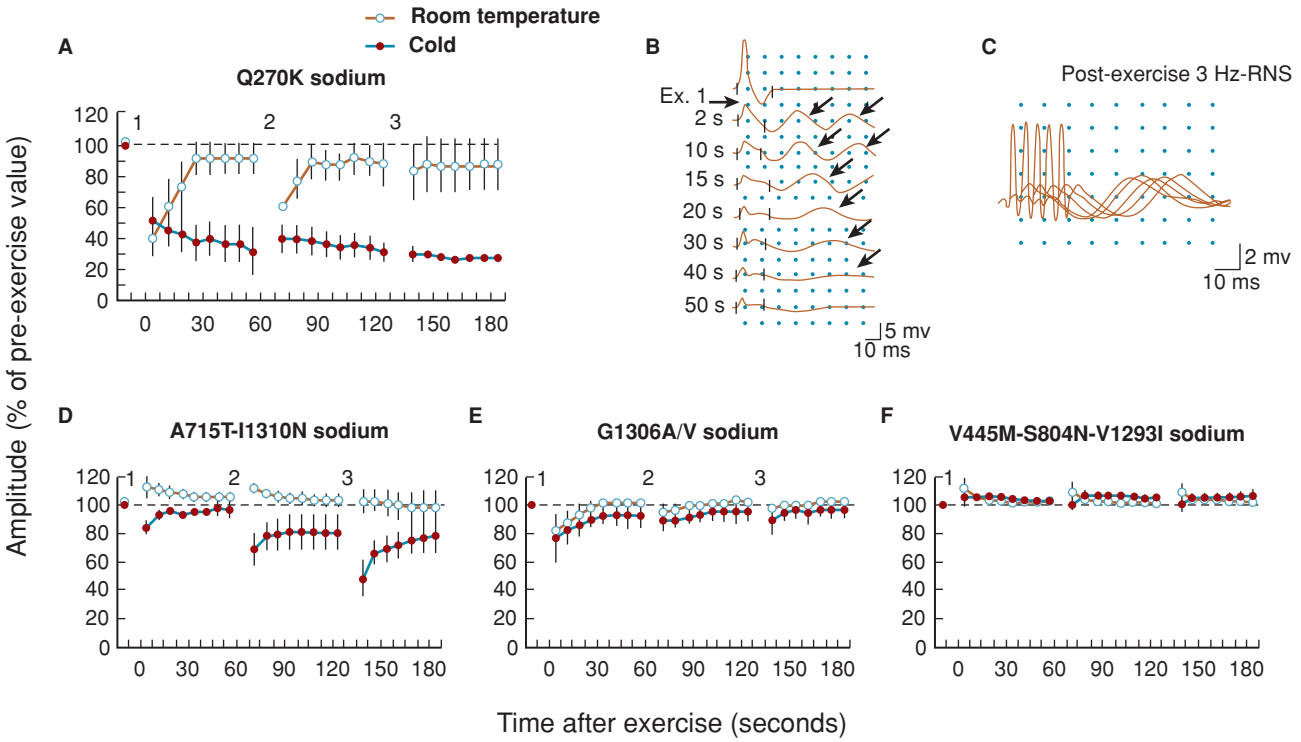

Figure 29–10. Repeated short exercise test in paramyotonia congenita (PC) patients with Q270K sodium channel mutations and sodium channel myotonia (SCM) patients. (A, D–F) Changes in compound muscle action potential (CMAP) amplitude after three short exercises (noted as *1, 2, 3*) in three PC patients with Q270K sodium channel mutations (A), in four SCM patients with A715T or I1310N sodium channel mutations (C), five SCM patients with G1306A or G1306V sodium channel mutations (D), and five SCM patients with V445M, S804N, or V1293I sodium channel mutations (E), at room temperature (*open circles*) and at cold (*filled circles*). The amplitude of the CMAP, expressed as a percentage of its value before the trials, is plotted against the time elapsed after the first exercise trial. *Symbols* and *vertical bars* represent mean ± standard error of the mean. (B) CMAP recordings before (top trace) and at different times after the first short exercise performed at cold in a patient carrying the Q270K sodium channel mutation. Note the decrease in CMAP amplitude and the appearance of postexercise waves (PEWs; *arrows*). Scale between two dots: 10 milliseconds, 5 mV. (C) Repetitive stimulation of the ulnar nerve (RNS; 5 stimuli at 3Hz) 2 seconds after the first exercise performed at cold in another Q270K patient. Note that PEWs persisted after each CMAP during the 3 Hz stimulation. Scale between two dots: 10 milliseconds, 2 mV. (Reproduced with permission from Fournier E, Viala K, Gervais H, et al. Cold extends electromyography distinction between ion channel mutations causing myotonia. *Ann Neurol* 2006;60:356–365.) (Figure 4, page 361.)

Histopathology

Muscle biopsies may be normal or show increased internalized nuclei and fiber size variability.[32] Subsarcolemmal vacuoles may be appreciated on EM.[31]

Molecular Genetics and Pathogenesis

Myotonia fluctuans permanens is caused by mutations in *SCN4A*.[7,32,63]

Treatment

Mexilitine and avaidance of high-potassium foods may be helpful.

MYOTONIA PERMANENS

Clinical Features

Myotonia permanens is associated with constant muscle stiffness that is aggravated by potassium and following activity.[20,21,40,61] Affected people may develop dyspnea, acidosis, and hypoxia related to severe myotonia affecting respiratory muscles. Neither episodic weakness nor exacerbation of myotonia with cold is seen.

Laboratory Features

Serum CK levels are normal or only mildly elevated.

Histopathology

Biopsy results have not been well described.

Molecular Genetics and Pathogenesis

Myotonia permanens is usually caused by G1306A mutations in *SCN4A*.[20,61]

Treatment

Mexilitine may be beneficial.

ACETAZOLAMIDE-RESPONSIVE MYOTONIA

Clinical Features

Individuals with this disorder complain of painful muscle stiffness that begins in childhood but worsens with age into early adulthood.[7,23,64] The myotonia is most severe in the face and hands and is aggravated by potassium, fasting, and to a lesser extent by exercise. Muscle stiffness and pain may be eased by ingestion of high carbohydrate meals. Action and percussion myotonia are appreciated. Paradoxical myotonia may be found in the eyelids. Strength is normal.

Laboratory Features

Serum CK is usually mildly elevated. The short exercise test may be normal or show mild reduction in amplitude that improves with repetitive activity (i.e., Fornier Pattern 2) that is similar to what is seen in MC and there is no change with cooling.[1,2]

Histopathology

Muscle biopsies have been performed in only a few patients and have been normal or revealed generalized muscle fiber hypertrophy.

Molecular Genetics and Pathogenesis

Acetazolamide-responsive myotonia is also caused by mutations in *SCN4A*.[7,23,28]

Treatment

Acetazolamide may help diminish muscle stiffness and pain. We initiate treatment with acetazolamide 125 mg per day and titrated as tolerated to 250 mg TID. Mexilitine may also be helpful.

FAMILIAL HYPOKALEMIC PERIODIC PARALYSIS TYPE 2

Clinical Features

Most cases of familial hypokalemic periodic paralysis (hypoKPP) are caused by mutations in the skeletal muscle voltage-gated calcium channel α-1 subunit (*CACL1A3*) gene (HypoKPP1) (see the section on HypoKPP).[6,25,42] However, several families have been identified with mutations in the *SCN4A* gene, so-called HypoKPP2.[6,23–25] HypoKPP2 is for the most part clinically indistinguishable from HypoKPP1. However, in a large retrospective series of molecularly defined HypoKPP1 and HypoKPP2 cases, the age of onset was earlier (average 10 years) and the duration of episodes longer (average 20 hours) in HypoKPP1 compared with HypoKPP2 (16 years of age and 1 hour of duration, respectively).[25] However, a study by a different group demonstrated a slightly older onset of symptoms in some cases of HypoKPP1 depending on the cite of the mutation compared to HypoKPP2.[6] Greater than 70% of HypoKPP1 patients developed fixed proximal weakness compared with none of the HypoKPP2 patients.[25] Also, in regards to treatment, acetozolamide, which can be helpful in HypoKPP1 can occasionally exacerbate attacks of weakness in HypoPP2.[25]

Laboratory Features

Serum potassium is reduced during the attacks. Serum CK may be normal or elevated. On the long exercise test, a decrease of CMAP amplitudes are seen approximately 10–20 minutes after cessation of exercise (Table 29–1).[1] However, this decrement is less than what is typically observed in patients with a HyperKPP. EMG between attacks of muscle paralysis is usually normal and in particular there are no myotonic discharges.[1,24,25]

Histopathology

While muscle biopsies in HypoKPP1 often demonstrate non-rimmed vacuoles within muscle fibers, biopsies in HypoPP2 often reveal muscle fibers with tubular aggregates.[24,25]

Treatment

Unlike patients with hypoKPP1 or hyperKPP, individuals with hypoKPP2 may actually experience an exacerbation of weakness with acetazolamide rather than improvement. Therefore, initiation of a trial of acetazolamide should be done cautiously in a patient with hypoKPP2 or hypoKPP in whom the genotype is unknown.

MOLECULAR GENETICS AND PATHOGENESIS/PATHOPHYSIOLOGY OF THE SODIUM CHANNELOPATHIES

The voltage-gated muscle sodium channel is a heterodimer composed of α and β subunits that are encoded on chromosomes 17q23–25 and 19q13.1, respectively.[7,42] Point mutations in the α subunit gene, *SCN4A*, are responsible for hyperKPP, PMC, and the various

PAMs as previously discussed. No disorders are known to be caused by mutations in the β-subunit. The α subunit has four homologous domains (I–IV) each containing six hydrophobic segments (S1–S6) that transverse the sarcolemmal membrane (Fig. 29–6).[7,19,22] An extracellular loop dips within the plasma membrane between S5 and S6 of each domain and participates in the formation of the pore. The S4 helix contains a repeating motif of positively charged amino acids at every third position suggesting that this region serves as the voltage sensor.[22] The S4 segment appears to be critical for inactivation of the open channel, while the S3 segment is important in the recovery of inactivated channels.[40] The interaction between the S3 and S4 segments is important for transition to and from inactivation states (Fig. 29–11).

Over 30 different point mutations in *SCN4A* have been reported and most are located in regions of the α-subunit critical for fast inactivation. Most of these missense mutations are associated with gain-of-function defects, which is either disrupted inactivation or enhanced activation. The notable exception are the mutations associated with HypoKPP2, which are all clustered in the voltage-sensor region of the second repeat (D2S4) and diminish activity by enhancing inactivation. The fast inactivation of channels limits the number of sodium channels available for activation which in turn lead to a refractory period until there is repolarization of the muscle membrane.[7,20,40,50,65] The gain-of-function mutations associated with PMC and PAM typically slow the rate of inactivation three- to fivefold, resulting in a longer duration of the action potentials and increased availability of Na^+ channels (i.e., fraction not inactivated) at the end of each action potential that augment the membrane excitability and resulting myotonic discharges. In addition to slow inactivation, many PMC mutations also disrupt the final extent of inactivation. The steady inward Na current generated through the small fraction of mutant channels that have failed to inactivate, depolarizes the membrane to a new stable resting potential of approximately −50 mV. This results in inactivation of the wild-type and most of the mutant Na channels, resulting in a system that is refractory from generating an action potential, leading to a paralytic attack.[20,50,65] In these individuals, increased extracellular potassium results in further depolarization of the muscle membrane, thus leading to muscle fiber inexcitability.

In contrast to fast inactivation is a process called "slow inactivation" that limits the availability of sodium channels on a time scale of seconds to minutes, which can also affect muscle membrane excitability. Rare patients with *SCN4A* mutations manifesting as hyperKPP and myotonia have impaired slow inactivation as opposed to defective fast inactivation.[66]

Patch clamp studies of intercostal muscles of patients with PMC demonstrate normal resting membrane potentials at 37°C, but cooling to 27°C, leads to depolarization of the muscle membrane to approximately −40 mV.[50,65] As a result, spontaneous action potentials are generated secondary to the approximation of the resting membrane and threshold potentials that correlate with the cold-induced myotonia. Subsequently, the muscle membrane may remain in a depolarized state for a prolonged period of time such that is no longer capable of generating further action potentials, and therefore, the muscles becomes weak.[20,50,65]

In HyperKPP1, mutant sodium channels are associated with large persistent currents that further increase when extracellular potassium levels are elevated.[20,50,65] Increased extracellular potassium leads to depolarization of the muscle membrane and increased late openings of the noninactivated sodium channels.[40] The continued sodium influx sustains the depolarization of the membrane which in turn leads to inactivation of normal sodium channels and subsequent muscle fiber inexcitability.

In HypoKPP2, mutations in gating-charge-carrying arginine residues in an S4 segment induce a hyperpolarization-activated cationic leak through the voltage sensor of the skeletal muscle sodium channel.[67,68] A sustained proton leak may contribute to instability of ion conductance indirectly, by interfering with intracellular pH homeostasis.[68]

▶ CALCIUM CHANNELOPATHIES

PRIMARY HYPOKALEMIC PERIODIC PARALYSIS TYPE 1 (HYPOKPP 1)

Clinical Features

HypoKPP 1 is the most frequent form of periodic paralysis with a prevalence of approximately 1/100,000.[6,7,18] It is an autosomal dominant disorder, with reduced penetrance in women (a male to female ratio of 3 or 4–1). Onset of episodic weakness usually occurs in the first two decades of life. Individuals with hypoKPP1 do not have clinical or electrophysiological myotonia or paramyotonia which may be useful in distinguishing from the hyperKPP and PMC.

Attacks of weakness may be precipitated by strenuous physical activity followed by rest or sleep, high carbohydrates and sodium meals, alcohol consumption, emotional stress, concurrent viral illness, lack of sleep, menstruation. Specific medications (e.g. beta agonists, corticosteroids, and insulin) are also triggers for attacks. Episodes of weakness can occur at any time of day, although most occur in the morning.

The severity of an attack can range from mild focal weakness of an isolated muscle group to severe generalized paralysis. Facial and ventilatory muscles as well as the sphincter muscles are typically spared or

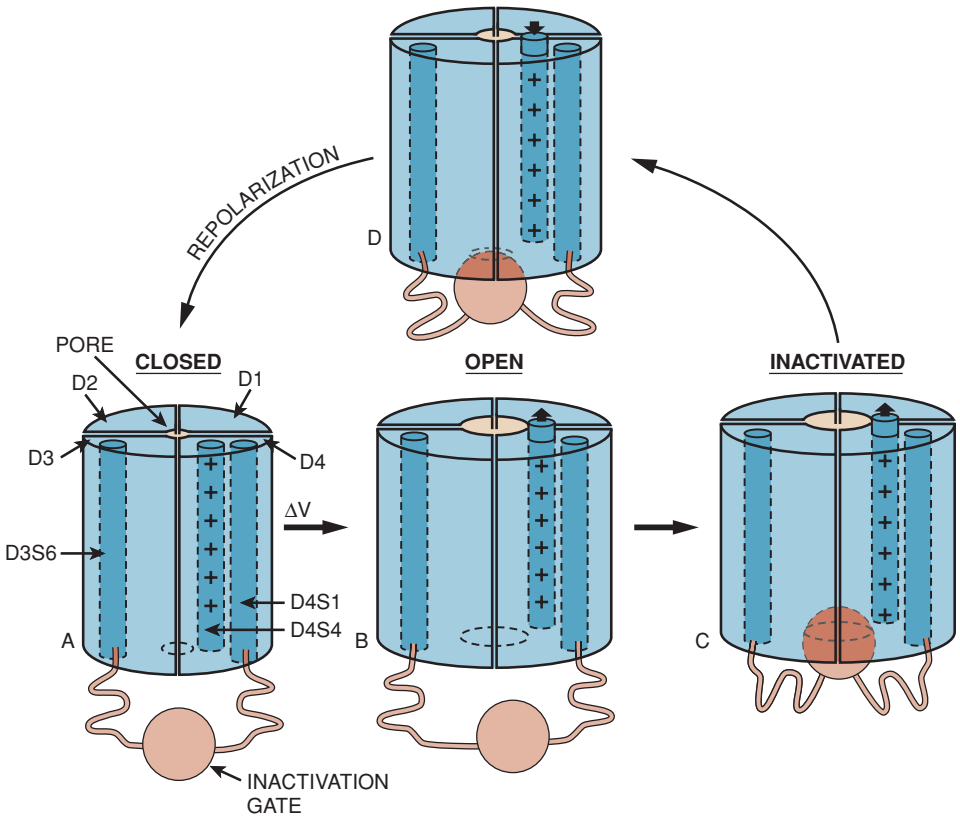

Figure 29–11. Cation Channel Model. Voltage-gated sodium and calcium channels are believed to have similar structures and physiology. These cations channels have four domains (D1–D4) each containing six transmembrane segments (also see Figure 21–6). Cation channel model. This model shows the four domains (D1–D4, *blue*) of the cation channel arranged around the ion pore (*purple*) in the membrane. The S4 segments of cation channels contain a repeating motif of positively charged (+) amino acids (arginine or lysine) at every third position separated by two neutral amino acids. In the closed state (**A**), the pore (*purple*) is closed and the inactivation gate (*red*) is open. In response to depolarization, the S4 segments (*darker blue*) shown here move slightly under the influence of electrostatic forces. The S4 segment of domain 4 is the site of two of the recognized mutations in patients with paramyotonia congenita. Depolarization leads to a conformational shift that results in the pore (*purple*) opening (**B**). Channel closing is thought to result from a "ball-valve" mechanism where the cytoplasmic loop (*red*) between domains D3 and D4 (see Figure 29–12) falls into the ion pore, thus blocking it (**C**). In this model, repolarization would then result in the protein assuming its closed conformation (**D**) and release of the inactivation gate. The channel is now in the closed state (**A**) and is ready to open in response to the next depolarization. (Reproduced with permission from Ptacek LJ. The familial periodic paralyses and nondystrophic myotonias. *Am J Med* 1998;105:58–70.) (Figure 2, page 62.)

only minimally affected. Nevertheless, ventilatory muscle involvement and cardiac arrhythmia secondary to hypokalemia have occurred.[69] When weakness is profound, the muscle is electrically unexcitable. Reflexes are absent in severely affected muscle groups. Severe muscle weakness usually last for several hours to more than a day, though many individuals note a residual weakness for several days following an attack. Typically, those muscles affected last are the first to recover.

The frequency of these attacks of weakness is also highly variable and can occur several times a week to less than once a year. After the age of 30 years the frequency of the attacks often diminish and some individuals become free of attacks in their 40s or 50s. On the other hand, many patients develop permanent fixed or slowly progressive weakness over time.[6,70] The proximal muscles, especially in the legs, are more prone to developing fixed weakness.

Often an attack of periodic weakness is heralded by a sensation of heaviness or aching in the low back, thighs, and calves which spreads to involve other muscle groups, primarily those in the proximal upper limbs. Mild exercise during this prodrome may stave off the full blown attack of weakness, however this is not always successful.

Laboratory Features

Serum potassium levels are usually below 3.0 mEq/L during an attack of weakness though between attacks the serum potassium is normal. The EKG may demonstrate bradycardia, flattened T waves, prolonged PR and QT intervals, and notably U waves secondary to the hypokalemia. Serum CK levels are usually mildly elevated between attacks and increase during an attack of weakness. Provocative testing using intravenous glucose load and sometimes insulin in order to lower the serum potassium was used in the past to assist in diagnosis, but is rarely necessary now.

Sensory and motor NCS are normal between attacks of weakness.[70,71] However, surface recordings have revealed reduced muscle fiber conduction velocity between paralytic attacks.[72] During paralytic attacks, sensory studies remain normal but the CMAP amplitudes are reduced secondary to muscle membrane inexcitability. Repetitive stimulation of mildly affected muscles can maintain the CMAP amplitudes to some degree, supporting the clinical impression that mild exercise can stave off an attack.

In contrast to individuals with HyperKPP, there are minimal changes in CMAP amplitudes immediately after the exercise phase of the short or long exercise tests in those with HypoKPP (Table 29–1).[1] However, with the long exercise test, there is usually a delayed decline in CMAP amplitudes ($-51 \pm 10\%$). The reduction in amplitudes is less in those with HypoKPP2 compared to HypoKPP1.[1]

EMG between attacks of muscle paralysis is usually normal.[71] However, EMG early in an attack of weakness reveals a slight increase in insertional and spontaneous potentials (e.g., fibrillation potentials and positive sharp waves), which are a reflection of the hyperirritable muscle membranes and not indicative of denervation. As the paralytic attack progresses, there is a decrease in the amplitude and duration of voluntary MUAPs as well as an overall decrease in the number of MUAPs contributing to the interference pattern. When the paralytic attack is maximal there is marked reduction or complete absence of insertional activity, and there are minimal, if any, voluntary MUAPs. In patients who develop persistent muscle weakness, small amplitude, short duration, polyphasic MUAPs that recruit early may be appreciated in weak muscles along with rare fibrillation potentials and positive sharp waves.

Between attacks, single fiber EMG shows normal jitter along with a slight increase in fiber density. The latter is likely the result of a mild myopathic process which is also noted on histopathology. During an attack, the reduction in muscle membrane excitability results in a dropout of single muscle fibers and a decrease in fiber density, compared to both normal and interattack values for the patients. This is accompanied by a slight increase in jitter with occasional blocking of potentials.[73]

Histopathology

Muscle biopsies may reveal intracellular vacuoles, tubular aggregates, and dilation of the sarcoplasmic reticulum.[6,25,49] HypoKPP1 is more likely be associated with vacuoles on biopsy, while tubular aggregates are more common in HypoKPP2.[6,25] Muscle fiber size variation, split fibers, hypertrophic and some atrophic fibers can also be present. Rarely, necrotic and degenerating muscle fibers are noted.

Molecular Genetics and Pathogenesis

Approximately 70% of cases of familial hypokalemic periodic paralysis (HypoKPP1) are caused by mutations in the α-subunits of skeletal muscle L-type calcium channel gene (*CACN1AS*) located on chromosome 1q31–3245.[7,24,69] In 10% of affected individuals (HypoKPP2), the mutations are present in the α-subunits of skeletal muscle sodium channel gene, *SCN4A*, and no identifiable mutation is found in the remaining 20% of patients. For both HypoKPP1 and HypoKPP2, the mutations occur in highly conserved arginine residues in the voltage-sensing segments of the calcium channel.[7,24] In addition, rare cases of hypokalemic periodic paralysis have been associated with mutations in another potassium channel gene, *KCNE3*.[74] Further, Gitelman syndrome, caused by mutations affecting the thiazide-sensitive sodium chloride cotransporter, may also cause hypokalemic paralysis.[75]

The calcium channel (CaV1.1) is composed of five subunits (α1, α2, β, δ and γ). The α1-subunit is composed of four domains, each containing six transmembrane segments (S1–S6), and contains the dihydropyridine (DHP) receptor (Fig. 29–12).[26] This receptor functions not only as a calcium ion channel for the T-tubule of skeletal muscle, but also as a voltage-sensor for excitation–contraction coupling (Fig. 29–13).[19] The other subunits of the calcium channel regulate the function of the α1-subunit.[26] The S4 segment of the α1-subunit confers the voltage-sensing properties to the channel, and is the site for most of the mutations identified in patients with HypoKPP1.

The mechanism for the induced attacks of weakness in HypoKPP1 is not completely understood.[7,69,76–79] As with other forms of periodic paralysis, muscle fibers are

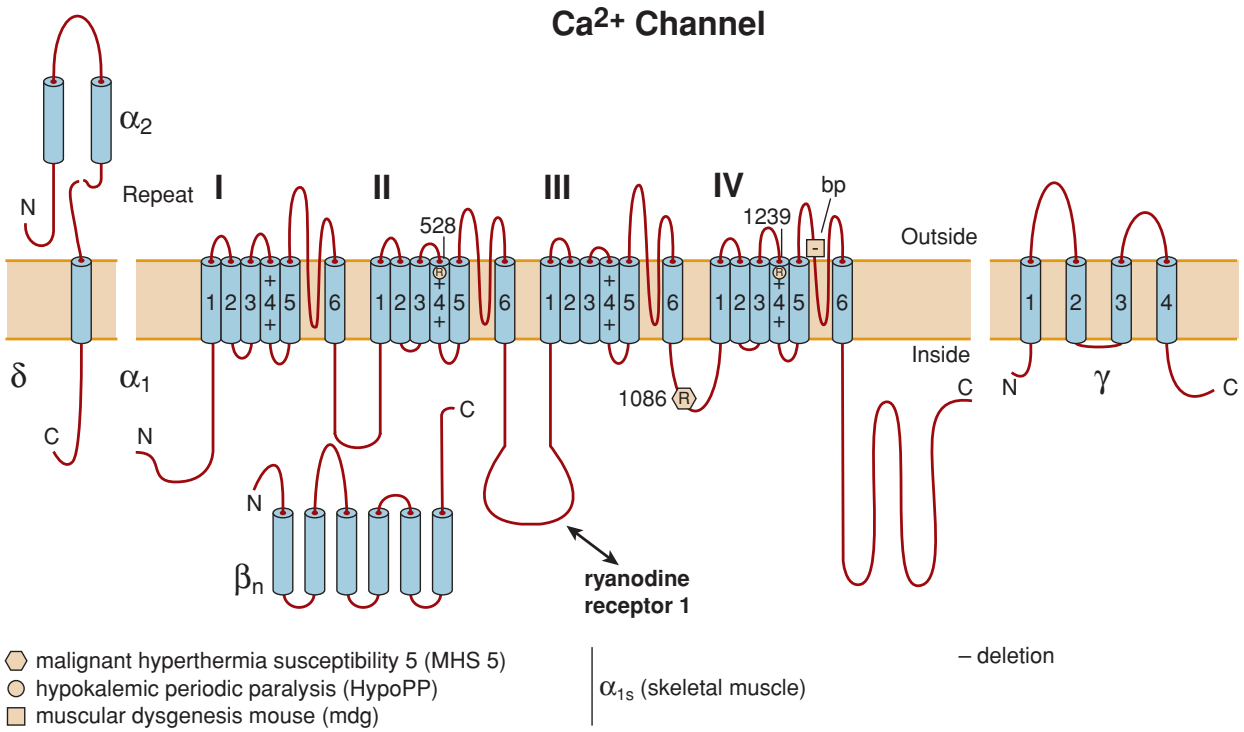

Figure 29–12. Subunits of voltage-gated calcium channel. α-Subunit resembles that of sodium channel; however, function of various parts, e.g., III–IV linker, may not be same. α_2/δ, $\beta_1 - \beta_4$, and γ are auxiliary subunits. Mutations shown here, α_{1S}-subunit of skeletal muscle L-type calcium channel (= dihydropyridine receptor), have been described for humans (HypoPP, MHS 5) and mice (mdg). Conventional one-letter abbreviations are used for replaced amino acids whose positions are given by respective numbers of α_{1S}-subunit. Symbols used for point mutations indicate resulting diseases as explained at *bottom left*. (Reproduced with permission from Lehmann-Horn F, Jurkat-Rott K. Voltage-gated ion channels and hereditary disease. *Physiol Rev* 1999;79:1317–1372.) (Figure 7, page 1328.)

depolarized and inexcitable during an attack. In vitro, muscle fibers from patients with HypoKPP1 exposed to low K solutions paradoxically depolarize. However, the source of the depolarizing current has remained elusive. The available data suggest a loss-of-function defect with reduced ionic current density. A study on fibers biopsied from a patient with an R528H calcium channel mutation detected a reduction in ATP-sensitive K current, more easily tying it to the depolarization seen with hypokalemia and suggesting a secondary channelopathy resulting from altered calcium homeostasis. It has been also suggested that reduced calcium influx through the T-tubule may be the cause of impaired excitation–contraction coupling.

The DHP receptor functions as a calcium channel as well as a voltage-sensor for excitation–contraction coupling. Electrophysiological recordings of myotubes expressing mutant calcium channels reveal diminished calcium current and a negative shift of the steady-state inactivation current.[69] Decreased calcium influx through the T-tubule may impair excitation–contraction coupling. Further, the kinetics of the sodium channel also appear to be influenced by mutations involving *CACN1AS*. The sodium conductance is increased in the resting state leading depolarization of the resting membrane potential from about −80 mV to around −50 mV. In this partially depolarized state, the number of sodium channels available to activate is likely reduced, thus, creating an inexcitable membrane and clinical weakness.

Treatment

The primary mode of therapy is reducing exposure to known triggers (e.g., avoiding ingestion of high-carbohydrate meals, extremely strenuous exercise). Acetazolamide (125–1500 mg/d) and potassium salts (0.25–0.5 mEq/kg) are often prescribed prophylactically in order to prevent hypokalemia and reduce attacks of weakness. Importantly, acetazolamide may actually induce attacks of weakness in individuals with HypoKPP2 caused by *SCNA4* mutations.[6,25] Dichlorphenamide (50–150 mg/d) also may be effective in reducing attack frequency and severity, but unfortunately it is no longer

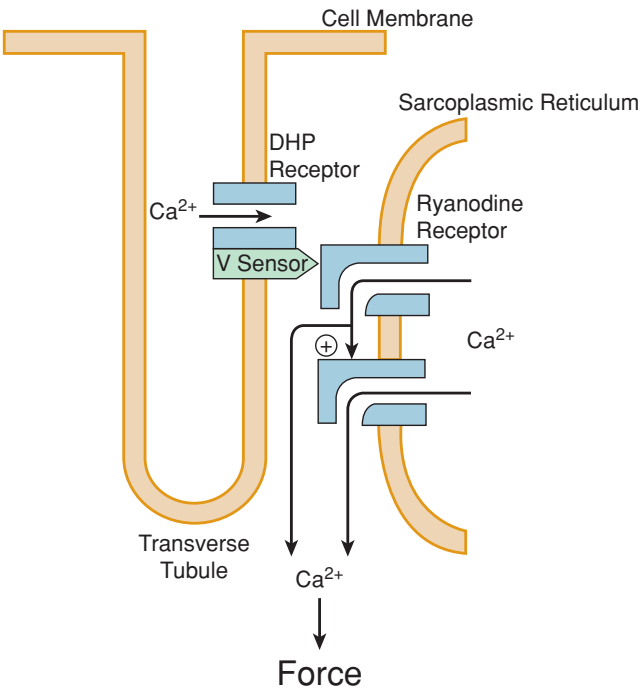

Figure 29–13. Triadic junction between a transverse tubule and sarcoplasmic reticulum: position of two calcium channels of skeletal muscle, L-type calcium channel, also called dihydropyridine (DHP) receptor, and calcium release channel, also called ryanodine receptor. Coupling between the two channels is not fully elucidated. Mutations in respective genes cause hypokalemic periodic paralysis, malignant hyperthermia, or central core disease. (Reproduced with permission from Lehmann-Horn F, Jurkat-Rott K. Voltage–gated ion channels and hereditary disease. *Physiol Rev* 1999;79:1317–1372.) (Figure 8, page 1329.)

available.[10] Triamterene (25–100 mg/d) or spironolactone (25–100 mg/d) may be tried to prevent attacks and perhaps improve interattack weakness, when acetazolamide is not effective. Acute attacks of weakness can be treated with oral potassium salts (0.25 mEq/kg body wt) every 30 minutes until strength improves.

In severe attacks and if the patient's condition precludes oral potassium, intravenous potassium (KCL bolus 0.05–0.1 mEq/kg body wt. or 20–40 mEq/L of KCL in 5% mannitol) may be administered. Cardiac monitoring is essential throughout treatment. HypoKPP1 may be allelic with malignant hyperthermia (MH), so it is not surprising that MH without periodic paralysis has been described with mutation in *CACN1AS*. Hence, all HypoKPP patients undergoing surgery should be monitored for malignant hyperthermia-like reactions (rigidity and marked elevation in CK). However, postoperative paralysis in this group of patients is more likely related to the stress of surgery.

SECONDARY HYPOKALEMIC PARALYSIS

Secondary hypoKPP needs to be excluded in all patients, particularly if there is no family history in those with onset after the third decade of life (Table 29–2). Urinary or gastrointestinal dumping of potassium may precipitate attacks of weakness and s cause a necrotizing myopathy. Muscle strength improves with correction of the hypokalemia.

THYROTOXIC PERIODIC PARALYSIS

Thyrotoxic periodic paralysis (TPP) resembles hypoKPP, except that it is sporadic in occurrence. TPP is more common in Asian adults, but it occurs worldwide. Interestingly, although, hyperthyroidism is more common in women, the majority of cases of TPP occur in men. Affected individuals can also develop progressive muscle weakness secondary to hyperthyroidism itself. The attacks of weakness dissipate with treatment and correction of the dysthyroid state but can recur with redevelopment of hyperthyroidism. Unlike the familial forms of hypokalemic and hyperkalemic periodic paralysis, acetazolamide does not appear to have any significant benefit. However, β-blockers may be effective in reducing the frequently and severity of the paralytic attacks in thyrotoxic patients.

▶ OTHER FORMS OF PERIODIC PARALYSIS

ANDERSEN–TAWIL SYNDROME (ATS) (ANDERSEN SYNDROME, OR KLEIN–LISAK–ANDERSEN SYNDROME)

Clinical Features

Andersen–Tawil syndrome (ATS) is a rare ion channel disorder characterized the clinical triad of periodic paralysis, ventricular arrhythmias associated with long QT, and skeletal developmental anomalies.[80–84] A diagnosis of ATS can be made when an individual exhibits two of these three cardinal features. Only about 60% of affected individuals manifest the complete triad while approximately 80% express two of the three cardinal features. Inheritance is autosomal dominant although de novo mutations are frequent, and phenotypic expression is extremely variable. Prevalence is unknown but estimated at one-tenth that of HypoKPP.

The neuromuscular manifestations of ATS consist of episodic weakness that may arise spontaneously or be triggered by rest following exertion rest. The attacks of paralysis usually begin in the first or second decade

of life and may be associated with elevated, normal or most commonly decreased serum potassium levels. The attacks vary in duration (hours to days), severity, and frequency ranging from a single lifetime event to daily bouts of weakness. Permanent proximal weakness often develops over time. Patients with ATS do not show evidence of myotonia or paramyotonia.

Cardiac manifestations include potentially life-threatening arrhythmias, including bidirectional ventricular tachycardia (VT), polymorphic VT and Torsades de Pointes. The cardiac arrhythmias may be asymptomatic or manifest as palpitations, syncope or even cardiac arrest necessitating defibrillator implantation. No specific triggers have been associated with the ventricular arrhythmias of ATS. One of the most common ECG findings is a long QT interval, which is recognized as an integral feature of ATS and may serve as a trigger for fatal ventricular arrhythmias. Thus, ATS must be considered in all individuals presenting with episodic weakness and/or a long QT syndrome.

Developmental anomalies associated with ATS include clinodactyly, hypertelorism, low set ears, mandibular hypoplasia, syndactyly, and scoliosis. Other features less commonly associated are short stature, a broad nose and forehead, cleft or high-arched palate, short digits, vaginal atresia, brachydactyly, cardiac valve abnormalities, and hypoplastic kidney. Neurocognitive abnormalities may occur characterized by deficits in executive function and abstract reasoning.

Laboratory Features

Serum CK can be normal or only slightly elevated. Serum potassium levels may be normal, elevated or decreased during attacks of weakness. A prolonged QT interval is present in 80% of patients, while some have even more ominous ventricular tachyarrhythmias as previously discussed. Motor and sensory NCS are normal. EMG is usually normal as well between attacks of weakness. Myotonic discharges are not seen.

Histopathology

Tubular aggregates similar to those observed in other forms of periodic paralysis may be appreciated on muscle biopsies.

Molecular Genetics and Pathogenesis

Approximately two thirds of ATS patients have missense mutations or small deletions in the *KCNJ2* gene (ATS1).[80,82,85] This gene encodes for the inwardly rectifying potassium channel (Kir2.1) and is predominantly expressed in heart, skeletal muscle and brain. This mutation leads to impairment of muscle membrane and perhaps neuronal depolarization and repolarization, but its role in the associated skeletal developmental anomalies is not well understood. Kir2.1 channels help stabilize resting membrane potentials. The majority of *KCNJ2* mutations result in the failure of appropriate conduction, and many alter the binding of phosphatidylinositol 4, 5 bisphosphate, an important regulator of Kir2.1 channel function. It is postulated that reduced Kir2.1 channel function in skeletal muscle may result in sustained membrane depolarization, failure of action potential propagation and flaccid paralysis. It may also prolong the most terminal phase of repolarization in the heart and lead to delayed after-depolarizations. In approximately 20% of patients with an ATS phenotype, no mutation of *KCJN2* has been identified (ATS2).

Treatment

It is important to be aware of and recognize the potential cardiac conduction abnormalities. Malignant arrhythmias may be treated with antiarrhythmic agents or pacemaker insertion. Small doses of acetazolamide may prevent paralytic attacks in some patients.

▶ OTHER SKELETAL MUSCLE CHANNELOPATHIES

OTHER POTASSIUM CHANNELOPATHIES

A few kindreds with periodic paralysis have been found to have mutations in another potassium channel gene, *KCNE3*.[74] Attacks of weakness have been associated with low serum potassium levels in some but not other cases.

OTHER CALCIUM CHANNELOPATHIES

Some cases of central core disease and malignant hyperthermia are caused by mutations in the ryanodine receptor encoded on chromosome 19q13.1.[86] The ryanodine receptor is responsible for the release of calcium from the sarcoplasmic reticulum. Central core disease is discussed in Chapter 25 regarding Congenital Myopathies. Brody disease is caused by mutations affecting a different calcium channels that is located on the sarcoplasmic reticulum.

MALIGNANT HYPERTHERMIA

Clinical Features

Malignant hyperthermia (MH) is a syndrome rather than a specific disorder that is characterized by severe muscle rigidity, myoglobinuria, fever, tachycardia, cyanosis, and

cardiac arrhythmias precipitated by depolarizing muscle relaxants (e.g. succinylcholine) and inhalational anesthetic agents (e.g., halothane).[87] The incidence of MH in patients exposed to general anesthesia varies form 0.5–0.0005%.[87] Importantly, at least 50% of patients who developed MH had previous anesthesia without any problem—so a negative history in this regard is not helpful. Signs of MH usually develop during surgery, but they can occur postoperatively. Rarely, attacks of MH have been induced following strenuous activity, ingestion of caffeine, or by stress.

Laboratory Features

Serum CK can be normal or mildly elevated between attacks. However during an episode of MH, the serum CK levels become markedly elevated and myoglobinuria and renal insufficiency can ensue. In addition, metabolic and respiratory acidosis may develop with lactic acidosis, hypoxia, hypercarbia, and hyperkalemia. NCS and EMG are usually normal between episodes of MH unless the patient has a predisposing myopathic disorder, for example, PMC. Determining susceptibility to MH in absence of genetic testing requires in vitro muscle contracture test. Unfortunately, this test is not readily available.[87]

Histopathology

Muscle biopsies demonstrate nonspecific myopathic features including fiber size variability, increased internal nuclei, moth-eaten fibers, and necrotic fibers after an attack of MH.

Pathogenesis and Molecular Genetics

MH susceptibility is genetically heterogeneic. MHS1 is caused by mutations in the ryanodine receptor gene located on chromosome 19q13.1.[86] These mutations may lead to an excessive release of calcium into the cytoplasm upon activation. Of note, mutations in this gene are also responsible for the congenital myopathy, central core disease. However, only a minority of patients with MH have mutations in the ryanodine receptor gene. MHS2 localizes to chromosome 17q11.2-q24 (possibly the gene for the α subunit of the sodium channel). Thus, MHS2 may be allelic to hyperKPP1, PMC, and PAM. MHS3 has been linked to chromosome 7q21-q22 (possibly to another gene encoding a calcium channel subunit). MHS4 localizes to chromosome 3q13.1, but the gene has yet to be identified. MHS5 is caused by mutations in the dihydropteridine receptor gene on chromosome 1q31 (allelic to HypoKPP1). Linkage to chromosome 5p has been demonstrated in still other families (MHS6). Besides these disorders, it is well known that patients with dystrophinopathies are susceptible to developing MH. Thus, it appears that malignant hyperthermia may occur in various myopathic disorders affecting the structural proteins of the muscle membrane or ion channels.

Treatment

Anesthetic agents should be administered cautiously in people at risk for MH. If MH develops the initial step is discontinuing the offending anesthetic agent while 100% oxygen is delivered.[87] Dantrolene 2–3 mg/kg every 5 minutes for a total of 10 mg/kg should be administered. The patient should be covered with cooling blankets and may even require lavage of the stomach, bladder, and lower gastrointestinal tract with iced saline solution. Acidosis and hyperkalemia are treated with sodium bicarbonate, hyperventilation, dextrose, insulin, and occasionally calcium chloride while the patient is monitored and treated for possible secondary cardiac arrhythmias. Urinary output must be maintained with hydration, furosemide, or mannitol.

BRODY DISEASE

Clinical Features

This rare disorder characterized by impaired skeletal muscle relaxation following exercise.[47,88,89] Affected individuals complain of exercised induced cramping and stiffness in the arms and legs. Recurrent myoglobinuria is an uncommon complication. Having the patient repeatedly open and close their fists or do several deep knee bends may induce delayed muscle relaxation that can be painful. Some patients also have impaired relaxation of the eyelids after forced eyelid closure. The muscle stiffness resembles paramyotonia as the stiffness worsens with activity. However, there is no percussion myotonia. Some people have mild proximal weakness on examination.

Laboratory Features

Serum CK levels are normal or only slightly elevated. Potassium levels are normal. Unlike the dynamic glycogen storage disorders which it may mimic due to the exercise induced cramps, an exercise forearm test reveals a normal rise in lactic acid and ammonia in Brody disease. NCS and EMG are normal.[47,88,89] Importantly, muscles exhibiting impaired relaxation are electrically silent unlike what is observed in myotonia.

Histopathology

Muscle biopsies demonstrate type 2 muscle fiber atrophy and increased internalized nuclei. Decrease in calcium-ATPase in type 2 muscle fibers is appreciated with immunohistochemistry staining. On electron microscopy, swollen mitochondria with crystalline inclusions are rarely noted. As with MH, skeletal muscle fibers are extremely sensitive to caffeine.

Molecular Genetics and Pathogenesis

Brody disease is an autosomal recessive disorder caused by mutations in the *ATP2A1* gene located on chromosome 16p12.2–12.2.[89] This gene encodes for sarcoplasmic reticulum calcium-ATPase (SERCA1), a calcium channel present on the sarcoplasmic reticulum of type 2 muscle fibers. These mutations cause a decreased rate of ATP-dependent calcium transport across the channel.[88,89] Normally, upon depolarization of the T tubules, calcium ions are released from the lateral cisterns of the sarcoplasmic reticulum into the sarcoplasm. Relaxation requires that the calcium concentration in the sarcoplasm to return to baseline which is accomplished by calcium-ATPase located in the sarcoplasmic reticulum membrane. This enzyme pumps calcium back into the sarcoplasmic reticulum but the activity is reduced in Brody's disease. The results in an increased intracellular calcium and impaired relaxation following phasic (fast-twitch) activity. Not all patients with Brody's disease have been found to have mutations in the *ATP2A1* gene, thus, the disorder is genetically heterogeneic.

Treatment

Dantrolene has been tried with variable success in a few patients as has verapamil. Dantrolene and verapamil were also demonstrated to improve muscle function in-vitro in muscle biopsy specimens from patients with Brody disease.[88]

SCHWARTZ–JAMPEL SYNDROME (CHONDRODYSTROPHIC MYOTONIA)

Clinical Features

Schwartz–Jampel syndrome (SJS) is an autosomal recessive disorder associated with developmental skeletal abnormalities and myotonia.[63,90–98] Affected children often have dysmorphic facies with micrognathia, narrowed palpebral fissures, and low set ears. Additionally, over time kyphoscoliosis, bowing of the diaphyses, irregular epiphyses, reduced stature, and pectus carinatum become apparent. Infants may have a decreased suck and a weak high-pitched cry. As seen in MC, facial muscles may distort during or following a crying spell due to myotonia. Muscles often appear hypertrophied and movement is slow due to stiffness related to the myotonia. Developmental motor milestones may be delayed.

Laboratory Features

Serum CK levels can be normal or mildly elevated. Routine motor and sensory NCS are usually normal.[69] Needle EMG reveals complex repetitive discharges,[98] myokymic discharges,[96] myotonic or pseudomyotonic discharges.[87,90–95,99]

Histopathology

Muscle biopsies reveal variation in fiber size with hypertrophic and atrophic fibers along with scattered degeneration and regenerating fibers.[98] Replacement of muscle fibers by fatty and connective tissue may be seen over tome.

Molecular Genetics and Pathogenesis

SJS results from mutations in the *HSPG2* gene located on chromosome 1p34–36.1, which encodes perlecan, the major heparan sulfate proteoglycan component of basement membranes.[100–103] Analyses of HSPG2 messenger RNA (mRNA) and perlecan immunostaining on patients' cells revealed a hypomorphic effect of the studied mutations.[103] Truncating mutations result in instability of HSPG2 mRNA through nonsense mRNA-mediated decay, whereas missense mutations involving cysteine residues led to intracellular retention of perlecan.

How mutations in the perlecan gene lead to myotonia is unclear but may indirectly effect the kinetics of the skeletal muscle sodium channel. Synchronous opening of sodium channels following a stimulus to the muscle membrane following repolarization of the membrane and delayed sodium channel activation have been demonstrated.[60]

Treatment

Procainamide or mexilitine may be beneficial in reducing the muscle stiffness associated with SJS.

▶ SUMMARY

Mutations affecting different muscle ion channels (sodium, calcium, chloride, and potassium) are associated with a variety of neuromuscular manifestations including clinical and electrical myotonia, periodic and sometimes progressive abnormalities, and occasionally skeletal deformities as seen in ATS. The overlapping features in these disorders can make then difficult to diagnose. The combination of a good clinical history (including family history), neuromuscular exam, and electrophysiological studies (EMG combined with long and short exercise tests performed at room temperature and with the extremity cooled) can be very helpful in guiding which genetic tests may be more useful to order to confirm the diagnosis. Attacks of periodic paralysis may be reduced in some patients with acetazolamide, but this may worsen in others (i.e., HypoKPP2). Mexilitine appears to be beneficial in alleviating bothersome

myotonia is some patients. Further studies correlating genotype with electrophysiological phenotype and response to various treatments are needed.

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CHAPTER 30

Inflammatory Myopathies

There are four major categories of idiopathic inflammatory myopathy: dermatomyositis (DM), polymyositis (PM), immune-mediated necrotizing myopathy, and inclusion body myositis (IBM), which are clinically, histologically, and pathogenically distinct (Tables 30–1 to 30–3).[1–5] These myositides may occur in isolation or in association with cancer or various connective tissue diseases (overlap syndromes). Other less common idiopathic myositides (i.e., granulomatous myositis) and infections will also be discussed in this chapter. DM and IBM are rather homogeneous clinically and histologically. On the other hand, what has been called "PM" in the literature is likely a heterogeneous group of disorders. It is important to emphasize that not all myopathies with inflammation are classified as the so-called "inflammatory myopathies." In this regard, various muscular dystrophies (e.g., congenital, facioscapulohumeral, and dysferlinopathies) may be associated with profound inflammation and are not uncommonly misdiagnosed as PM.

There are a few reports of DM, PM, and IBM occurring in parents, children, and siblings of affected patients, suggesting a genetic predisposition to developing these disorders, possibly secondary to inherited human leukocyte antigens (HLA) haplotypes.[6–9] There are hereditary forms of inclusion body *myopathy*, but with rare exceptions, the muscle biopsies in these cases lack inflammation and the clinical phenotype (i.e., age of onset and pattern of weakness) is different from sporadic IBM.[10]

The annual incidence of these disorders has been estimated to be around 1:100,000.[3,11] However, defining the actual incidence of the individual myositides has been limited by the different diagnostic criteria employed in various epidemiological studies. Most published papers regarding epidemiology and treatment of DM and PM have used Bohan and Peter criteria (Table 30–4).[12–14] PM will be overdiagnosed with Bohan and Peter criteria.[15,16] These criteria were fine in 1975, but as one can see, a muscle biopsy is not required for the diagnosis of PM and DM and the only feature that distinguishes PM from DM is the presence of a rash in DM. Further, the biopsy abnormalities as listed are nonspecific (except for perifascicular atrophy—a finding specific for DM but not seen in PM) and do not help in distinguishing PM from DM or for that matter any myopathy with necrosis, including muscular dystrophies. Importantly, the histological criteria do not take into account the advances in histopathology, particularly in regard to immunohistochemistry. It is now appreciated that DM is a humorally mediated microangiopathy, while PM is an HLA-restricted, antigen-specific, cell-mediated immune response directed against muscle fibers.[1,17]

Criteria for diagnosis of DM and PM need to take into account the advances in understanding of the pathogeneses of the inflammatory myopathies. We emphasize that DM is not simply PM with a rash (or the converse: PM is not DM without a rash) and IBM is not PM with inclusions (or the converse: IBM is not PM with inclusions). For this reason, revised criteria for the various idiopathic inflammatory myopathies have been devised to take into account the recent advancements in the field (Tables 30–2 and 30–3).[5,10] For definitive histopathological diagnosis of PM in the biopsy, we like to see endomysial infiltrates composed of CD8+ T cells and macrophages invading *non-necrotic* muscle fibers that express major histocompatibility-1 (MHC-1) antigen.[5,17,18] Even so, this biopsy feature is not diagnostic for PM, as it also is seen in IBM and rarely in dystrophies. Likewise, perivascular and perimysial inflammations are nonspecific and can be found in DM, PM, IBM, dystrophies, and, even occasionally, normal muscle biopsies. With the caveats noted above, we will begin our discussion of the individual inflammatory myopathies.

▶ DERMATOMYOSITIS

CLINICAL FEATURES

DM can present at any age, including infancy. Similar to most other autoimmune disorders, there is an increased incidence of DM in women compared to men.[11,19] Although the pathogenesis of childhood and adult DM is presumably similar, there are important differences in some of the clinical features and associated disorders. Weakness can develop rather acutely (over several weeks), or insidiously (over months).[13,20,21] Proximal leg and arm muscles are usually the earliest and most severely affected muscle groups. Thus, the earliest patient complaints are often difficulty lifting their arms over their heads, climbing steps, and arising from chairs. Distal muscles are also involved. Children are more likely to present with an insidious onset of muscle weakness and myalgias that are often preceded by fatigue, low-grade

▶ TABLE 30–1. IDIOPATHIC INFLAMMATORY MYOPATHIES: CLINICAL AND LABORATORY FEATURES

Disorder	Sex	Age of Onset	Rash	Pattern of Weakness	Serum CK	Muscle Biopsy	Cellular Infiltrate	Response to IS Therapy	Common Associated Conditions
DM	F > M	Childhood and adult	Yes	Proximal > distal	Increased (up to 50× normal)	Perimysial and perivascular inflammation; MXA, MAC, Ig, and C deposition on vessels	CD4+ dendritic cells; B cells; macrophages	Yes	Myocarditis, interstitial lung disease, malignancy, vasculitis, and other connective tissue diseases
PM	F > M	Adult	No	Proximal > distal	Increased (up to 50× normal)	Endomysial inflammation	CD8+ T cells; macrophages; plasma cells	Yes	Myocarditis, interstitial lung disease, and other connective tissue diseases
IBM	M > F	Elderly (> 50 yr)	No	Proximal and distal; predilection for: finger/wrist flexors, knee extensors	Normal or mildly increased (<10× normal)	Endomysial inflammation; rimmed vacuoles; amyloid deposits; EM: 15–18 nm tubulofilaments	CD8+ T cells; macrophages; plasma cells	None or minimal	Neuropathy; autoimmune disorders—uncommon

DM, dermatomyositis; PM, polymyositis; IBM, inclusion body myositis; F, female; M, male; IS, immunosuppressive; Ig, immunoglobulin; MAC, membrane attack complex; C, complement, CK, creatine kinase; MXA, interferon-α-β-inducible protein myxovirus resistance 1.
From Amato AA, Barohn RJ. Idiopathic inflammatory myopathies. Neurol Clin 1997;15:615–648, with permission.

▶ TABLE 30–2. DIAGNOSTIC CRITERIA FOR INCLUSION BODY MYOSITIS

I. Characteristic features—inclusion criteria
  A. Clinical features
    1. Duration of illness >6 months
    2. Age of onset >30 yr
    3. Muscle weakness
    4. Must predominantly affect proximal and distal muscles of the arms *and* legs and the patient muscle exhibit at least one of the following features:
      a. Finger flexor weakness
      b. Wrist flexor > wrist extensor weakness
      c. Quadriceps muscle weakness (+ or < MRC grade 4)
  B. Laboratory features
    1. Serum creatine kinase < 12 times normal
    2. Muscle biopsy
      a. Inflammatory myopathy characterized by mononuclear cell invasion of non-necrotic muscle fibers
      b. Vacuolated muscle fibers
      c. Either
        i. Intracellular amyloid deposits (must use fluorescent method of identification before amyloid excluded) or
        ii. 15–1-nm tubulofilaments by electron microscopy
    3. Electromyography must be consistent with features of an inflammatory myopathy (however, long-duration potentials are commonly observed and do not exclude the diagnosis of inclusion body myositis [IBM])
  C. Family history: Rarely, IBM may be observed in families. This condition is different from hereditary inclusion body *myopathy* without inflammation. The diagnosis of familial IBM requires specific documentation of mononuclear inflammatory cells invading non necrotic muscle fibers by muscle biopsy in addition to vacuolated muscle fibers and intracellular amyloid deposits or 15–18-nm tubulofilaments
II. Associated disorders: IBM occurs with a variety of other, especially immune-mediated conditions. An associated condition does not preclude a diagnosis of IBM if the diagnostic criteria are fulfilled
III. Diagnostic criteria for IBM
  A. *Definite* IBM
    1. Patients' muscle exhibit all muscle biopsy features including invasion of non-necrotic muscle fibers by mononuclear cells, vacuolated muscle fibers, and intracellular amyloid deposits or 15–18-nm tubulofilaments
    2. None of the other clinical or laboratory features are mandatory if the muscle biopsy features are diagnostic
  B. *Possible* IBM: If the muscle biopsy shows only inflammation (invasion of non-necrotic muscle fibers by mononuclear cells) without other pathological features of IBM, then a diagnosis of possible IBM can be made if the patient exhibits the characteristic clinical (A1,2,3,4) and laboratory (B1,3) features.

With permission from Griggs et al. Ann Neurol 1995;38:705–713.

fevers, and a rash. Dysphagia occurs in approximately 30% of patients with DM probably due to involvement of oropharyngeal and esophageal muscles.[3] Speech, chewing, and swallowing difficulties can arise secondary to involvement of the masseter muscle. We have even seen dysarthria and speech as a result of involvement of the pharyngeal and the tongue muscles. Sensation is normal, and muscle stretch reflexes are preserved until a severe degree of weakness has developed.

DM is usually diagnosed earlier than other forms of myositis because of the characteristic rash, which typically accompanies or precedes the onset of muscle weakness.[1,3,20,22] However, the rash can develop years after the onset of weakness, which could lead to an erroneous diagnosis of PM. Some patients have the characteristic rash but never develop weakness (the so-called amyopathic DM or DM *sine* myositis).[23] Less well appreciated is the fact that rare patients who do not have an appreciable rash at the time present with weakness. We have seen some patients with histopathological features characteristic of DM who have developed the rash months or years after onset of weakness or not at all (adermatopathic DM or DM *sine* dermatitis). These patients would be erroneously classified as PM using Bohan and Peter criteria.[12,13,15] We suspect that there is a spectrum of DM. Most patients have both skin and muscle involvement, but on either end of the spectrum are rare patients who have only muscle or skin involvement.

The classical skin manifestations include a purplish discoloration of the eyelids (heliotrope rash) often associated with periorbital edema and a papular, erythematous rash over the knuckles (Gottron papules) (Fig. 30–1).[22] In addition, an erythematous, macular, sun-sensitive rash may appear on the face, neck and anterior chest (V-sign), shoulders and upper back (shawl sign), hips (holster sign), and extensor surfaces of elbows, knuckles, knees, and malleoli (Gottron sign). The nail beds often have dilated capillary loops occasionally with thrombi or hemorrhage. The skin lesions can be subtle at

▶ TABLE 30–3. DIAGNOSTIC CRITERIA FOR POLYMYOSITIS, DERMATOMYOSITIS, IMMUNE-MEDIATED NECROTIZING MYOPATHY, AND NONSPECIFIC/UNSPECIFIED MYOSITIS

I. *Polymyositis (PM)*
  1. Clinical features
    a. Inclusion criteria
      i. Onset usually over 18 yr (post puberty)
      ii. Subacute or insidious onset
      iii. Pattern of weakness: symmetric proximal > distal weakness
    b. Exclusion criteria
      i. Clinical features of IBM (see Griggs et al.: asymmetric weakness, wrist/finger flexors same or worse than deltoids; knee extensors and/or ankle dorsiflexors same or worse than hip flexors)
      ii. Ocular weakness, isolated dysarthria, neck extensor > neck flexor weakness
    c. Exposure to myotoxic drugs, active endocrinopathy (hyper- or hypothyroid and hyperparathyroid), amyloidosis, family history of muscular dystrophy or proximal motor neuropathies (e.g., SMA)
  2. Serum creatine kinase level must be elevated
  3. Other laboratory criteria (one of three): EMG criteria, skeletal muscle MRI, or presence of myositis-specific antibodies
    a. Electromyography:
      i. Inclusion criteria
        • Increased insertional and spontaneous activity in the form of fibrillation potentials, positive sharp waves, or complex repetitive discharges
        • Morphometric analysis reveals the presence of short-duration, small-amplitude, polyphasic MUAPs
      ii. Exclusion criteria
        • Prominent myotonic discharges that would suggest proximal myotonic dystrophy or other channelopathy
        • Morphometric analysis reveals predominantly long-duration, large-amplitude MUAPs
        • Decreased recruitment pattern of MUAPs
    b. Skeletal muscle MRI shows diffuse or patchy increased signal (edema) within muscle tissue on STIR images
    c. Myositis-specific antibodies are detected in the serum
  4. Muscle biopsy
    a. Definite PM requires endomysial inflammatory cell infiltrate (T cells) surrounding and invading non-necrotic muscle fibers
    b. Probable PM
      i. Endomysial CD8+ T cells surrounding and but no definite invasions of non-necrotic muscle fibers
      or
      ii. Ubiquitous MHC-1 expression
      iii. Also requires exclusion of "necrotizing myopathies" and dystrophies with immunopathology/electron microscopy and clinical history/examination
    c. Exclusion criteria
      i. Rimmed vacuoles, ragged red fibers, cytochrome oxidase-negative fibers that would suggest IBM
      ii. Perifascicular atrophy, deposition of MAC on small blood vessels, reduced capillary density, tubuloreticular inclusions in endothelial cells, or pipestem capillaries that would suggest dermatomyositis (DM) or another type of humorally mediated microangiopathy
      iii. Dystrophic features or MAC deposition on non-necrotic muscle fibers that would suggest a muscular dystrophy

  A. Definite PM
    1. All clinical criteria
    2. Elevated serum CK
    3. Muscle biopsy with features of histological features of definite PM
  B. Probable PM
    1. All clinical criteria
    2. Elevated serum CK
    3. Other laboratory criteria (one of three)
    4. Muscle biopsy with features of histological features of probable PM

II. *Dermatomyositis (DM)*
  1. Clinical features
    a. Inclusion criteria
      i. Onset in childhood (juvenile DM) or adulthood (adult DM)
      ii. Subacute or insidious onset
      iii. Pattern of weakness: symmetric proximal legs > arms, neck flexors > neck extensors
      iv. Rash suggestive of DM: heliotrope, Gottron papules/sign, V-sign, shawl sign, holster sign

(*continued*)

▶ **TABLE 30–3. (CONTINUED)**

b. Exclusion criteria
   i. Ocular weakness, isolated dysarthria, neck extensor > neck flexor weakness
   ii. Exclusion of other causes of weakness (see PM clinical exclusion criteria)

2. Muscle biopsy:
   a. Definite DM requires perifascicular atrophy
   b. Probable DM requires:
   Myxovirus resistance 1 protein (or other type 1 interferon regulated proteins) deposition on small blood vessels or muscle fibers
   Or
   MAC deposition on small blood vessels
   Or
   Reduced capillary density
   Or
   Tubuloreticular inclusions in endothelial walls on EM
   Or
   MHC-1 expression of perifascicular fibers
   Or
   Perivascular, perimysial inflammatory cell infiltrate (this is a nonspecific abnormality in and of itself)

A. Definite DM
   1. All clinical criteria
   2. Muscle biopsy demonstrates perifascicular atrophy

B. Probable DM
   1. All clinical criteria
   2. Muscle biopsy fulfills probable DM histological criteria or elevated serum CK or other laboratory criteria (one of three: EMG, MRI, or MSA)

C. Amyopathic DM
   1. Rash typical of DM: heliotrope, Gottron papules/sign, V-sign, shawl sign, and holster sign
   2. Skin biopsy demonstrates a reduced capillary density, deposition of MAC on small blood vessels along the dermal–epidermal junction, and variable keratinocyte decoration for MAC
   3. No subjective or objective muscle weakness
   4. Normal serum CK
   5. Normal EMG

D. Possible DM *sine* dermatitis
   1. Clinical criteria but classic DM rash is absent
   2. Muscle biopsy demonstrates:
   Perifascicular atrophy
   Or
   MxA deposition on small blood vessels or muscle fibers
   Or
   MAC deposition on small blood vessels
   Or
   Reduced capillary density
   Or
   Tubuloreticular inclusions in endothelial walls on EM
   Or
   MHC-1 expression of perifascicular fibers
   3. Elevated CK plus other laboratory criteria (one of three: EMG, MRI, or MSA)

III. *Nonspecific/unspecified myositis*
   1. Clinical features
      a. Inclusion criteria
         i. Onset in childhood or adulthood
         ii. Subacute or insidious onset
         iii. Pattern of weakness: symmetric proximal > distal weakness
      b. Exclusion criteria: Rash typical of DM; PM clinical exclusion criteria

(*continued*)

▶ **TABLE 30–3. (CONTINUED)**

2. Muscle biopsy
   a. Perivascular, perimysial inflammatory cell infiltrate but there is no perifascicular atrophy, perifascicular MHC-1 expression, MAC deposition on small blood vessels, reduced capillary density, or tubuloreticular inclusions on EM
   Or
   b. Scattered endomysial CD8+ T cells infiltrate but that does not clearly surround or invade muscle fibers
   And
   c. Requires exclusion of "necrotizing myopathies," dystrophies, and "possible IBM" with immunopathology/electron microscopy and clinical history/examination
3. Serum creatine kinase (CK) level is elevated
4. Other laboratory criteria (one of three): EMG criteria, skeletal muscle MRI, or presence of myositis-specific antibodies

IV. *Immune-mediated necrotizing myopathy*
1. Clinical features
   a. Inclusion criteria
      i. Onset usually over 18 yr (post puberty)
      ii. Subacute or insidious onset
      iii. Pattern of weakness: symmetric proximal > distal weakness
   b. Exclusion criteria: Rash typical of DM; PM clinical exclusion criteria
2. Muscle biopsy
   a. The predominant abnormal histological feature of the muscle biopsy is the presence of many necrotic muscle fibers
   b. Inflammatory cells are sparse or only slightly perivascular; perimysial infiltrate is evident
   c. MAC deposition on small blood vessels may be seen
   d. Tubuloreticular inclusions in endothelial cells are uncommon or not evident
   e. Pipestem capillaries may be evident on EM
   f. No evidence of mononuclear inflammatory cells invading non-necrotic muscle fibers
   g. No perifascicular atrophy
3. Serum CK level must be elevated
4. Other laboratory criteria (one of three): EMG criteria, skeletal muscle MRI, or presence of myositis-specific antibodies

IBM, inclusion body myositis; MRI, magnetic resonance imaging; DM, dermatomyositis; MUAP, motor unit action potential; MHC-1, major histocompatibility-1; MAC, membrane attack complex; CK, creatine kinase; EM, electron microscopy; MSA, myositis-specific antibody; MxA, myxovirus resistance 1 protein.
Modified with permission from Griggs RC, Askanas V, et al. Inclusion body myositis and myopathies. Ann Neurol 1995;38(5):705–713; and Hoogendijk JE, Amato AA, et al. 119th ENMC international workshop: Trial design in adult idiopathic inflammatory myopathies, with the exception of inclusion body myositis, 10–12 October 2003, Naarden, the Netherlands. Neuromuscul Disord 2004;14(5): 337–345.

times and difficult to appreciate in individuals who are darker skinned—another common reason for misdiagnosing patients with PM rather than DM.

Subcutaneous calcifications occur in 30–70% of children, but in our experience these are less common in adults.[24,25] These lesions tend to develop over pressure points (buttocks, knees, and elbows) and can be complicated by ulceration of the overlying skin. Once the calcinosis appears, treatment is very difficult. Colchicine, probenecid, warfarin, and phosphate buffers have been tried with limited success. Surgery may be performed, but the lesions may recur or worsen.

ASSOCIATED MANIFESTATIONS

Cardiac

Conduction defects, arrhythmias, ventricular and septal wall motion abnormalities, and reduced ejection fractions may be seen on electrocardiograms, echocardiography, and radionucleotide scintigraphy.[20,21,26–30] Nevertheless, most patients do not develop any cardiac symptoms. However, pericarditis, myocarditis, and congestive heart failure can occasionally develop secondary to involvement or cardiac muscle and may be lethal.[20,28]

Pulmonary

Interstitial lung disease (ILD) complicates approximately 10–20% of patients with DM.[20,31–34] Rarely, patients develop bronchiolitis obliterans with organizing pneumonia. ILD manifests clinically as dyspnea and nonproductive cough. It can begin abruptly or insidiously and even precede the development of the characteristic rash and muscle weakness. Chest radiographs reveal a diffuse reticulonodular pattern with a predilection for involvement at the lung bases. A diffuse alveolar pattern or ground-glass appearance is seen in the more fulminant cases.[31] A restrictive defect with reduced forced vital capacity and decreased diffusion capacity are evident on pulmonary function tests. Antibodies directed against t-histidyl transfer RNA synthetase, the so-called Jo-1 antibodies, are present in at least 50% of ILD cases associated with inflammatory myopathies.[35–37] A less common pulmonary complication is aspiration pneumonia due to oropharyngeal and esophageal weakness.

▶ TABLE 30–4. BOHAN AND PETER CRITERIA FOR PM AND DM

1. Symmetrical weakness of the limb-girdle muscles and anterior neck flexors, progressing over weeks to months, with or without dysphagia or entilatory muscle involvement
2. Muscle biopsy evidence of necrosis of myofibers, phagocytosis, regeneration with basophilia, and large vesicular sarcolemmal nuclei, prominent nucleoli, atrophy in a perifascicular distribution, variation in fiber size, and an inflammatory exudate, often perivascular.
3. Elevation in serum skeletal muscle enzymes, particularly the CK and often aldolase AST, ALT, and LDH.
4. EMG triad of short, small polyphasic motor units; fibrillation potentials; positive sharp waves; insertional irritability; and complex repetitive discharges

Three of four of the above features are needed for a diagnosis of PM. The diagnosis of DM is made if the patient also has characteristic rash.
PM, polymyositis; DM, dermatomyositis; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Gastrointestinal

Involvement of the skeletal and smooth muscles of the gastrointestinal tract can lead to dysphagia, aspiration, and delayed gastric emptying. Vasculopathy affecting of the gastrointestinal tract is serious complication that appears to be much more common in juvenile DM compared to adult DM. The vasculopathy can result in mucosal ulceration, perforation, and life-threatening hemorrhage.

Joints

Arthralgias of large and small joints with or without arthritis are common. Joint and muscle pain often eases when the limbs are flexed, and this can lead to the formation of flexion contractures across the major joints. This emphasizes the importance of early physical therapy and range of motion exercises to prevent contractures from developing. Flexion contractures at the ankles leading to toe walking are a common early finding in childhood DM.

Vasculopathy

A vasculopathy affects the skin, muscle, and gastrointestinal system. Rarely, massive muscle infarction can lead to myoglobinuria and acute renal tubular necrosis.

Malignancy

There is an increased incidence of cancer ranging from 6% to 45% in DM.[13,14,20,21,38,39] The association with cancer has not been demonstrated in juvenile DM and the increased risk is predominantly seen in adults over the age of 40 years. Although women are more likely to develop DM than men, the risk of malignancy is equal in both sexes. Most malignancies are identified within 2 years of the presentation of the myositis. The clinical severity of rash or muscle weakness does not appear to correlate with the presence or absence of a neoplasm. Treatment of the underlying malignancy sometimes results in improvement of muscle strength.

We perform a comprehensive history and annual physical examinations with breast and pelvic examinations for women and testicular and prostate examinations for men to search for an underlying malignancy. In addition, we obtain a complete blood count (CBC), routine blood chemistries, urinalysis, and stool specimens for occult blood. Chest, abdominal, and pelvic computerd tomography (CT) scans, and mammogram are also ordered. Colonoscopy should be done on all patients over the age of 50 years or in those who have attributable gastrointestinal symptoms (e.g., abdominal pain, constipation, and blood in the stool).

LABORATORY FEATURES

Necrosis of muscle fibers usually leads to increases in serum creatine kinase (CK), aldolase, myoglobin, lactate dehydrogenase, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels. Serum CK is the most sensitive and specific marker for muscle damage and is elevated in at least 90% of patients with DM.[13,20,21] However, serum CK levels do not correlate with the severity of weakness and can be normal even in individuals who are markedly weak, particularly in childhood DM and in patients with slow, insidious disease. Rarely, an aldolase level is elevated while the serum CK is still within normal limits. Erythrocyte sedimentation rate (ESR) is usually normal or only mildly elevated and is not a reliable indicator of disease severity.

Antinuclear antibodies (ANAs) are detected in 24–60% of patients with DM.[20,36,37] These antibodies are much more common in patients with overlap syndromes (to be discussed later). Some patients have the so-called "myositis-specific antibodies" (MSAs).[20,36,37,40–44] These antibodies may be useful in predicting response to therapy and prognosis. However, the MSAs are found in a minority of patients with inflammatory myopathy and have never been studied prospectively in regard to their predictive value. These antibodies have not been demonstrated to be pathogenic themselves, and they may represent an epiphenomon.

The MSAs include (1) the cytoplasmic antibodies directed against translational proteins (i.e., various tRNA synthetases and the antisignal recognition particle) and (2) those directed against Mi-2 and Mas antigens. The most common of the antisynthetases are Jo-1 antibodies, which are associated with ILD and demonstrated in as many as 20% of patients with inflammatory myopathy.[35–37] The other antisynthetases are much less common and are each found in <23% of patients

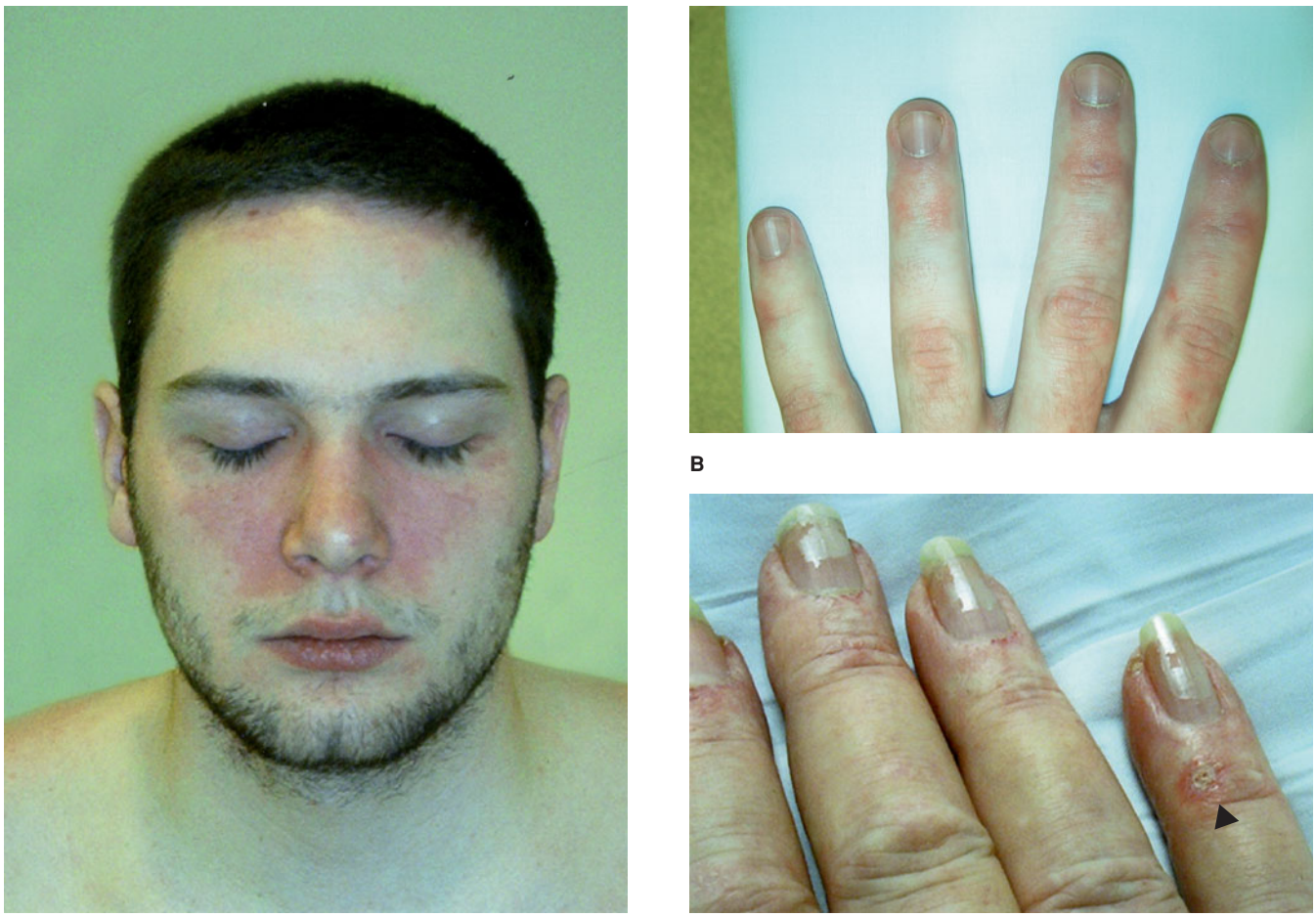


Figure 30–1. Dermatomyositis. Moderate erythematous rash is appreciated along the hairline of the scalp, the malar region of the face, and the eyelids—later the heliotrope rash (A). Macular erythematous rash is seen over the extensor surface of the knuckles (Gottron's sign) (B). Dilated capillary loops are evident in the nail bed changes as well as a small ulceration involving the distal aspect of the little finger (C).

with inflammatory myopathy. It has been suggested that the presence of Jo-1 antibodies is associated with only a moderate response to treatment and a poor long-term prognosis.[42,44] However, there has not been a prospective study of treatment outcomes comparing patients with myositis ILD and with Jo-1 antibodies with patients without these antibodies.

Mi-2 antibodies are found in 15–20% of patients with DM. Mi-2 is a 240-kD nuclear protein of unknown function. The Mi-2 antibodies are associated with an acute onset, a florid rash, a good response to therapy, and a favorable prognosis.[36,37,42,44,] However, again it is not known whether patients with DM with Mi-2 antibodies respond differently than patients with DM without the antibody.

Magnetic resonance imaging (MRI) can provide information on the pattern of muscle involvement by looking at the cross-sectional area of axial and limb muscles.[45–49] MRI may demonstrate signal abnormalities in affected muscles secondary to inflammation and edema or replacement by fibrotic tissue. Some have advocated MRI as a method to guide which muscle to biopsy.[49,50] However, we have found that MRI usually adds little to a good clinical examination and EMG in defining the pattern of muscle involvement and determination which muscle to biopsy.

ELECTROPHYSIOLOGICAL FEATURES

The characteristic electromyography (EMG) abnormalities observed in patients with myositis include (1) increased insertional and spontaneous activity with fibrillation potentials, positive sharp waves, and occasionally pseudomyotonic or complex repetitive discharges; (2) small-duration, low-amplitude, polyphasic motor unit action potentials (MUAPs); and (3) MUAPs that recruit early but at normal frequencies.[51] Recruitment may be decreased (fast firing MUAPs) in advanced disease if there is marked loss of muscle fibers.

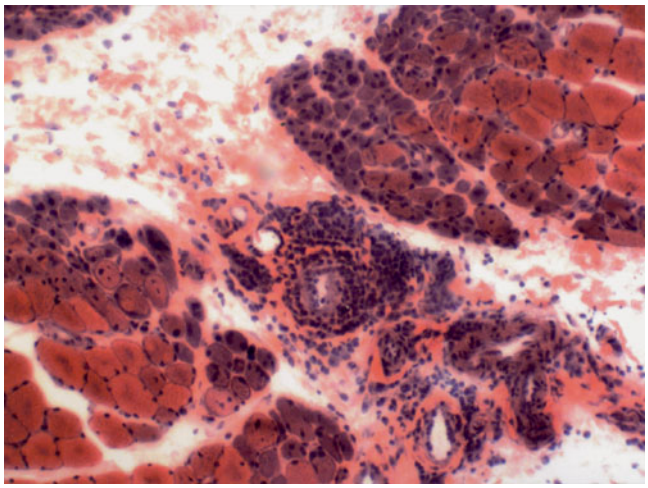


Figure 30–2. Dermatomyositis. Muscle biopsy demonstrates classic perifascicular atrophy of muscle fibers and perivascular inflammation within the perimysium. Hematoxylin and eosin (H&E).

Decreased insertional activity may be seen in chronic disease secondary to fibrosis. In addition, large-duration, polyphasic MUAPs may also be evident later in long-standing disease due to muscle fiber splitting and regeneration rather than a superimposed neurogenic process.

The degree of abnormal spontaneous EMG activity reflects the ongoing disease activity. EMG can be used to assist determining which muscle to biopsy in patients with only mild weakness. In addition, EMG may also be useful in the assessment of previously responsive patients with myositis who become weaker by differentiating an increase in disease activity from weakness secondary to type 2 muscle fiber atrophy from disuse or chronic steroid administration. Abnormal insertional and spontaneous activity is expected in active myositis, while isolated type 2 muscle fiber atrophy is not associated with such abnormal activity on EMG. Along these lines, it is our opinion that a multifocal or diffuse pattern of abnormal insertional and spontaneous activity without obvious changes in MUAP morphology or recruitment is much more likely to represent an acute myopathy like DM than a neurogenic disorder.

HISTOPATHOLOGY

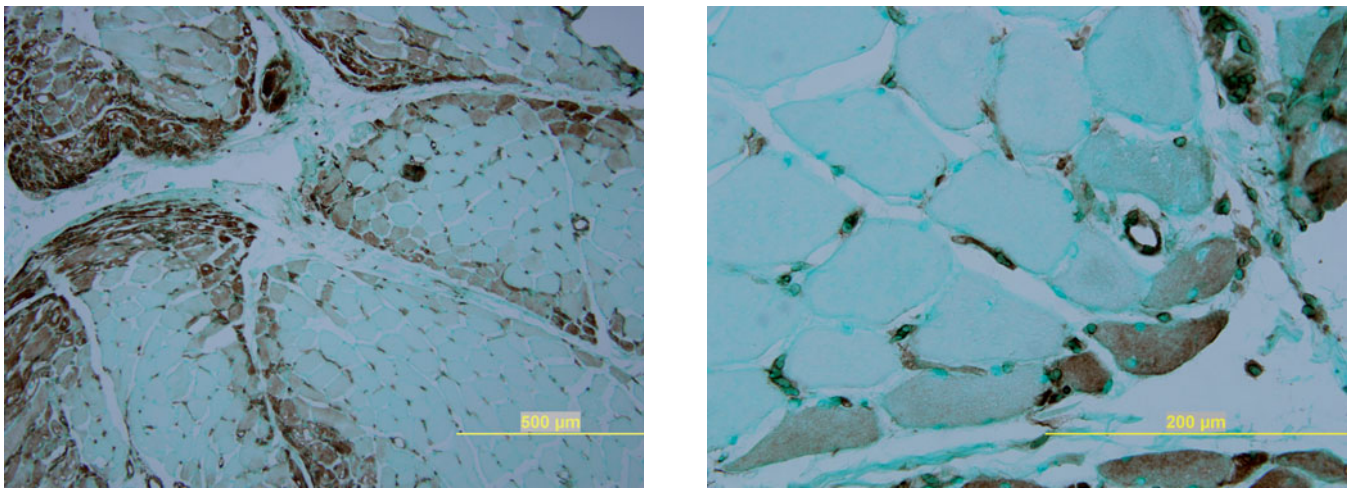
The pathological process is multifocal, and the frequency and severity of histologic abnormalities can vary within the muscle biopsy specimens. The pathognomonic histologic feature is perifascicular atrophy (Fig. 30–2), although this is a late finding and in our experience is found in <50% of patients. The perifascicular area contains small regenerating and degenerating fibers. Oxidative enzyme stains highlight the microvacuolation within these fibers. Scattered necrotic fibers and wedged-shaped microinfarcts may be evident. However, occasionally inflammatory cell infiltrates are not evident with routine histochemistry. The inflammatory infiltrate is composed primarily of macrophages, B cells, and CD4+ cells in the perivascular and perimysial regions around blood vessels (perivascular).[18,52] Recent studies have demonstrated that there are many more CD4+ cells in the endomysium than previously appreciated and that these are, for the most part, plasmacytoid dendritic cells (PDCs) and not T-helper cells.[53] Importantly, in contrast to PM and IBM (discussed later), invasion of non-necrotic fibers is not prominent. Muscle fibers express MHC-1 antigen, STAT1, and interferon-α/β-inducible protein myxovirus resistance 1 (MxA) (Fig. 30–3) on the sarcolemma, particularly in the perifascicular regions, and can be seen even before the development of perifascicular atrophy.[53]

DM is an immune-mediated microangiopathy and is associated with a reduction in the capillary density (number of capillaries per area of muscle) and compensatory dilation of the remaining small vessels.[54] One of the earliest demonstrable histologic abnormalities in DM is deposition of the C5b-9 complement membrane attack complex (MAC) around small blood vessels (Fig. 30–4).[54–56] Deposition often MAC precedes inflammation and other structural abnormalities (e.g., perifascicular atrophy) in the muscle on light microscopy and is relatively specific for DM.[54] Other complement components (C3 and C9) and immunoglobulins (IgM and less often IgG) are also deposited on or around the walls of intramuscular blood vessels.[57] These observations have led to the hypothesis that DM is caused by deposition of immunoglobulins on capillaries, subsequent activation of complement, and MAC-induced necrosis of the vessels, which then lead to ischemic damage of muscle. However, as discussed in the "Pathogenesis" section, this hypothesis is purely speculative and may in fact be wrong. In addition to expression of MxA on muscle fibers, MxA also is expressed on capillaries in DM (Fig. 30–3).

Electron microscopy (EM) reveals small intramuscular blood vessels (arterioles and capillaries) with endothelial hyperplasia, microvacuoles, and tubuloreticular cytoplasmic inclusions.[7,58]

PATHOGENESIS

The immunological studies and other histological features on muscle biopsies suggest that DM is a humorally/complement mediated microangiopathy, although this is far from proven.[59] Although the presence of MAC is well established, its frequency is not, and this is important with regard to the possibility of varied mechanisms of disease and distinct subtypes of DM. Its presence on blood vessels could be due to either immune complex deposition, or complement activation by either the classical antibody-mediated or the alternative pathways.



A B

Figure 30–3. Dermatomyositis. Immunoperoxidase stain reveals the expression of the interferon-α/β-inducible myxovirus resistance 1 (MxA) protein on perifascicular muscle fibers (A) as well as small arterioles and capillaries (B).

Even classical pathway activation, which is antibody-dependent, can still be relatively antigen nonspecific; some IgM antibodies are highly polyclonal, binding with low avidity to many self-antigens. The specificity of MAC presence is also in question, as it is present in abnormal vascular tissue (e.g., atherosclerotic coronary arteries). It may be that the microvasculature is damaged by some other mechanism (e.g., interferon- or other cytokine-related toxicity), and the deposition of immunoglobulins and complement on the damaged vascular tissue might be secondary phenomena. The fact that some patients have developed DM with hereditary complement deficiencies argues against primary destruction of capillaries by complement and MAC.[60,61]

The microangiopathy has been postulated to cause ischemic damage and occasionally infarction of muscle fibers. It has been suggested that the perifascicular atrophy is the result of hypoperfusion to the watershed region of muscle fascicles. However, it has never been demonstrated that the perifascicular region is indeed the watershed area in muscle fibers and such perifascicular fibers are more prone to ischemic damage.[62] Perifascicular atrophy and endomysial capillary MAC deposition were found, in one study, to be inversely correlated,[55] and another study found no correlation between perifascicular atrophy and capillary depletion.[54] Furthermore, perifascicular atrophy has not been reported in vasculitis, a condition with known muscle ischemia and infarction, nor has perifascicular atrophy been found in experimental models of skeletal muscle ischemia.[62] In another model of ischemic myopathy, resulting from microarterial embolization with particles 20–80 µm in diameter, the pathological changes were located centrally within fascicles and the perifascicular regions were instead preferentially spared.[63] In addition, perifascicular atrophy is not evident in ischemic muscle damaged from vasculitis or in animal models of small vessel ischemia.

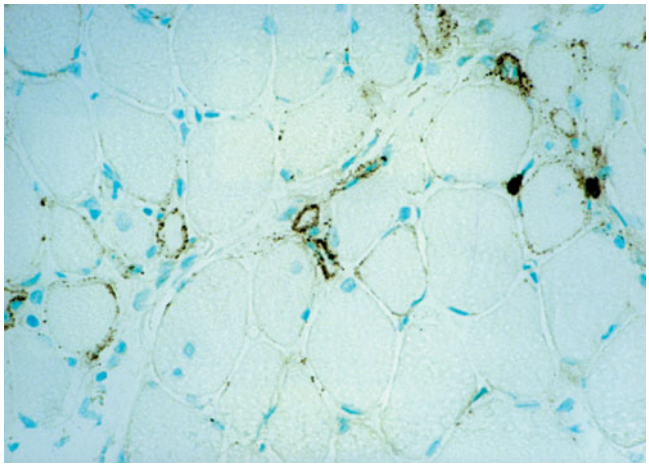


Figure 30–4. Dermatomyositis. Immunoperoxidase stain demonstrates deposition of membrane attack complex (MAC) around small blood vessels and capillaries.

Gene microarray studies of biopsied muscle tissue demonstrate an increased expression of genes induced by type 1 interferons.[53,64,65] Although this is not specific, it is compatible with the hypothesis of a viral infection triggering the autoimmune attack as interferon-α has a well-defined role in antiviral innate immunity. However, there are other possibilities. Interferon-α is synthesized by PDCs in response to a serum factor(s) containing immune complexes of antibody, double-stranded DNA, or RNA viruses. Abundant PDCs are evident in the muscle biopsies of patients with DM.[53] PDCs are CD4+ and comprise a large component of the inflammatory cell infiltrate in DM. These CD4+ cells were originally thought to be CD4+ T-helper cells, but a recent study demonstrated that most are CD3- and thus are PDC and

not lymphocytes. Increased expression of interferon-α/β-inducible protein MxA is evident on blood vessels and muscle fibers (with a predilection for the perifascicular fibers). Interestingly, one postulated function of MxA is to form tubuloreticular inclusions around RNA viruses. These inclusions have the same morphology as the tubuloreticular inclusions seen on EM in blood vessels in DM. Using immunoelectron microscopy, MxA was demonstrated within inclusions in vessels in DM muscle biopsies.[53] Interestingly, increased expression of type 1 interferon regulated genes are also evident in the peripheral blood of patients with active dermatomyositis, similar to what has been described in systemic lupus erythematosus. Further, the levels of expression in the blood appears to correlate with disease activity. We suspect that dysregulated interferon-α/β production plays a major role in the pathogenesis of DM and could be directly toxic to the small blood vessels and muscle fibers themselves.

PROGNOSIS

In absence of malignancy, prognosis is generally favorable in patients with DM. Poor prognostic features are increased age, associated ILD, cardiac disease, and late or previous inadequate treatment with 5-year survival rates ranging from 70% to 93%.[21,42,66,67]

▶ POLYMYOSITIS

PM, as reported in the literature, is likely to be a heterogeneous group of disorders rather than a distinct entity. A major source of debate among clinicians who primarily take care of patients with PM (e.g., neurologists and rheumatologists) is the criteria for diagnosing PM. The most commonly employed criteria were developed by Bohan and Peter in 1975 (Table 30–4),[12,13] but these do not take into account advancements in our understanding of the immunopathogenesis of the various inflammatory myopathies or even the existence of IBM and immune-mediated necrotizing myopathy. Revised criteria for the various idiopathic inflammatory myopathies have been proposed (Tables 30–2 and 30–3).[5,10,17] For definitive histopathologic diagnosis of PM, these criteria require CD8+ T cells invading *non-necrotic* muscle fibers that express MHC-1 antigen.[5,17,18] Even so, this biopsy feature is not diagnostic for PM, as it also is seen in IBM and rarely in dystrophies. Further, mononuclear cell invasion of non-necrotic muscle fibers is uncommon in suspected cases of PM,[16] and some argue that it is not necessary for diagnosis of PM.[41,68] More frequently on biopsy we appreciate perivascular, perimysial inflammatory cell infiltrates or endomysial inflammatory cells, but no actual invasion on non-necrotic muscle fibers. Whether or not these cases represent "PM," with the absence of CD8+ T cells invading non-necrotic muscle fibers representing or a distinct type of inflammatory myopathy, is unclear. Such perivascular, perimysial inflammation is common, particularly in patients with overlap myositis, but can be seen in DM and IBM and, occasionally, in dystrophies.

For the various reasons listed above, it is impossible to extract from the literature the true incidence and prognosis of PM or its subtypes and the associated laboratory abnormalities, medical conditions (e.g., connective tissue disorder [CTD], ILD, myocarditis, and cancer). We need prospective trials using contemporary clinical, laboratory, and histopathological criteria for PM to address these issues.[5] Nevertheless, we will summarize the available literature regarding "PM."

CLINICAL FEATURES

PM generally presents in patients over the age of 20 years. Unlike DM, we have never seen a case of PM in a child. As in DM and other autoimmune disorders, PM is more prevalent in females.[11–13,20,21] The diagnosis of PM is often delayed compared to DM. As with DM, patients present with symmetric proximal arm and leg weakness that typically develops over several weeks or months. Distal muscles may also become involved but are not as weak as the more proximal muscles. Muscle pain and tenderness are frequently noted but these are not the primary symptoms—weakness is the primary complaint. Approximately one-third of patients complain of swallowing difficulties. Mild facial weakness occasionally may be demonstrated on examination. Sensation is normal and muscle stretch reflexes are usually preserved.

ASSOCIATED MANIFESTATIONS

The cardiac and pulmonary complications of PM are reportedly similar to that described in the DM section. Myositis with secondary congestive heart failure or conduction abnormalities occur in up to one-third of patients, but again histopathologic confirmation of definite PM using more up-to-date criteria is lacking in most of these studies.[20,21,26–30] Anti-signal recognition particle (SRP) antibodies have been associated with myocarditis and were felt to be specific for PM, although the histopathology is more often that of a necrotizing myopathy.[69,70] In studies in which detailed immunohistochemistries were performed, the biopsies were not suggestive of PM (i.e., inflammatory infiltrate was scant) and rather resembled DM in that there is an apparent microvasculopathy.[53,71] ILD has been reported to occur in at least 10% of patient with PM, with at least half having Jo-1 antibodies.[20,31–34,36,37,42,44] Muscle biopsies from patients with Jo-1 antibodies demonstrated features more characteristic of DM than PM in our experience.

Polyarthritis has been reported in as many as 45% of patients with PM at the time of diagnosis.[21] The risk of

malignancy with PM is lower than that seen in DM, but it may be slightly higher than expected in the general population.[14,21,38,39] Once again, the diagnosis of PM in these studies was not based on recent histopathological criteria,[5,17] so it is unclear if there actually is an increased risk of malignancy in PM.

LABORATORY FEATURES

Serum CK level is elevated fivefold or more in most PM cases.[13,14,20,21] Unlike DM and IBM (to be discussed later) in which the CK can be normal, the serum CK should never be normal in active PM. Serum CK can be useful in monitoring response to therapy but only in conjunction with the physical examination, as the CK level does not necessarily correlate with the degree of weakness. ESR is normal in most patients and does not correlate with disease activity or severity.

Positive ANAs are reportedly present in 16–40% of patients with PM.[13,20,21,36] However, again the exact relationship of ANAs and connective tissue diseases (CTD) in patients with histologically defined PM is unclear. The questionable relationships of MSAs to PM were previously addressed.

MRI may demonstrate signal abnormalities in affected muscles secondary to inflammation and edema or replacement by fibrotic tissue (Fig. 30–5).[45,47–49]

ELECTROPHYSIOLOGICAL FEATURES

EMG is usually abnormal in PM with increased insertional and spontaneous activity, small polyphasic MUAPs, and early recruitment.[51] These abnormal features do not distinguish PM from other inflammatory myopathies or myopathies with muscle membrane instability.

HISTOPATHOLOGY

The histologic features of PM are distinct from DM. The predominant histologic features in PM are variability in fiber size, scattered necrotic and regenerating fibers, and inflammatory cell infiltrate. However, as mentioned previously, the specific characteristics of this inflammatory cell infiltrate have been the subject of recent debate. Small studies of PM reported that muscle biopsies demonstrate CD8+ T cells and macrophages invading non-necrotic muscle fibers expressing MHC-1 antigen (Fig. 30–6).[5,17,18,52,72] Subsequently, some have argued that this histopathologic feature is required for the diagnosis of definite PM.[5,17] Others argue that invasion of non-necrotic muscle fibers is not necessary and perivascular, perimysial, or endomysial inflammation without actual invasion of non-necrotic muscle fibers can suffice for diagnosis of PM in the proper clinical context.[41,73] In our opinion, however, we feel that demonstrating invasion of non-necrotic endomysial muscle fibers by T cells is very helpful in making a definite diagnosis of PM on *histopathological* grounds, as perivascular, perimysial, and even endomysial inflammatory cell infiltrates can be seen in IBM, DM, and some dystrophies.

The endomysial inflammatory cells consist primarily of activated CD8+ (cytotoxic), *alpha, and beta* T cells and macrophages.[18,52,72] Rare cases of PM with CD4- and CD8-*gamma/delta* T-cell infiltrates have been

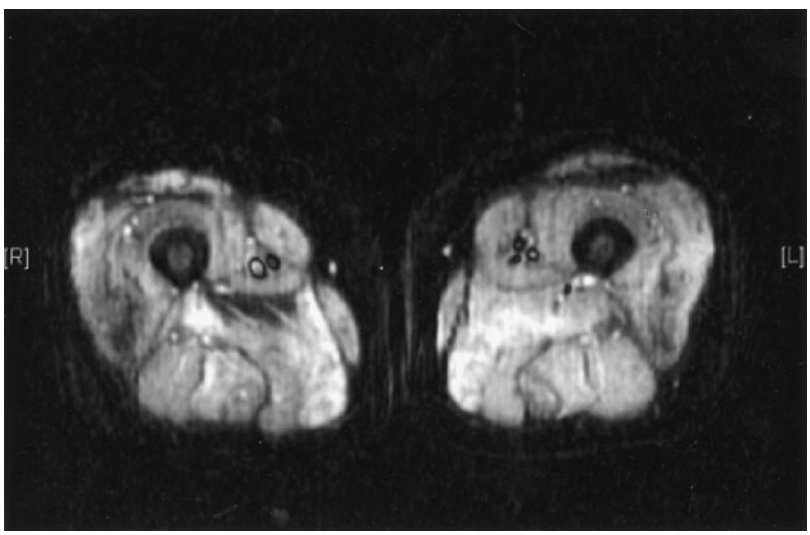


Figure 30–5. Polymyositis. Skeletal muscle MRI (STIR image) reveals patchy areas of increased signal consistent with edema/inflammation in the semitendinosis and semimembranosis in the posterior thigh and to a lesser extent in the quadriceps muscles on both legs.

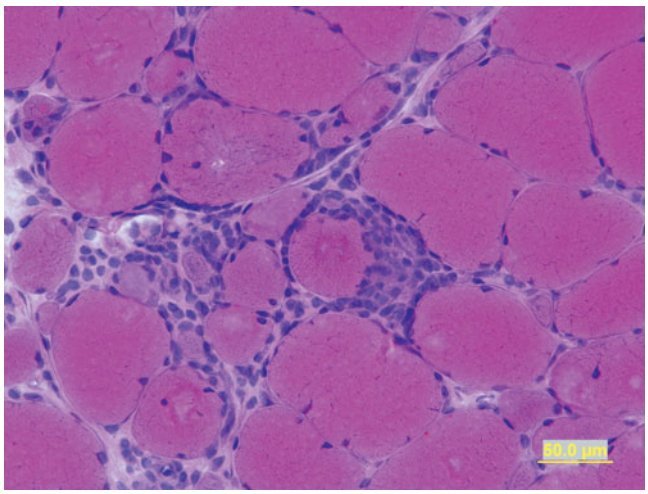


Figure 30–6. Polymyositis. Muscle biopsy demonstrates endomysial mononuclear inflammatory cell infiltrate surrounding and invading non-necrotic muscle fibers. H&E.

reported.[74,75] The T-cell receptors of endomysial T cells have an oligoclonal pattern of gene rearrangements and a restricted motif in the CD3R region, suggesting that the immune response is antigen specific.[76,77] Further, there are many myeloid dendritic cells in the endomysium that appear to surround non-necrotic muscle fibers and may serve to present antigens to cytotoxic T-cells. Although B cells are rare, plasma cells are common in the endomysium and likely account for the increased expression of immunoglobulin genes on microarray experiments.[78] There is also evidence of oligoclonal pattern of gene rearrangements plasma cells in PM muscle biopsies. Unlike DM, MAC, complement, or immunoglobulins are not deposited on the microvasculature in PM.

PATHOGENESIS

PM is believed to be the result of an HLA-restricted, antigen-specific, cell-mediated immune response directed against muscle fibers.[17] The trigger of this autoimmune attack is not known, but viral infections have been speculated. However, there is no conclusive evidence supporting this hypothesis.[79] MHC-1 molecules on the surface of cells usually express endogenous self-peptides rather than viral particles. Neither viral proteins nor DNA have been identified in muscle fibers. Thus, the autoimmune response may be directed against endogenous self-antigens rather than processed viral antigens. Nonetheless, a viral infection could indirectly trigger an immune response secondary to antigenic mimicry with muscle proteins, altering the expression of proteins on the surface of muscle fibers such that these become antigenic, or by the loss of physiologic self-tolerance. Myositis may complicate human immunodeficiency virus (HIV) and human T-lymphocyte virus-1 (HTLV-1) infections.[80] In these cases, the myositis appears to be the result of such indirect triggering of the immune response against muscle fibers.

The cytotoxic T cells appear to destroy muscle fibers via the perforin pathway. These autoinvasive T cells contain perforin granules oriented next to the sarcolemma of muscle fibers.[81] Upon release of these granules by exocytosis, pore formations are induced on the sarcolemma, leading to osmolysis of muscle fibers.

DIFFERENTIAL DIAGNOSIS

A diagnosis of PM relies on a thorough search to exclude other causes of weakness (Table 30–5).[15,82] A detailed clinical examination of an appreciation of the pattern of weakness can help differentiate IBM and muscular dystrophies with inflammation from PM. Serum CK must be elevated in PM, while it is normal in patients with "fibromyalgia" and polymyalgia rheumatica and can be normal in IBM. Skeletal muscle MRI is often interpreted as showing "myositis." However, these increased signal abnormalities are not specific and can be seen in dystrophies, rhabdomyolysis from toxic medications (e.g., statins) metabolic myopathy, and muscle infarcts from various causes (e.g., vasculitis and diabetic vasculopathy). The specific pattern of muscle involvement and extensive fatty replacement in absence of

▶ **TABLE 30–5. DISORDERS THAT CAN RESEMBLE POLYMYOSITIS**

Inclusion body myositis
Dermatomyositis *sine* dermatitis
Necrotizing myopathy
Inflammatory myopathy associated with infections (e.g., HIV, HTLV-1, and hepatitis B and C)
Muscular dystrophies (e.g., facioscapulohumeral, congenital, dysferlinopathies, and other limb-girdle dystrophies)
Proximal myotonic myopathy (myotonic dystrophy type 2)
Amyloid myopathy (light chain or familial)
Metabolic myopathy with rhabdomyolysis
Endocrine myopathies (e.g., hypothyroidism, hyperparathyroidism, and diabetic muscle infarction)
Drug-induced myopathies (e.g., cholesterol lowering agents, cyclosporine, chloroquine, amiodarone, colchicine, and D-penicillamine)
Juvenile or adult-onset spinal muscular atrophy (including Kennedy disease)
Polymyalgia rheumatica

HIV, human immunodeficiency virus; HTLV-1, human T-lymphocyte virus-1.
Modified with permission from Amato AA, Griggs RC. Unicorns, dragons, polymyositis, and other mythological beasts. Neurology 2003;61(3):288–289.

edematous changes on MRI scans would be helpful, suggesting a dystrophy as opposed to PM. EMG can be useful, as the presence of diffuse myotonic discharges should lead to the consideration of proximal myotonic myopathy—a condition that we have frequently seen misdiagnosed as PM.

Importantly, the diagnosis of PM requires a muscle biopsy. It is essential to look for histopathological features that would suggest IBM: rimmed vacuoles, eosinophilic inclusions, ragged red fibers, cytochrome oxidase negative fibers, amyloid deposits, and inclusions on EM. However, the absence of these findings does not exclude the diagnosis of IBM. Muscle biopsy is essential to look for features that might suggest a dystrophy, metabolic myopathy such as acid maltase deficiency, or necrotizing myopathy.

PROGNOSIS

Most patients with PM improve with immunosuppressive therapies but usually require life-long treatment.[20,42,66] Some retrospective studies suggest that PM does not respond to immunosuppressive agents as well as DM. However, interpretation of the results of these retrospective series is difficult, as the diagnosis of PM was usually made on the basis of Bohan and Peter criteria rather than on more current criteria based on strict clinical and histological criteria.

▶ OVERLAP SYNDROMES

The term "overlap syndrome" is applied when DM or PM is associated with other well-defined connective tissue diseases (CTDs) such as scleroderma, mixed connective tissue disease (MCTD), Sjögren syndrome, systemic lupus erythematosus (SLE), or rheumatoid arthritis.[1,3] In our experience[53,83,64] and others,[16] the muscle biopsies in patients with overlap syndrome resemble DM, a necrotizing myopathy, or are associated with nonspecific (e.g., perivascular and perimysial) inflammatory cell infiltrates as opposed to PM (at least if defined by CD8+ cells invading non-necrotic muscle fibers). The prognoses are related in part to the underlying CTD. Retrospective series of patients that suggest that myositis associated with overlap syndromes is more responsive to immunosuppressive treatment than isolated DM and PM, but again prospective studies are lacking.[20,35,42,66]

SCLERODERMA

Weakness is common in scleroderma. Most patients have normal serum CKs and EMG, while muscle biopsies demonstrate only mild variability in fiber size with atrophy of type 2 muscle fibers and perimysial fibrosis. However, 5–17% of patients with scleroderma have myositis which can occur in either of its two major forms—progressive systemic sclerosis or CREST (Calcinosis, Raynaud's phenomena, Esophageal dysmotility, Sclerodactyly, Telangiectasia) syndrome.[21,83–86] Patients with scleroderma-myositis have increased serum CK levels and irritable and myopathic EMGs. Detailed descriptions of the immunohistopathology on muscle biopsies are lacking, and therefore it is difficult to ascertain if these can have features of DM or PM.

Most patients with CREST syndrome have anticentromere antibodies, while anti-Scl-70 antibodies are common in patients with progressive systemic sclerosis. Some patients with scleroderma myositis have anti-PM-Scl (also called anti-PM-1) antibodies.[37,87]

SJÖGREN SYNDROME

Sjögren syndrome is characterized by dryness of the eyes and mouth (sicca syndrome) and other mucosal membranes. Muscle pain and weakness are common in Sjögren syndrome, but true myositis is rare. Muscle weakness is usually due to disuse atrophy secondary to arthritis and pain. Nonetheless, myositis can occur with Sjögren syndrome.[21,88–90] About 90% of patients have ANAs directed against ribonucleoproteins, specifically SS-A (Ro) and less commonly SS-B (La) antibodies.

SYSTEMIC LUPUS ERYTHEMATOSUS

SLE is an autoimmune disorder affecting multiple organ systems. As with other CTDs, weakness is not unusual in SLE but is most often the result of disuse atrophy. Nevertheless, myositis can occur with SLE.[21,53,91,92]

Most patients with SLE have positive ANA titers that are directed against native DNA (highly specific for SLE) and ribonuclear proteins (RNPs). The anti-RNP antibodies are present in less than half of patients with SLE and include anti-SS-A and anti-SS-B (also present in Sjögren's syndrome), anti-U1 RNP (also present in mixed connective tissue disease), and anti-Sm (specific for SLE).

Of note, gene expression studies in peripheral blood of patients with SLE demonstrated an upregulation of type 1 interferon-inducible genes, similar to what is seen in gene expression studies of muscle biopsies in DM.[53] In this regard, MxA is highly expressed in both SLE blood and DM muscle. Both disorders are also associated with tubular reticular inclusions in endothelial cells on EM. Thus, DM and SLE likely share a similar pathogenic basis with abnormalities involving the innate immune system.

RHEUMATOID ARTHRITIS

The most common etiology of weakness in RA is type 2 muscle fiber atrophy from chronic steroids or disuse secondary to arthritis, but myositis can infrequently occur.[21]

MIXED CONNECTIVE TISSUE DISEASE

Patients with MCTD have clinical features of scleroderma, SLE, rheumatoid arthritis, and myositis.[93] In terms of the myositis, DM is reported more commonly than PM.[21,53,83,93] This is certainly our experience. Necrotizing myopathy can also complicated MCTD. High titers of anti-U1 RNP antibodies are common in mixed connective tissue disease but are nonspecific, as these can also be detected in SLE.

▶ INCLUSION BODY MYOSITIS

CLINICAL FEATURES

IBM is characterized clinically by the insidious onset of slowly progressive proximal and distal weakness, which generally develops after the age of 50 years (Tables 30–1 and 30–2).[1–3,10,94] In fact, it is the most common myopathy (apart from sarcopenia of aging) in patients over the age of 50 years. The slow progressive nature of the myopathy probably accounts in part for the delay in diagnosis that averages 6–7 years after the onset of symptoms. Males are much more commonly affected than females, in contrast to the female predominance seen in DM and PM.

The clinical hallmark of IBM is early weakness and atrophy of the quadriceps, flexor forearm muscles (i.e., wrist and finger flexors) (Fig. 30–7), and the ankle dorsiflexors.[1–3,10,94] This pattern of weakness is present in about two-thirds of patients with IBM. With manual muscle testing, the MRC grades of the finger and wrist flexors (in particular the deep finger flexors such as the flexor pollicis longus) are lower than those of the shoulder abductors, and the muscle scores of the knee extensors and ankle dorsiflexor are the same or lower than those of the hip flexors in patients with IBM.[2] In contrast, the proximal muscles (shoulder abductors and hip flexors) are usually weaker than distal muscle groups by manual muscle testing grades in DM and PM. In addition, muscle involvement in IBM is often asymmetric, in contrast to the symmetrical involvement in DM and PM. The asymmetric involvement of muscle, not uncommonly, leads to the misdiagnosis of amyotrophic lateral sclerosis (ALS). However, the muscle groups affected early are different in IBM compared to ALS. Again in IBM, there is an atrophy of the flexor forearm compartment but the hand intrinsics (thenar and hypothenar eminence) are spared, in contrast to ALS in which atrophy in the upper

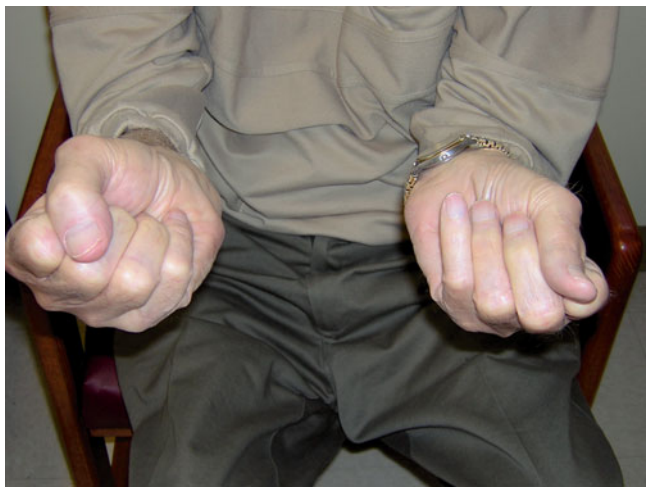


Figure 30–7. Inclusion body myositis. The clinical hallmark of IBM is early, and often asymmetric, weakness of flexor forearm muscles. This patient has marked difficulty flexing the fingers of the left hand, particularly the deep finger flexors and flexor pollicis longus.

limps usually is first seen in the hand intrinsics. The presence of slowly progressive, asymmetric, quadriceps and wrist/finger flexor weakness and atrophy in a patient over 50 years of age strongly suggests the diagnosis of IBM even in the absence of histological confirmation.

Swallowing difficulties develop in up to 40% of patients due to esophageal and pharyngeal muscle involvement. This can lead to weight loss or aspiration. In severe cases, cricopharyngeal myotomy may be beneficial.[94–96] Mild facial weakness is evident in one-third of cases.[2,94] In keeping with other inflammatory myopathies, neck flexor weakness is the rule. Most patients have no sensory symptoms, but as many as 30% have evidence of a generalized sensory peripheral neuropathy on clinical examination and electrophysiological testing.[2] Muscle stretch reflexes are normal or slightly decreased. In particular, the patellar reflexes are lost early.

ASSOCIATED MANIFESTATIONS

Unlike DM and PM, IBM is not associated with myocarditis, lung disease, or an increased risk of malignancy. However, as many as 15% of patients with IBM have underlying autoimmune disorders such as SLE, Sjögren syndrome, scleroderma, sarcoidosis, variable immunoglobulin deficiency, or thrombocytopenia.[97,98]

LABORATORY FEATURES

Serum CK is normal or only mildly elevated (usually less than 10-fold above normal).[2,10,94] Positive ANAs are found in approximately 20% of patients with IBM but

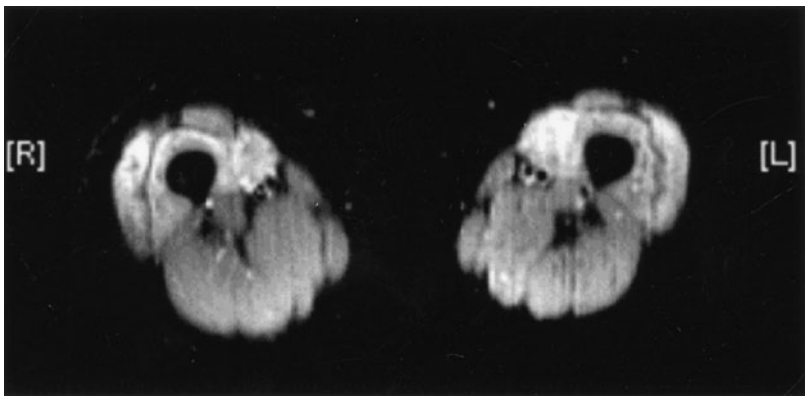


Figure 30–8. Inclusion body myositis. Skeletal muscle MRI (STIR images) reveals patchy areas of increased signal in the vastus lateralis and vastus medialis with relative sparing of the rectus femoris.

MSAs are usually absent.[36,98,99] There is a significant incidence of the HLA DR3 phenotype (*0301/0302) in IBM.[100] Skeletal muscle MRI scans demonstrate atrophy and signal abnormalities in affected muscle groups (Fig. 30–8).[46,101]

ELECTROPHYSIOLOGICAL STUDIES

Nerve conduction studies reveal evidence of a mild axonal sensory neuropathy in up to a 30% of patients.[2] EMG demonstrates increased spontaneous and insertional activity, small polyphasic MUAPs, and early recruitment.[51,94] In addition, large polyphasic MUAPs can also be demonstrated in one-third of patients, which has led to the misinterpretation of a neurogenic process and misdiagnosis in some patients as having ALS.[94,102,103] However, large polyphasic MUAPs can also be seen in myopathies (i.e., PM, DM, and muscular dystrophies) and probably reflects the chronicity of the disease process rather than a neurogenic etiology.

HISTOPATHOLOGY

Muscle biopsy characteristically reveals endomysial inflammation, small groups of atrophic fibers, eosinophilic cytoplasmic inclusions, and muscle fibers with one or more rimmed vacuoles lined with granular material (Fig. 30–9).[2,10,94] Amyloid deposition in vacuolated muscle fibers and to a lesser extent within nuclei can be demonstrated on Congo red staining using polarized light or fluorescence techniques (Fig. 30–10).[104,105] We have found that the number of vacuolated and amyloid-positive fibers may increase with time in individual patients.[106] An increased number of ragged red fibers and COX-negative fibers are also evident in patients with IBM compared to patients with DM and PM and age-matched controls.[107] The myonuclei also appear strikingly abnormal. Some are enlarged, contain eosinophilic inclusions, or are located within the vacuoles and appear to be exploding into the vacuoles themselves. Interestingly, the rimmed vacuoles immunostain with antibodies directed against the nuclear proteins such as emerin, lamin A/C, and valosin-containing protein suggesting a component of the rimmed vacuoles may be secondary to remnants of destroyed myonuclei. With EM, 15–21-nm cytoplasmic and intranuclear tubulofilaments are found in vacuolated muscle fibers, although a minimum of three vacuolated fibers often need to be scrutinized to confirm their presence (Fig. 30–11).[94] Vacuolated fibers also contain cytoplasmic clusters of 6–10-nm amyloid-like fibrils.[10] Because of sampling error, repeat muscle biopsies may be required to demonstrate the rimmed vacuoles and abnormal tubulofilament or amyloid accumulation, in order to histologically confirm the diagnosis of "definite" IBM.[2] This sampling error, no doubt, accounts for many cases of IBM being misdiagnosed as PM.

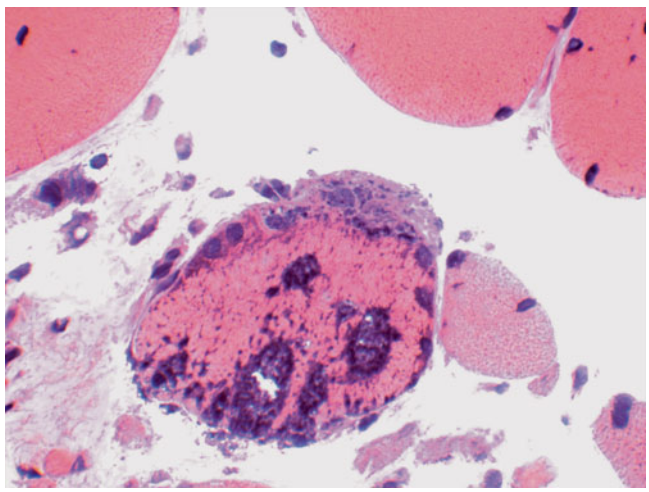


Figure 30–9. Inclusion body myositis. Muscle biopsy reveals muscle fiber with rimmed vacuoles. H&E.

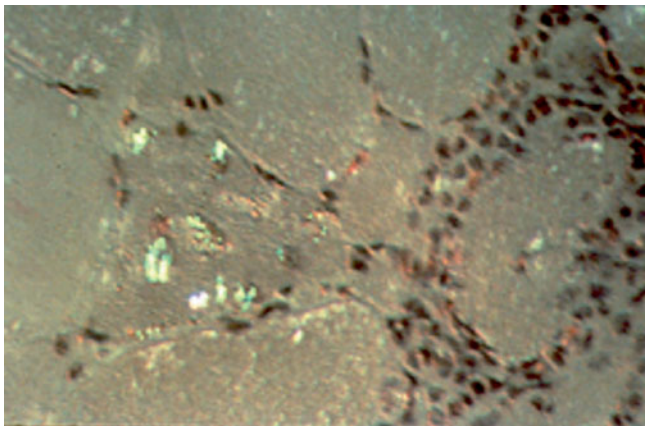


Figure 30–10. Inclusion body myositis. The vacuolated muscle fibers are may contain intracytoplasmic and sometimes intranuclear amyloid inclusions, seen here as small apple-green birefringent deposits with Congo-red stain under polarized light.

As with PM, in IBM there is endomysial inflammatory cell infiltrate composed of macrophages and CD8+ cytotoxic/suppressor T lymphocytes, which surround and invade non-necrotic fibers.[10,52] In addition, there are many myeloid dendritic cells in the endomysium that appear to surround non-necrotic muscle fibers and may serve to present antigens to cytotoxic T-cells. MHC class 1 antigens are expressed on necrotic and non-necrotic muscle fibers.[72] The T-cell receptor repertoire of the inflammatory cells has an oligoclonal pattern of gene rearrangement, although there is heterogeneity in the CDR3 domain.[77,108] These findings suggest that the T-cell response is not directed against a muscle-specific antigen, although a superantigen could trigger the response. However, Dalakas and colleagues have found persistent clonal restriction of T-cell receptors in infiltrating lymphocytes on repeated muscle biopsies in some individual patients, suggesting that there is a continuous antigen-driven attack against the muscle fibers.[109] Plasma cells are also quite prominent in the endomysium, but their pathogenic role is unclear.[78]

PATHOGENESIS

The pathogenesis of IBM is unknown. It is unclear if IBM is a primary inflammatory myopathy like DM and PM, or a primary degenerative myopathy with a secondary inflammatory response (such as seen in a variety of muscular dystrophies). The clonally restricted inflammatory cell infiltrate is suggestive of an autoimmune disorder mediated by cytotoxic T cells. The frequency of muscle fibers invaded by inflammatory cells is usually greater than necrotic or amyloidogenic fibers, suggesting that the inflammatory response plays a more important role than the accumulation of vacuoles or amyloidogenic filaments in the pathogenesis of IBM.[110] The autoinvasive T cells in IBM release perforin granules; pores form on the muscle membrane, resulting in osmolysis. RNA expression studies demonstrate an increase in

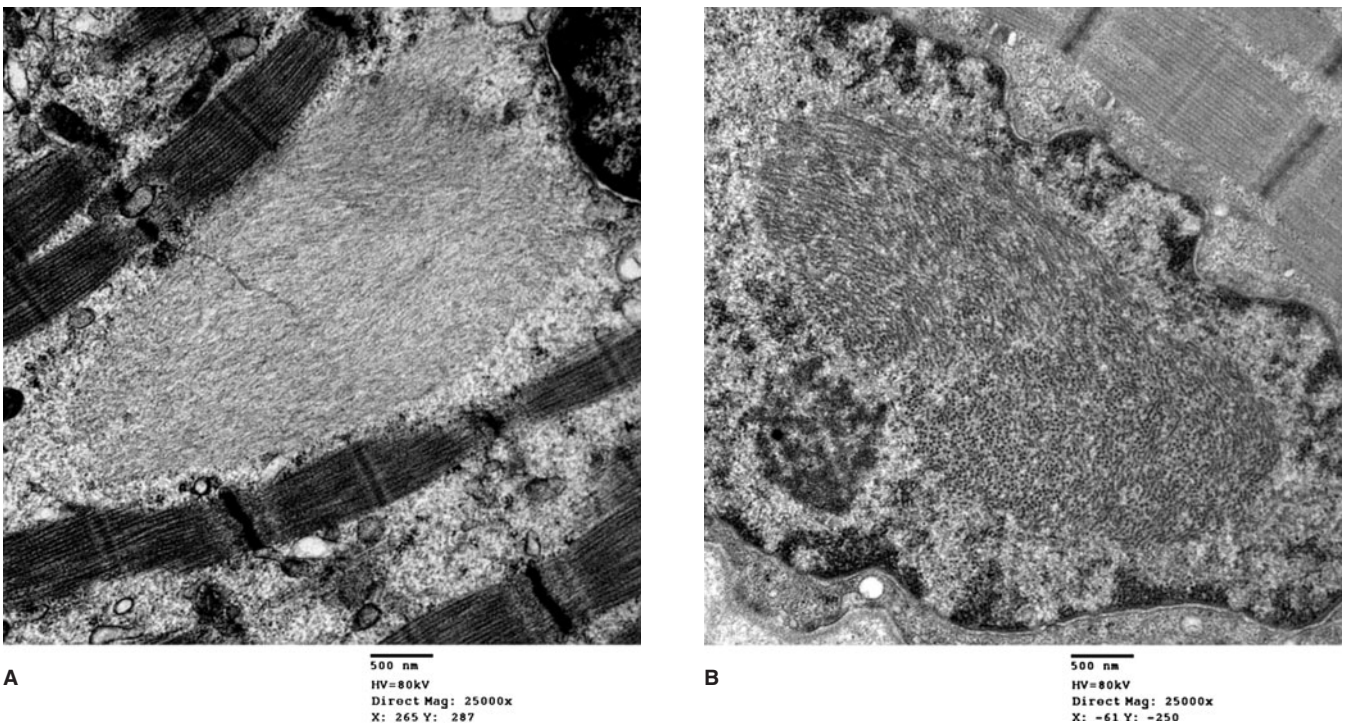


Figure 30–11. Inclusion body myositis. Electron microscopy demonstrates 15–21-nm tubulofilamentous inclusions in the cytoplasm (A) and nucleus (B).

immunoglobulin-related genes.[64] This may be explained by the prominent plasma cell infiltration in the endomysium. However, the pathogenic role, if any, of these plasma cells and immunoglobulins is unclear. No abnormal deposition of immunoglobulins or complement has been demonstrated on muscle fibers or the vasculature in IBM (as opposed to DM).

However, the lack of significant clinical response with various immunosuppressives argues against IBM being a primary autoimmune disorder. We treated eight patients with IBM for 6–24 months with immunosuppressive medications.[106] None of the patients improved in strength or function despite lower serum CK levels and reduced inflammation on the posttreatment muscle biopsies. Interestingly, the amounts of vacuolated muscle fibers and fibers with amyloid deposition were increased in the follow-up biopsies. We suggested that inflammation may play a secondary role in the pathogenesis of IBM.

IBM could be a degenerative disorder of muscle. Interestingly, "Alzheimer-characteristic proteins" accumulate in vacuolated muscle fibers.[10] Abnormal depositions of B-amyloid, C- and N-terminal epitopes of B-amyloid precursor protein, prion protein, apolipoprotein E, α1-antichymotrypsin, ubiquitin, hyperphosphorylated tau protein, and neurofilament heavy chain similar to that observed in the brains of Alzheimer's patients are evident within IBM vacuolated fibers.[111] However, we found similar degrees of increased mRNA of the so-called Alzheimer characteristic proteins in muscle biopsies of patients with PM and DM.[64] Thus, the increased expression of these proteins in IBM is not likely secondary to increased transcription of mRNA but involves a more distal mechanism. Perhaps, one or more of these proteins become modified post translation, causing misfolding and impaired elimination by the proteosomes.[111]

Ragged red fibers and mitochondrial DNA mutations are more frequent in patients with IBM than in the other inflammatory myopathies and in age-matched controls but are thought to be secondary abnormalities.[10,107,112] Vacuolated muscle fibers express increased nitrotyrosine and both the inducible and the nuclear forms of nitric oxide synthase, suggesting that nitric oxide-induced oxidative stress (NOS) may play a role in muscle fiber destruction in IBM.[113] Of note, αB crystallin, a member of the heat-shock protein family, is also overexpressed in both normal and abnormal muscle fibers, indicating that the pathologic stress is acting upstream from the development of rimmed vacuoles and the accumulation of Alzheimer-like proteins, NOS expression, and mitochondrial mutations.[114]

A viral etiology has been speculated to be involved in the pathogenesis of IBM but has never been proven. Chronic persistent mumps was previously hypothesized based on immunostaining of inclusions by antimumps antibodies[115] but was subsequently rejected after in situ hybridization and polymerase chain reaction studies failed to confirm mumps infection.[116,117] Interestingly, patients with retroviral infections (HIV and HTLV-1) and post-polio syndrome can have histologic abnormalities on muscle biopsy similar to IBM.[118,119]

DIFFERENTIAL DIAGNOSIS

Most of the patients that we have seen with IBM were previously diagnosed as having PM. It is important to remember that because of sampling error, histopathological confirmation of IBM is not always possible. The presence of slowly progressive, asymmetric, quadriceps, and wrist/finger flexor weakness and atrophy in a patient over 50 years of age strongly suggests the diagnosis of IBM even in the absence of histological confirmation.

The asymmetric muscle atrophy and distal weakness unfortunately often lead to the misdiagnosis of ALS. However, the muscle groups affected early are different in IBM compared to ALS. Again in IBM, there is atrophy of the flexor forearm compartment but the hand intrinsics (thenar and hypothenar eminence) are spared, in contrast to ALS in which atrophy in the arms usually is first seen in the hand intrinsics.

Rimmed vacuoles, amyloid deposition, and tubulofilamentous inclusions are not specific for IBM. These are characteristically observed in patients with various forms of hereditary inclusion body *myopathy* (h-IBM discussed in Chapter 24). The age of onset is usually in early adult life, and pattern of weakness differs (preferential involvement of the tibialis anterior muscles) in patients with autosomal-recessive h-IBM. Autosomal-dominant h-IBM is less common, and the clinical phenotype is more variable but usually predominantly affects the shoulder and hip girdle. One form of autosomal-dominant h-IBMs caused by mutations in the valosin-containing protein gene is associated with Paget disease and frontotemporal dementia.[120] Amyloid deposition can be seen in the h-IBM, but there is usually a lack of inflammatory cells invading non-necrotic muscle fibers. Rimmed vacuoles are also commonly seen in other types of muscular dystrophy, including limb-girdle muscular dystrophy type 1A (LGMD 1A) (myotilinopathies), LGMD 2J (titinopathy), oculopharyngeal dystrophy, Welander distal myopathy, and myofibrillar myopathy.

PROGNOSIS

Life expectancy is not significantly altered in IBM. The myopathy is slowly progressive, and unfortunately it is not responsive to immunosuppressive or immunomodulating therapies. Some patients have to use wheelchair within 10–15 years.[94]

▶ NECROTIZING MYOPATHY

CLINICAL FEATURES

This category of myopathy probably best fits under the category of inflammatory myopathy despite that lack of inflammatory cell infiltrate because it is likely autoimmune in nature.[16,70,121–124] Nearly 20% of patients with inflammatory myopathy in a recent series had necrotizing myopathy.[16] Patients present with proximal weakness, which may begin acutely or more insidiously. Some patients complain of myalgias. Patients may have an underlying connective tissue disease (usually scleroderma or MCTD), cancer (paraneoplastic necrotizing myopathy) or the cause may be idiopathic. The most common associated malignancies are gastrointestinal tract adenocarcinomas and small- and non-small-cell carcinomas of the lung. Muscular dystrophies and toxic myopathies (e.g., statin myopathies) need to be excluded. That said, we have seen a large number of necrotizing myopathies that developed in the setting of a patient taking a statin medication but continued to progress for 6 or more months after discontinuation of the statin. These patients only improved once they were treated with immunosuppressive therapy and often relapsed when these medications were tapered. Thus, we feel that statin medications may rarely induce an autoimmune necrotizing myopathies, besides the more typical toxic myopathy that may also be necrotizing in appearance. Patients with necrotizing myopathies generally improve with immunosuppressive and immunomodulating therapies but, in our experience, they are more difficult to treat than patients with DM or PM.

LABORATORY FEATURES

Serum CK is usually markedly elevated. Positive ANAs suggestive of an underlying CTD may be found. EMG demonstrates increased insertional and spontaneous activity, myopathic MUAPs, and early recruitment similar to the other described inflammatory myopathies.

HISTOPATHOLOGY

The most prominent features on muscle biopsy are scattered necrotic muscle fibers (Fig. 30–12).[16,70,121–124] Bohan and Peter criteria would have diagnosed patients with these necrotizing myopathies as PM. Nevertheless, the pathogenic basis appears to be quite distinct from PM and, in other reported cases, more closely resembles a microangiopathy. The so-called pipestem capillaries may be evident on routine histochemistry and EM.[122] Deposition of MAC on small blood vessels and depletion of capillaries can be seen, although not as prominent as that noted in DM. Further, there is no perifascicular atrophy, perivascular inflammation is sparse, and tubuloreticular inclusions in endothelium are not commonly seen on EM.

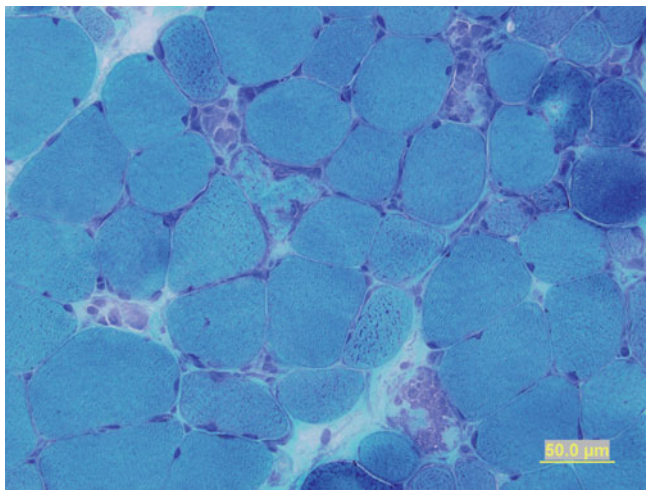


Figure 30–12. Necrotizing myositis. Muscle biopsy reveals scattered necrotic fibers, some in the process of undergoing phagocytosis. Unlike polymyositis, there is scant, if any, inflammatory cell infiltrate, except in fibers undergoing phagocytosis.

PATHOGENESIS

The pathogenesis of this necrotizing myopathy is unknown; however, the deposition of MAC on small arterioles and capillaries with thickened endothelial walls suggests an immune-mediated microangiopathy.

TREATMENT

In our experience, the necrotizing myopathies are more difficult to treat than DM and PM but generally improve with immunosuppressive treatments (corticosteroids plus a second-line agent). We have also found IVIG in combination with immunosuppression to be helpful.

▶ OTHER IDIOPATHIC INFLAMMATORY MYOPATHIES

EOSINOPHILIC MYOPATHY

Clinical Features

Eosinophilic myopathy may occur as part of the hypereosinophilic syndrome (HES) and has been subclassified into focal eosinophilic myositis, eosinophilic PM, and eosinophilic perimyositis.[125–130] The diagnostic criteria of an HES are (1) persistent eosinophilia of 1500 eosinophils/mm^3 for at least 6 months, (2)

no evidence of parasitic or other recognized causes of eosinophilia, and (3) signs and symptoms of organ system involvement related to infiltration of eosinophils. Patients with focal eosinophilic myositis and eosinophilic PM present with focal or generalized muscle weakness with or without myalgias and skin changes, while those with perimyositis typically have myalgias without significant weakness. Patients may have other systemic manifestations of HES, including encephalopathy, peripheral neuropathy, myocarditis/pericarditis (i.e. fibrosis, CHF, arrhythmia, and conduction block), pulmonary (i.e., fibrosis, pleuritis, and asthma), renal and gastrointestinal involvement, and skin changes (i.e., petechial rash, splinter hemorrhages of the nail beds, livedo reticularis, and Raynaud's phenomena). The constellation of clinical and laboratory features suggest than eosinophilic PM, HES, and Churg–Strauss syndrome may fall into the spectrum of the same or similar disease process.

Laboratory Features

Serum CK is usually elevated in focal eosinophilic myositis and eosinophilic PM but often normal in eosinophilic perimyositis. Hypereosinophilia is generally present. Hypergammaglobulinemia, anemia, and rheumatoid factor may also bee seen. ESR is elevated in <50%. Serum ANA is usually negative. EKG may demonstrate cardiac arrhythmia, and chest X-rays may reveal pulmonary infiltrates. Increased insertional and spontaneous activity (i.e., fibrillation potentials and PSWs) with early recruitment of small polyphasic MUAPs are observed on EMG. In addition, there may be evidence of superimposed multiple mononeuropathies, which may also be evident on EMG/NCS.

Histopathology

Muscle biopsies in patients with focal eosinophilic myositis and eosinophilic PM reveal an endomysial inflammatory cell infiltrate, often but not invariably, including eosinophils. Inflammatory cells may appear to surround and invade muscle fibers (Fig. 30–13). Nodular granulomas may also be seen. In patients with eosinophilic perimyositis, muscle biopsies reveal an inflammatory cell infiltrate (eosinophils are not a constant feature) restricted to the fascia and superficial perimysium.

Pathogenesis

The etiology of HES and the eosinophilic myopathies is unknown. Eosinophilia may be the result of a perverse effect on T-cell clones.[131,132] Of note, there is oligoclonal expansion of T cells within the muscle in PM.[76,77] T lymphocytes secrete interleukin-5 and interleukin-3, cytokines that are required for the growth and differentiation of eosinophils.[128] Eosinophils, in turn, damage muscle fibers by their release of the eosinophilic major

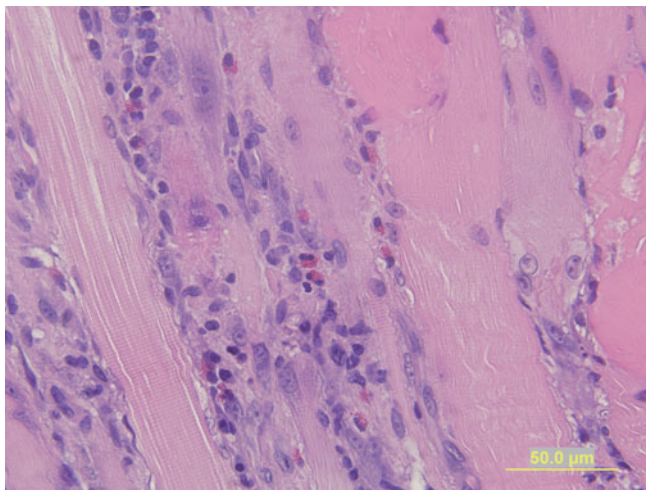


Figure 30–13. Eosinophilic myositis. Muscle biopsy demonstrates necrotic fibers and endomysial inflammatory cell infiltrate that includes many eosinophils. Paraffin-embedded tissue with H&E stain.

basic protein, which causes lysis of the membranes of target cells.[128]

Of note, a couple recent series have reported children and adults incorrectly diagnoses as having eosinophilic myositis who had mutations in the calpain-3 gene.[133] Thus, these patients actually had LGMD 2A.

Differential Diagnosis

The differential diagnosis of myopathies associated with eosinophilia includes parasitic infection, vasculitides (e.g., Churg–Straus syndrome), nonhematologic and hematological malignancies (T-cell lymphomas and aplastic anemia), toxic oil and L-tryptophan-induced eosinophilic-myalgia syndrome, idiopathic eosinophilic fasciitis (Shulman syndrome), HES, and eosinophilic myopathy as well as LGMD 2A. Peripheral blood eosinophil count is elevated in each condition.

Prognosis and Treatment

A poor prognosis for long-term survival with fewer than 20% of patients surviving 3 years was suggested in early reports, but these series of patients may have been biased by the inclusion of autopsied cases. Response to corticosteroids is variable, but some patients do respond. Most patients require the addition of second-line cytotoxic agents (see "Treatment" section). Bone marrow transplantation may be required for refractory cases. Certainly, in childhood cases and refractory adult cases, patients should be screened for mutations in the calpain-3 gene to make sure that they do not have muscular dystrophy.

DIFFUSE FASCIITIS WITH EOSINOPHILIA

Clinical Features

Diffuse fasciitis with eosinophilia or Shulman syndrome is characterized by diffuse fasciitis and peripheral eosinophilia.[134,135] Men are affected more commonly than women in a 2:1 ratio. Most patients are between 30 and 60 years of age; however, children can be affected. Patients complain of myalgias, muscle tenderness, arthralgias, and low-grade fever. On examination, proximal muscles may be weak, although the motor examination is often limited due to decreased effort because of the pain. Joint contractures may develop in the hands, elbows, and knees and, less commonly, at the shoulders and hips secondary to immobilization due to severe pain. Dermatological assessment reveals thickening of the skin with edema and dimpling (the so-called "peau d'orange") in the extremities and occasionally in the trunk. Unlike HES with eosinophilic PM, the heart, lungs, kidneys, and other visceral organs are usually not involved. However, there do appear to be a disproportionate number of hematological complications including aplastic anemia, idiopathic thrombocytopenia, leukemia, lymphoma, and other lymphoproliferative disorders.

Laboratory Features

Over two-thirds have peripheral eosinophilia >7%, while hypergammaglobulinemia and elevated ESR are evident in at least one-third of patients.[134,135] ANAs are detected in about 25% of patients. Serum CK is usually normal. EMG may demonstrate myopathic MUAPs and muscle membrane instability in the superficial subfascial layers.

Histopathology

A full-thickness biopsy extending from the skin to muscle reveals that the fascia is thickened and contains many lymphocytes, macrophages, plasma cells, and eosinophils.[134,135] Immunoglobulin and C3 deposition in the fascia have also been reported in some patients. The inflammatory infiltrate may invade the adjacent subcutaneous tissues: perimysium and endomysium. In addition, scattered necrotic fibers and perifascicular atrophy may be seen.

Pathogenesis

The etiology of diffuse fasciitis with eosinophilia is not known but is likely has an autoimmune basis. The clinical and histologic features overlap with the eosinophilic myalgia syndrome[136] and toxic oil syndromes,[137] which are caused by the ingestion of tryptophan and denatured rapeseed, respectively. This suggests the possibility of a toxin-induced fasciitis; however, the majority of patients with eosinophilic fasciitis report no known toxic exposures.

Prognosis and Treatment

Corticosteroid treatment usually leads to a rapid improvement. Spontaneous remission may have also been reported. Relapses occur in a minority of patients. The prognosis is not as favorable in cases with hematological complications.

GRANULOMATOUS AND GIANT CELL MYOSITIS

Clinical Features

Granulomatous or giant cell myositis most commonly occurs in patients who also have myasthenia gravis and/or thymoma.[138,139] The myositis may develop before or after the diagnosis of myasthenia gravis or thymoma, and the thymoma can be benign or malignant. In addition to proximal weakness, patients with concomitant myasthenia gravis also often have diplopia, ptosis, and bulbar dysfunction. Importantly, there is also an association with a severe and sometimes deadly granulomatous myocarditis.

Laboratory Features

Serum CK is usually elevated. Patients with myasthenia gravis may also have acetylcholine receptor value of striated muscle antibodies. EMG demonstrates myopathic MUAPs and muscle membrane instability. In patients with myasthenia gravis, repetitive nerve stimulation may reveal an abnormal decrement. Chest CT should be ordered to look for a thymoma. Echocardiogram can reveal reduced ejection fraction and ventricular wall motion abnormalities, and EKG may demonstrate conduction block or arrhythmia in patients with myocarditis.

Histopathology

Muscle biopsies of skeletal and often cardiac reveal granulomatous inflammation and multinucleated giant cells (Fig. 30–14).

Pathogenesis

The etiology of this disorder is unknown, but the granulomatous inflammation and giant cell formation suggest a disorder of cell-mediated immunity. However, the frequent occurrence of myasthenia gravis supports the fact that aberrant humorally mediated immunity may play a role as well.

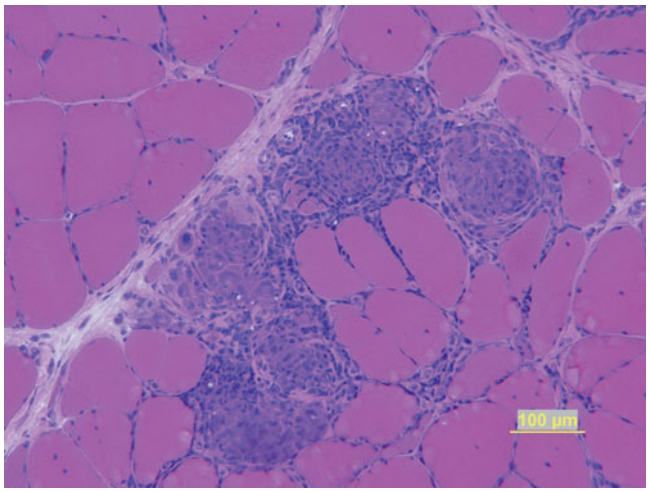


Figure 30–14. Granulomatous myositis. Muscle biopsy reveals granuloma formation in the endomysium. H&E.

Prognosis and Treatment

Some patients improve with corticosteroids; however, the response does not seem to be as favorable as evident in the more common idiopathic PM. This poorer response may be attributed to the frequent myocardial involvement and the superimposed myasthenia gravis and thymoma. Patients generally need aggressive immunosuppressive therapy with high-dose corticosteroids and second-line agents.

SARCOID MYOPATHY

Clinical Features

Incidental granulomas can be seen in muscle biopsies of patients with sarcoidosis even when they lack symptoms or signs of a myopathy.[140–142] The granulomas may even be palpated within the muscle. Weakness can be mainly proximal or distal. Some patients develop focal myalgias, tenderness, and atrophy. Others patients with sarcoid myopathy also have clinical and histologic features of DM or IBM. Signs and symptoms of a superimposed neuropathy due to sarcoidosis can also be seen.

Sarcoidosis is more prevalent in blacks than in whites and in women more than in men, and, although uncommon, it can occur in children. The majority of patients present with pulmonary symptoms and lymphadenopathy. Erythema nodosum and arthralgias are also early features.

Laboratory Features

Serum CK is usually normal or only mildly elevated.[140–142] Serum angiotension-converting enzyme levels can be normal or elevated. Patients are frequently anergic to antigen skin testing. Chest films usually demonstrate hilar lymphadenopathy and parenchymal involvement of the lungs. EMG can be normal or show myopathic features. Mixed myopathic and neurogenic MUAPs may be found in patients with a chronic myopathy or with a superimposed neuropathy.

Histopathology

Muscle biopsy reveals noncaseating granulomas consisting of clusters of epithelioid cells, lymphocytes, and giant cells usually around blood vessels in the perimysium and also in the endomysium.[140–142]

Pathogenesis

The exact pathogenic mechanism of sarcoidosis is unknown but likely involves abnormal cell-mediated immunity, given the presence of granulomas and the T-cell anergy in vitro and in vivo.

Prognosis and Treatment

Treatment of sarcoidosis is usually focused on other systemic manifestations, as the myositis is typically asymptomatic. Corticosteroids are usually effective in treating the myositis, although methotrexate or cyclosporine is occasionally required. In refractory patients, one should consider IBM and perform a repeat biopsy, as we have seen several cases of patients with both sarcoidosis and histologically confirmed IBM. In such cases, the granulomas may have been incidental with the weakness actually due to IBM.

BEHCET DISEASE

Clinical Features

Behcet disease is a multisystemic disorder characterized by recurrent mucocutaneous and ocular lesions (e.g., oral and genital ulcers, hypopyon, and iritis), erythema nodosum, thrombophlebitis, colitis, meningoencephalitis, and peripheral neuropathy. Onset can occur in childhood or late adult life. In addition, patients may develop focal or generalized myalgias with or without weakness due to myositis.[143–147] The lower extremities, particularly the calves, are primarily affected. Myocarditis may occur.

Laboratory Features

Serum CK levels are normal or mildly elevated. Usually there is leukocytosis, elevated ESR and C-reactive protein levels. Approximately 50% of patients are HLA-B5 positive.[147]

Histopathology

Muscle biopsy reveals macrophages along with CD4+ and CD8+ lymphocytes and neutrophils surrounding and invading non-necrotic muscles and widespread expression of MHC-1 antigen on muscle fibers similar to

PM.[147] In addition, deposits of complement factor C3 and immunoglobulins have been demonstrated in blood vessel walls as seen in DM.[147]

Pathogenesis

The immunohistological findings reveal a cell-mediated attack directed against muscle fibers, but the enhanced neutrophil migration and immune complex deposition on blood vessels support a leukocytoclastic vasculitis or vasculopathy in the pathogenesis of the disease.

Prognosis and Treatment

The myositis is responsive to immunosuppressive therapy.

FOCAL MYOSITIS

Clinical Features

Focal myositis is a rare disorder, which usually manifests as a solitary, painful, and rapidly expanding skeletal muscle.[148–152] It can develop at any age. The most common site of involvement is the leg, but focal myositis can also occur in the upper extremities, abdomen, head, and neck. Focal myositis may be mistaken for a malignant soft-tissue tumor (i.e., sarcoma). Rarely, a focal myositis generalizes to more typical PM.[150] The disorder needs to be distinguished from focal muscle infarction (most commonly seen in diabetes), sarcoidosis, Behcet's syndrome, and vasculitis and soft-tissue tumors and focal infections such as pyomyositis (bacterial infection of muscle seen in immunosuppressed patients). The lesions may resolve spontaneously or with corticosteroid treatment.

Laboratory Features

Serum CK and ESR are usually normal. MRI and CT imaging demonstrate edema within the affected muscle groups.[148,151,152]

Histopathology

Muscle biopsies reveal CD4+ and CD8+ T lymphocytes and macrophages in the endomysium along with necrosis and phagocytosis of muscle fibers.[148] In addition, fiber size variability, split fibers, increased centronuclei, and endomysial fibrosis are seen. One report noted that MHC class 1 antigens were not expressed on muscle fibers, in contrast to PM in which these antigens are typically abnormally expressed on the fibers.[148]

Pathogenesis

The etiology is unknown. Immunological studies suggest that the disorder is distinct from PM and not the result of a cell-mediated attack directed against a muscle-specific antigen.

▶ TABLE 30–6. INFLAMMATORY MYOPATHY ASSOCIATED WITH INFECTIONS

Viral
Human immunodeficiency virus (HIV)
Human T-leukemia virus 1 (HTLV-1)
Influenza types A, B, and C (rare)
Hepatitis B and C
Less common: adenovirus, coxsackie virus, echovirus, parainfluenza virus, Epstein–Barr Virus, arbovirus, respiratory syncytial virus, and cytomegalovirus herpes simplex
Bacterial
Staphylococcus aureus
Streptococci
E. coli
Yersinia
Legionella
Leptospirosis
Lyme disease
Fungal
Candida
Cryptococcus
Sporotrichosis
Actinomycosis
Histoplasmosis
Parasites
Protozoans
Toxoplasmosis
Sarcocystis
Trypanosomiasis
Cestodes (tapeworms)
Cysticercosis
Hydatidosis
Coenurosis
Sparganosis
Nematodes (unsegmented roundworms)
Trichinosis
Visceral/cutaneous larva migrans
Dracunculiasis

▶ MYOSITIS ASSOCIATED WITH INFECTIONS (Table 30-6)

VIRAL INFECTIONS

Human Immunodeficiency Virus

Clinical Features

Patients with HIV infection may develop an inflammatory myopathy.[80,153] This complication is more common in adults compared to children with HIV infection. Inflammatory myopathy usually develops in patients with AIDS but can occur in the early stages of HIV infection. The clinical presentation is similar to idiopathic PM with subacute or chronic, progressive, symmetrical proximal weakness and myalgias. Occasionally, patients with HIV have muscle biopsies that resemble IBM. Patients may have concurrent HIV-related neuropathy and may complain also of sensory loss and painful paresthesia.

Rhabdomyolysis has also been reported as a rare complication of HIV infection, usually but not always in association with antiretroviral therapies and/or statin medications.[154–157] HIV-related myositis need to be distinguished from zidovudine (AZT) myotoxicity, HIV-wasting syndrome, and other neuromuscular diseases that can complicate HIV infection.[80,158–161]

Laboratory Features

Serum CK is elevated in most patients. EMG demonstrates muscle membrane instability (i.e., fibrillation potentials, PSWs, and complex repetitive discharges) and small myopathic MUAPs.

Histopathology

Muscle biopsies reveal perimysial and endomysial inflammation consisting mainly of CD8+ cytotoxic T cells and macrophages, which surround and invade non-necrotic muscle fibers.[153] Perivascular inflammation is common, but actual necrotizing vasculitis is not seen. Occasional ragged red fibers, nemaline rods, and cytoplasmic bodies are found.[161] Rare patients may have rimmed vacuoles typical of IBM.[118]

Pathogenesis

HIV has been detected by polymerase chain reaction (PCR) in muscle biopsy specimens; however, the virus is evident by ultrastructural studies only in inflammatory cells.[162] The myositis is not a direct effect of infection of muscle by HIV. Rather, the HIV infection triggers a T-cell-mediated and MHC-1-restricted immune response against unknown antigen(s) on muscle fibers.

Prognosis and Treatment

There are no large uncontrolled studies assessing the efficacy of various treatment options in HIV-related myositis. A trial of antiretroviral medications may be of benefit, if these are not already prescribed. In our experience, IVIG has not been all that effective in improving strength. Corticosteroids are the most effective treatment but need to be used with caution, given the risk of further immunosuppression in the patient who is already immunocompromised.

Human T-Cell Leukemia Virus Type 1

Clinical Features

HTLV-1 infection can cause adult T-cell leukemia and tropical spastic paraparesis (TSP).[163–165] In addition, a myositis may occur in patients who are infected with or without leukemia or TSP. Patients develop progressive proximal muscle weakness and myalgias similar to HIV-related myositis. In a patient with TSP, concurrent myositis should be suspected if the patient has concurrent proximal upper extremity and neck weakness in addition to leg weakness and spasticity.

Laboratory Features

Serum CK is usually elevated. EMG demonstrates typical myopathic features. In addition, an upper motor neuron pattern of impaired modulation of recruitment can be seen in patients who also have TSP.

Histopathology

Muscle biopsy is similar to that observed in idiopathic PM and HIV myositis.[163–165] In addition, rimmed vacuoles similar to IBM can be seen.[118]

Pathogenesis

As with HIV-related myositis, HTLV-1 can be demonstrated within some inflammatory cells, but not in the muscle fibers themselves. A T-cell-mediated and MHC-1-restricted cytotoxic process similar to HIV is suspected.

Prognosis and Treatment

Although there are only a small number of patients reported who were treated with immunosuppressive agents, the myositis may improve with corticosteroid treatment. In contrast, the myelopathy is relatively refractory to immunosuppression.

Influenza Viruses

Clinical Features

Influenza A, B, and rarely C are associated with upper respiratory infection. As most of us who have experienced the common cold or flu know, myalgias are common when fever and other constitutional symptoms of influenza infection appear. The myalgias are usually an indirect affect of influenza infection, probably related to the systemic release of cytokines. Nevertheless, active myositis can develop, and the associated clinical syndromes appear different in children and adults.[166–170]

In children, the myositis manifests as severe pain, swelling, and tenderness of the calves when the upper respiratory infection symptoms begin to reside.[166,167,170] Because of the severe muscle pain, affected children may prefer to walk on the toes or crawl and limit their movements. Importantly, prolonged inactivity can lead to muscle contractures. The severe pain limits adequate assessment of muscle strength. Most cases are self-limited, with symptoms lasting <1 week. Myoglobinuria can complicate associated influenza infection, particularly if there is an underlying metabolic defect such as carnitine palmityl transferase deficiency.[133,171]

Influenza virus myositis tends to be more severe in adults.[168,169] Generalized or proximal weakness develops in half the adult patients. Myoglobinuria is more common in adults and can be complicated by renal failure. Patients complain of generalized muscle pain, but this a less prominent symptom then seen in children.

Laboratory Features

CK is usually elevated in patients with acute myositis, while it is typically normal in uncomplicated influenza infection. EMG may show the typical features of an active necrotizing myopathy.

Histopathology

In children, biopsies have revealed scattered necrotic and regenerating muscle fibers with interstitial mononuclear and polymorphonuclear inflammatory cells.[166] EM has not demonstrated any viral-like particles in the muscle biopsies. Viral cultures only rarely are positive.[172]

In adults, the muscle biopsies have demonstrated scattered necrotic and regenerating fibers; however, mononuclear inflammatory cell infiltration is scant. Rare muscle fibers containing viral particles within membrane-bound vacuoles near the sarcolemma have been seen on EM.[173] In addition, intranuclear inclusions consisting of 7–9-nm parallel filaments were present in fibers that did not contain viral particles.[173]

Pathogenesis

It is not known why only rare patients with influenza infection develop myositis. It is possible that the muscle destruction is a direct effect of the viral infection or alternatively an indirect effect secondary to altering the immune system.

Prognosis and Treatment

The disorder is usually self-limiting, although rare patients have been reported with recurrences associated with infection of different influenza types.[170] Treatment is supportive with bed rest and hydration to avoid renal failure from myoglobinuria. Acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) (avoid aspirin in children) can be used to treat myalgias and fever.

Other Viral-Related Myositis

Acute viral myositis can also occur in infections with coxsackie virus, parainfluenza, mumps, measles, adenovirus, herpes simplex, cytomegalovirus, hepatitis B and C, Epstein–Barr virus, respiratory syncytial virus, echovirus, and possibly arboviruses. Diagnoses requires acute and convalescent titers (3 or 4 weeks after infection) titers being measured in the serum. The blood, stool, urine, and throat can be cultured in an attempt to isolate the virus. As in influenza, the myositis associated with these other viruses is usually self-limited and requires only supportive therapy and treatment of myoglobinuria to prevent renal failure.

BACTERIAL INFECTIONS

Clinical Features

The term "pyomyositis" is used to describe focal or multifocal abscesses associated with bacterial infection of the muscle. Pyomyositis is more common in the tropics but has been increasing in frequency in developed countries secondary to HIV infection[174,175] and intravenous drug abuse.[176] Patients present with muscle pain, tenderness, and fever. The most common sites of the abscesses are the quadriceps, glutei, and deltoids.[177] If not treated early, the patients can become septic.

Laboratory Features

Serum CK may be normal or elevated. Neutrophilic pleocytosis and elevated ESRs are the rule. Initially, blood cultures may show no growth or organisms until the patient becomes septic.[178] Ultrasound, CT, and MRI of skeletal muscle can be useful in localizing pyogenic abscesses for fine-needle aspiration and diagnosis.[178,179]

Histopathology

Muscle biopsy reveals necrotic tissue containing neutrophils, macrophages, lymphocytes, and occasionally eosinophils.[174,176,177,179] Bacterial infection may be difficult to visualize on light microscopy, but the organisms can be cultured from the drained abscesses.

Pathogenesis

Staphylococcus aureus, streptococci, *Escherichia coli*, *Yersinia*, and *Legionella* are the most common organisms responsible for pyomyositis.[177–179] Pyomyositis usually arises as an extension of the infection from adjacent tissues or via hematologic spread of the organisms. Infection of the muscle does not usually develop in the absence of primary infection elsewhere.

Prognosis and Treatment

Early in the course of the illness, microabscesses may respond to appropriate antibiotics. More severe infections require incision and drainage of the abscesses in addition to antibiotics. Despite aggressive treatment, mortality rates range from 1% to 10% in cases complicated by sepsis.[177]

MYOSITIS ASSOCIATED WITH LYME DISEASE

Clinical Features

Lyme disease is often associated with central nervous system and peripheral nerve manifestations. Patients with Lyme disease often complain of myalgias, although true myositis is uncommon. Rarely, myositis can

complicate Lyme disease.[180–185] Patients with myositis usually present with focal or generalized weakness and myalgias.[180–185] Patients can have concomitant manifestations such as rash, arthritis, myocarditis, or neurologic syndromes associated with Lyme disease. Clinical features can resemble DM.[181] Rhabdomyolysis can complicate severe myositis.[182]

Laboratory Features

Serum CK levels are normal or only slightly increased in the majority of patients; very high levels are rare.[182] The most sensitive test for Lyme neuroborreliosis is the detection of an intrathecal synthesis of *Borrelia burgdorferi*-specific antibodies.[186,187] Intrathecal immunoglobulin production, especially IgG, may persist for years after treatment of Lyme neuroborreliosis without clinical signs of active disease. *B. burgdorferi* PCR in CSF has a reported sensitivity of approximately 20%.[186,187] Case series have reported patients with neuroborreliosis who had negative peripheral blood serology and positive antibody responses in the CSF; this appears to be more common in patients with early disease.[184,186]

Electrophysiological Features

EMG demonstrates myopathic findings often with concomitant polyradiculoneuropathy.[182,185]

Histopathology

Muscle biopsies of suspected Lyme-associated myositis have demonstrated focal nodular infiltrates, perimysial inflammation, and necrotic muscle fibers. Diffuse mononuclear infiltration and invasion of non-necrotic muscle fibers are usually not seen. Interstitial lymphohistiocytic infiltrates with plasma cells are found predominantly in the vicinity of small endomysial vessels. Immunohistology shows infiltrates that mainly consist of CD4+ T lymphocytes and macrophages and fewer CD8+ T and B cells. Occasionally, the organisms can be seen with silver stains. We have seen a case with perifascicular atropy characteristic of DM.

Pathogenesis

The histopathological features are suggestive of a vasculopathy.

Prognosis and Treatment

Corticosteroids can help with the myalgias, but the infection needs to be treated with appropriate antibiotics to ultimately improve muscle strength and function.

FUNGAL MYOSITIS

Fungal infection of the muscles is uncommon unless the patient is immunosuppressed. *Candida* is the most common fungal organism and almost always occurs in the setting of diffuse candidiasis.[188,189] Patients manifest with diffuse myalgias, tenderness, weakness, fever, and a papular erythematous rash. However, the myositis is often overshadowed by other systemic involvement. Muscle biopsy demonstrates infiltration of the muscle by hyphal and yeast forms of the organism, inflammation, and hemorrhagic necrosis. Myositis has also been reported complicating actinomyocosis, histoplasmosis, sporotrichosis, and cryptococcal infection.[190,191]

PARASITIC INFECTIONS

Trichinosis

Clinical Features

Trichinosis is caused by the nematode *Trichinella spirali* and is the most common parasitic disease of skeletal muscle. Two to 12 days following ingestion of inadequately cooked meat (usually pork), larvae disseminate through the blood stream and invade muscle tissue. The most frequent muscles involved in order of frequency are the diaphragm, extraocular, tongue, laryngeal, jaw, intercostal, trunk, and limbs.[192,193] Patients complain of generalized muscle pain and weakness, fever, abdominal pain, and diarrhea. In addition, periorbital edema, ptosis, subconjunctival hemorrhage, and an erythematous urticarial or petechial rash are often evident. Myalgias and weakness peak in the third week of the infection but can last for several months. Occasionally, the parasite invades the heart muscle leading to myocarditis and the central nervous system causing meningoencephalitis.

Laboratory Features

Most patients have eosinophilic leukocytosis and elevated serum CK. Serum antibodies against *T. spiralis* can be demonstrated 3–4 weeks after infection.[193]

Histopathology

Muscle biopsies reveal prominent infiltration of the muscle by eosinophils and polymorphonuclear leukocytes in the early stage of infection.[192,193] In chronic stages of infection, mononuclear inflammatory cells become more prevalent. Larvae, cysts, focal calcification of the cysts, fibrosis, and granulomas may be observed (Fig. 30–15).

Pathogenesis

Following ingestion of meat infected with encysted larvae, gastric juices liberate the larvae that infect the gut. Maturation of the parasite occurs in the gut. Subsequently, second-generation larvae disseminate into the bloodstream and lymphatics to invade muscle and provoke the inflammatory response.

Prognosis and Treatment

The treatment of choice for the larvae and adult nematode is thiabendazole, but efficacy has not been established against the encysted larvae. Mebendazole may be effective against both circulating and encysted

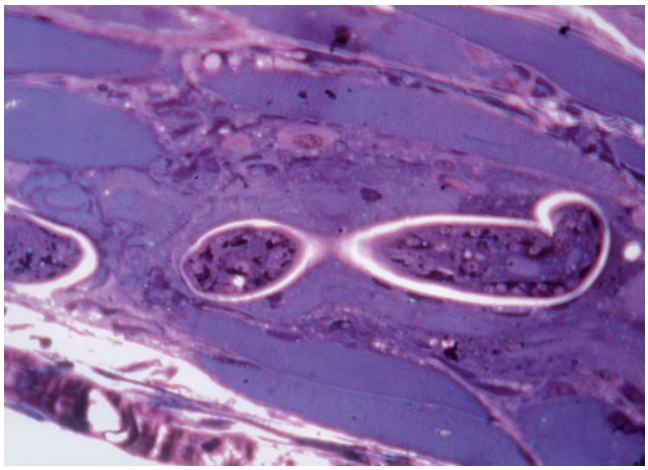


Figure 30–15. Trichinosis. Muscle biopsy demonstrates the paracyte cut multiple times. Toluidine blue.

larvae. A 2-week course of prednisone is recommended because a Herxheimer-like reaction may develop as the larvae degenerate. Most patients respond quickly to treatment.

Cysticercosis

Clinical Features

Cysticercosis is caused by the tape worm—*Taenia solium*. Infection of skeletal muscles is manifested by myalgias; tenderness; pseudohypertrophy of infected muscles, especially the tongue and calves; and mild weakness.[194,195] Involvement of the central nervous system may cause focal neurologic deficits, encephalopathy, and seizures.

Laboratory Features

Serum CK and peripheral eosinophil counts are usually increased.

Histopathology

Muscle biopsies reveal eosinophils, plasma cells, macrophages, lymphocytes, and occasionally giant cells along with larvae surrounded by fibrotic changes.[194,195] The encysted larvae eventually calcify.

Pathogenesis

Infection results from ingestion of undercooked meat, mainly pork, which contains the larva form of *T. solium*. The tape worms mature in the small intestine and release ova. Ingestion of food or water contaminated by these ova results in hematogenous spread and infection of the muscle.

Prognosis and Treatment

Praziquantel reduces the size and number of cysts in the central nervous system, but efficacy in myositis has not been established. Niclosamide and paromycin are the drugs of choice for removing the adult tapeworm. Concomitant administration of corticosteroids is helpful in decreasing the inflammatory reaction directed against degenerating parasites.

Toxoplasmosis

Clinical Features

Toxoplasmosis is caused by the protozoa *Toxoplasma gondii* and manifests as fever, lymphadenopathy, meningoencephalitis, hepatosplenomegaly, uveitis, pneumonia, myocarditis, or rash. Myositis is uncommon but can occur in isolation or associated with systemic symptoms and presents as fever, myalgias, and weakness.[196–198]

Laboratory Features

Serum CK is usually elevated. The diagnosis of toxoplasmosis can be confirmed with serologic studies (i.e., Sabin–Feldman dye, complement fixation, indirect hemagglutination, and indirect fluorescent antibody). EMG reveals typical features of an inflammatory myopathy.

Histopathology

Muscle biopsies reveal lymphocytes, macrophages, and occasionally giant cells in the endomysium and perimysium. Cysts containing the bradyzoite stage of *T. gondii* are more commonly identified in muscle than the free tachyzoite form.

Pathogenesis

The most common mode of infection is by ingestion of food contaminated by oocysts or ingestion of cysts containing bradyzoites in undercooked food. The organism usually matures to the tachyzoite form and invades the bloodstream and lymphatics and disseminates to other tissues. Systemic disease is most common in patients who are immunosuppressed.

Prognosis and Treatment

The combination of pyrimethamine and sulfadiazine or trisulfapyrimidines are treatments of choice. Combination therapy is effective against the trophozoites but not against encysted protozoa.

▶ TREATMENT OF INFLAMMATORY MYOPATHIES (Table 30–7)

There are many published retrospective studies and small case reports regarding the use of various immunosuppressive and immunomodulating therapies in different types of inflammatory myopathy. Unfortunately, most of these papers are difficult to interpret in many of the older studies because they group adult and childhood DM together with PM, IBM, and necrotizing myopathy. Many of these reports were retrospective and unblinded and lacked placebo controls. Further, in several reports, patients with subjective improvement

▶ **TABLE 30–7. IMMUNOSUPPRESSIVE THERAPY FOR NEUROMUSUCLAR DISORDERS**

Therapy	Route	Dose	Side Effects	Monitor
Prednisone	p.o.	100 mg/d for 2–4 weeks, then 100 mg every other day; single a.m. dose	Hypertension, fluid and weight gain, hyperglycemia, hypokalemia, cataracts, gastric irritation, osteoporosis, infection, and aseptic femoral necrosis	Weight, blood pressure, serum glucose/ potassium, and cataract formation
Methylprednisone	I.V.	1 g in 100 mL normal saline over 1–2 h, daily or every other day for three to six doses	Arrhythmia, flushing, dysgeusia, anxiety, insomnia, fluid and weight gain, hyperglycemia, hypokalemia, and infection	Heart rate, blood pressure, and serum glucose/potassium
Azathioprine	p.o.	2–3 mg/kg/d; single a.m. dose	Flu-like illness, hepatotoxicity, pancreatitis, leukopenia, macrocytosis, neoplasia, infection, and teratogenicity	Monthly blood count and liver enzymes avoid allopurinol
Methotrexate	p.o.	5.0–20 mg weekly, single or divided doses	Hepatotoxicity, pulmonary fibrosis, infection, neoplasia, infertility, leukopenia, alopecia, gastric irritation, stomatitis, and teratogenicity	Monthly liver enzymes, blood count; consider liver biopsy at 2 g cummulative dose
	I.V./I.M.	20–50 mg weekly; 1 day a week dosing	Same as p.o.	Same as p.o.
Cyclophosphamide	p.o.	1.5–2 mg/kg/d,; single a.m. dose	Bone marrow suppression, infertility, hemorrhagic cystitis, alopecia, infections, neoplasia, and teratogenicity	Monthly blood count and urinalysis
	I.V.	1 g/m^2	Same as p.o. (although more severe), and nausea/vomiting and alopecia	Daily to weekly blood count and urinalysis
Chlorambucil	p.o.	4–6 mg/d; single a.m. dose	Bone marrow suppression, hepatotoxicity, neoplasia, infertility, teratogenicity, and infection	Monthly blood count and liver enzymes
Cyclosporine	p.o.	4–6 mg/kg/d, split into two daily doses	Nephrotoxicity, hypertension, infection, hepatotoxicity, hirsuitism, tremor, gum hyperplasia, and teratogenicity	Blood pressure, monthly cyclosporine level, creatinine/BUN, and liver enzymes
Mycophenolate mofetil	p.o.	Adults (1 g BID to 1.5 g BID) Children (600 mg/m^2/ dose BID) (no more than 1 g/d in patients with renal failure)	Bone marrow suppression, hypertension, tremor, diarrhea, nausea, vomiting, headache, sinusitis, confusion, amblyopia, cough, teratogenicity, infection, and neoplasia	Blood counts are performed weekly × 1 month, twice monthly for the second and third month, and once a month for the first year
Intravenous immunoglobulin	I.V.	2 g/kg over 2–5 d; then every 4–8 weeks as needed	Hypotension, arrhythmia, diaphoresis, flushing, nephrotoxicity, headache, aseptic meningitis, anaphylaxis, and stroke	Heart rate, blood pressure, and creatinine/BUN

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or lower serum CK levels were defined as positive responses rather than the more important objective improvement in muscle strength and function.[42,199] There are only a few published prospective, double-blinded, placebo-controlled trials in the treatment of PM,[82,200] DM,[201] and IBM.[202–207] Nevertheless, there has been a trend in recent years to perform more rigorous studies. Despite the paucity of prospective, double-blinded, placebo-controlled trials, it is clear to experienced clinicians that various modes of immunotherapy are helpful in DM and PM in improving muscle strength and function. In contrast, IBM is generally refractory to immunosuppressive therapy.

CORTICOSTEROIDS

Prednisone is our first-line treatment of choice for DM and PM.[1,15,82] In patients with severe weakness, we initiate treatment with a short course of intravenous Solumedrol (1 g daily for 3 days) prior to starting

oral agents. High-dose prednisone appears to reduce morbidity and improve muscle strength and function.[21,42,66,67,208] Retrospective series report that 58–100% of patients with DM at least partially improve, while 30–66% respond completely with prednisone.[2,42] Over 80% of patients with PM at least partially improve, but only 10–33% completely respond to prednisone.[2,42] Noticeable clinical improvement begins within 3–6 months of starting prednisone in most patients with DM or PM.[2,21] When no response is noted after an adequate trial of high-dose prednisone, other alternative diagnoses (e.g., IBM or an inflammatory muscular dystrophy) and repeat muscle biopsy should be considered.

Others and we have found minimal, if any, clinically significant improvement in strength of function with prednisone or other second-line agents in patients with IBM.[2,4,82,94,106,209] However, a few retrospective, unblinded studies reported mild or transient improvement with prednisone.[42,199] A partial response to prednisone was noted in 40–58% of patients with IBM, although none had complete return of strength. Careful review of these retrospective, unblinded studies shows that the investigators considered *subjective* improvement or lower serum CK levels with treatment a "positive" response. No demonstration of objective improvement in muscle strength was evident. These same investigators performed a small (11 patients) unblinded, prospective, cross-over designed study comparing prednisone plus azathioprine plus oral methotrexate with prednisone plus intravenous methotrexate.[199] There was no clinically significant change in strength over the 6-month treatment period in both study arms, although they found that the serum CK levels decreased in 66–70% of the patients. On this basis, the investigators concluded that the combination of immunosuppressive medications stabilized the disease process. As IBM is slowly progressive and the study was neither unblinded nor placebo controlled, any assertion of treatment efficacy would be premature after a trial of only 6 months duration.

In patients with DM, PM, presumed autoimmune necrotizing myopathy, and other idiopathic inflammatory myositides other than IBM (i.e., sarcoidosis), we initiate treatment with single-dose prednisone (1.5 mg/kg up to 100 mg) every morning.[15,82] After 2–4 weeks of daily prednisone, we switch directly to alternate-day dosing (i.e., 100 mg every other day). Patients with more severe disease may need to be slowly tapered to alternate-day dosing over 2–3 months (e.g., decrease alternate dose by 10 mg every week until they are on 100 mg every other day). Patients are followed initially at least every 2–4 weeks. We maintain the high-dose prednisone until patients are back to normal strength or until improvement in strength has reached a plateau (usually 4–6 months). Subsequently, we slowly taper the prednisone by 5 mg every 2–3 weeks. Once the dose is reduced to 20 mg every other day, we taper prednisone no faster than 2.5 mg every 2 weeks.

We add on the second-line agents (methotrexate, azathioprine, mycophenolate, or IVIG) in patients who do not significantly improve after 4–6 months of prednisone, or if there is an exacerbation during the taper.[15,82] In patients who relapse during the taper, we double the dose of prednisone and return to daily treatment (no more than 100 mg/d) for at least 2 weeks before switching back to every other day dosing. Once a patient has regained their strength, we resume the prednisone taper at a slower rate.

We monitor the serum CK levels; however, adjustments of prednisone and other immunosuppressive agents should be based on the objective clinical examination and not the CK levels or the patients' subjective response. Serum CKs can be elevated in patients with no objective weakness or can be normal or only mildly elevated in patients with active disease. An increasing serum CK can herald a relapse, but, without objective clinical deterioration, we would not increase the dose of the immunosuppressive agent. However, we may hold the dose or the slow the taper. A maintenance dose of prednisone may be required to sustain the clinical response.

Some authorities advocate initiating and maintaining treatment with daily prednisone rather than switching to alternate-day therapy and splitting the daily dose of prednisone (e.g., three times a day) instead of consolidating the prednisone into a single morning dose.[210] We have found no advantage in splitting the dose of prednisone or maintaining daily dosing. We feel that alternate-day dosing of prednisone is as effective and is associated with less side effects than daily prednisone in most patients.[211] However, daily dosing of prednisone is often necessary in patients with diabetes due to marked fluctuation in glucose control with alternate-day therapy and those few patients who do not have a good response to alternate-day regimen.

Relapse of the myositis needs to be distinguished from steroid myopathy. This quandary may occur in patients who initially improved but then start developing progressive muscle weakness following long-term corticosteroid treatment because it can cause type 2 muscle fiber atrophy. Features that would suggest a "steroid myopathy" as opposed to relapse of myositis would be a normal serum CK, and absense of muscle membrance irritability on EMG. In contrast, patients who become weaker during prednisone taper, have increasing serum CK levels, and abnormal spontaneous activity on EMG are more likely experiencing a flare of the myositis.

CONCURRENT MANAGEMENT

We obtain a chest X-ray and a PPD skin test with controls on patients prior to initiating immunosuppressive medications. Patients with prior history of tuberculosis or a positive PPD may need to be treated

prophylactically with isoniazid. If patients have ILD and are to be placed on prednisone plus another immunosuppressive agent, we also start Bactrim for pneumocystis prophylaxis.

We measure bone density with dual-energy X-ray absorptiometry at baseline and every 6 months while patients are receiving corticosteroids. A bone density score <2.5 standard deviations below normal is considered positive for osteoporosis. Calcium supplementation (1 g/d) and vitamin D (400–800 IU/d) are started for prophylaxis against steroid-induced osteoporosis. Postmenopausal women are also started on a bisphosphonate for prevention and treatment of osteoporosis. We prescribe alendronate 35 mg/week (or another bisphosphonate) as prophylaxis against steroid-induced osteoporosis or 70 mg/week in those with osteoporosis. Because the long-term side effects of bisphosphonates are not known, particularly in men and young premenopausal women, we prophylactically treat (alendronate 35 mg/week) these individuals only if the dual-energy X-ray absorptiometry scan demonstrates a density between 1 and 2.5 standard deviations below normal at baseline or if significant bone loss occurs on follow-up scans. If bone densities are in the osteoporosis range, these are treated with alendronate 70 mg/week. Alendronate can cause severe esophagitis, and absorption is impaired if taken with meals. Therefore, patients must be instructed to remain upright and not to eat for at least 30 minutes following the dose of alendronate in the morning.

Antihistamine-H_2 blockers are not started unless the patient develops gastrointestinal discomfort or has a history of peptic ulcer disease. We instruct patients to start a low-sodium, low-carbohydrate, high-protein diet to prevent excessive weight gain. Physical therapy and an aerobic exercise program are helpful in fending off side affects of prednisone (e.g., weight gain) and preventing contractures and calcinosis that may result from immobility. Blood pressure is measured at each visit as accelerated hypertension and renal failure may occur, particularly in patients with scleroderma or MCTD.[83] In addition, periodic eye examinations for cataracts and glaucoma should be performed. We periodically check fasting blood glucose and serum potassium levels while they are on high doses of prednisone. Potassium supplementation may be required, if the patient becomes hypokalemic.

SECOND-LINE THERAPIES

These agents are used primarily in patients poorly responsive to prednisone or who relapse during prednisone taper as well as for their potential steroid-sparing effect (Table 30–2).[15,82] In addition, we initiate a second-line agent at the same time we start prednisone in patients with severe weakness or associated comorbidity (i.e., ILD and myocarditis) and diabetes mellitus (for possible steroid-sparing effect) or in elderly or those with known osteoporosis (again for possible steroid-sparing effect).

INTRAVENOUS IMMUNOGLOBULIN

IVIG has become increasing popular in the treatment of refractory myositis. Small, uncontrolled studies have reported beneficial response in DM and PM with IVIG.[9,41,87,103,141,205,212,213,258] A mild improvement in muscle strength was reported in three of four patients with IBM treated with IVIG.[214] However, we were unable to document any significant clinical improvement in nine patients with IBM treated with IVIG.[209] Subsequently two prospective, double-blind, placebo-controlled studies of IVIG in IBM revealed no significant improvement.[203,204]

A prospective, double-blind, placebo-controlled study of IVIG in 15 patients with DM demonstrated significant clinical improvement with IVIG.[201] In support of the clinical observations, repeat biopsies in five of the responsive patients revealed an increase in muscle fiber diameter, increase in the number and decrease in the diameter of capillaries, resolution of complement on capillaries, and a reduction in the expression of intercellular adhesion molecule 1 (ICAM-1) and MHC-1 antigens.

We initiate IVIG (2 g/kg) slowly over 2–5 days and repeat infusions at monthly intervals for at least 3 months.[15,82] Subsequently, we try to decrease or spread out the dose: 2 g/kg every 2 months or 1 g/kg per month. Treatment needs to be individualized. Our own anecdotal experience suggests that IVIG is effective for DM and necrotizing myopathies but is less to for PM and not at all for IBM. We generally give IVIG in combination with prednisone. There is little evidence that it is effective as a monotherapy. Prior to treatment, patients should have an IgA level checked. Patients with low IgA levels may have anti-IgA antibodies in their sera, which predispose them to anaphylactic reactions to IVIG, because IVIG contains small amounts of IgA. Patients should also have renal function checked, especially those with diabetes mellitus, because of a risk of IVIG-induced renal failure. Flu-like symptoms—headaches, myalgias, fever, chills, nausea, and vomiting—are common and occur in as many as half the patients. Rash, aseptic meningitis, and stroke can also occur.

METHOTREXATE

There are no prospective, blinded, controlled studies of methotrexate in DM or PM. However, retrospective studies report that as many as 71–88% of patients with DM and PM, including those refractory to prednisone,

improve at least partially with the addition of methotrexate.[42,215–218] Methotrexate may be more effective than azathioprine in patients with antisynthetase antibodies and in those patients previously refractory to prednisone.[217] Methotrexate appears to reduce morbidity in refractory childhood DM,[219] but its side-effect profile has limited its use in children.

Methotrexate is administered only 1 day a week. We usually begin methotrexate orally at 5.0 mg/week.[15,82] The dose is gradually increased by 2.5 mg each week up to 20 mg/week given in three divided doses 12 hours apart. The dose should be reduced and used cautiously in patients with renal insufficiency. If there is no improvement after 1 month of 20 mg/week of oral methotrexate, we switch to weekly parenteral (usually subcutaneous) methotrexate and increase the dose by 5 mg every week up to 60 mg/week. The major side effects of methotrexate are alopecia, stomatitis, ILD, teratogenicity, oncogenicity, risk of infection, and pulmonary fibrosis, along with bone marrow, renal, and liver toxicity. Doses over 50 mg/week require leukovorin rescue, although we rarely use such high doses. However, all patients are concomitantly treated with folate.

Because methotrexate can cause pulmonary fibrosis, we do not recommend its use in patients with myositis who already have the associated ILD and try to avoid its use in patients with Jo-1 antibodies. We obtain baseline and periodic pulmonary function tests forced vital capacity and diffusion capacity and repeat these periodically on patients treated with methotrexate. We monitor CBC and liver function tests (LFTs)—AST, ALT, bilirubin, and gamma-glutamyl transpeptidase (GGT) every 2 weeks until the patient is on a stable dose of methotrexate, then every 1–3 months. It is important to check the gamma-glutamyl transpeptidase, as it is the most reliable indicator of hepatic dysfunction, because the AST and ALT can be elevated from muscle involvement.

AZATHIOPRINE

Retrospective studies indicate that azathioprine is an effective therapy in DM and PM.[21,42] In one study, the addition of azathioprine was associated with improvement in 64% of patients with DM and PM, although a complete response occurred in only 11%.[42] Not surprisingly, patients who previously responded to prednisone were more likely than patients who are prednisone-refractory to improve with the addition of azathioprine. A prospective, double-blind study comparing azathioprine (2 mg/kg) in combination with prednisone to placebo plus prednisone found no significant difference in objective improvement at 3 months.[200] However, in the open-label follow-up period, patients on the combination of azathioprine and prednisone did better than those on prednisone alone and required lower doses of prednisone.[220] Azathioprine appears to be effective in some cases of childhood DM but is generally avoided, given its oncogenic potential with long-term use.

Prior to beginning azathioprine, patient should be screened for thiopurine methyltransferase (TPMT) deficiency. Patients who are heterozygous for a mutation in TPMT may be able to tolerate azathioprine at lower dosages but those who are homozygous for TPMT mutations should not receive drug as they cannot metabolize it and may have severe bone marrow toxicity. In those patients without TPMT mutations, we initiate azathioprine at a dose of 50 mg/d in adults and increase the dose by 50 mg every 2 weeks up to 2–3 mg/kg/d.[15,82] Approximately 12% of patients develop a systemic reaction characterized by fever, abdominal pain, nausea, vomiting, and anorexia that requires discontinuation of the drug.[221] This systemic reaction generally occurs within the first few weeks of therapy and resolves within a few days of discontinuing the medication. Recurrence of the systemic reaction usually follows restarting azathioprine. Other major side effects of azathioprine are bone marrow suppression, hepatic toxicity, pancreatitis, teratogenicity, oncogenicity, and increased risk of infection. Allopurinol should be avoided, because combination with azathioprine increases the risk of bone marrow and liver toxicity. A major drawback of azathioprine is that it may take 6–18 months to be effective.

CBCs and LFTs need to be followed closely. If the white blood count (WBC) falls below 4000/mm^3, we decrease the dose. Azathioprine is held if the WBC declines to 2500/mm^3 or the absolute neutrophil count falls to 1000/mm^3. Leukopenia can develop as early as 1 week or as late as 2 years after initiating azathioprine. The leukopenia usually reverses within 1 month, and it is possible to then rechallenge the patient with azathioprine without recurrence of the severe leukopenia.[221] In addition, we discontinue azathioprine if the LFTs increase more than twice the baseline values. Liver toxicity generally develops within the first several months of treatment and can take several months to resolve. Patients can occasionally be successfully rechallenged with azathioprine after LFTs return to baseline without recurrence of hepatic dysfunction.[221]

MYCOPHENOLATE MOFETIL

Mycophenylate mofetil inhibits the proliferation of T and B lymphocytes by blocking purine synthesis in only lymphocytes. Mycophenylate has been used in patients who require transplant to prevent rejection and has recently been tried in a few patients with myositis with reported benefit. The starting dose is 1.0 g twice daily and can be increased to 3 g daily in divided doses if necessary. Mycophenylate is renally excreted; therefore, the dose should be decreased (no more than 1 g/d total

dose) in patients with renal insufficiency. A benefit of mycophenylate compared to other immunosuppressive agents is the lack of renal or liver toxicity with the drug. Mycophenolate appears to be beneficial in some patients; however, we have seen a number of severe infections as a complication.[50] The most frequent side effect is diarrhea. Less common side effects include abdominal discomfort, nausea, peripheral edema, fever, and leukopenia.

CYCLOPHOSPHAMIDE

Some reports note improvement in individual patients with oral and intravenous cyclophosphamide.[21,222–226] However, other reports have found increased morbidity with intravenous cyclophosphamide without significant benefit.[227,228] Cyclophosphamide has been advocated for use in myositis associated with ILD or vasculitis, but clinical studies are lacking. Given the controversy regarding the efficacy and the toxicity profile of cyclophosphamide, we reserve it for patients refractory to prednisone, azathioprine, mycophenolate, IVIG, and methotrexate. When used, we usually pulse patients with cyclophosphamide at 0.5–1 g intravenously/m^2/month for 6–12 months.[15,82] Cyclophosphamide can be given orally at a dose of 1.0–2.0 mg/kg/d, but there may be a greater risk of hemorrhagic cystitis. The major side effects are gastrointestinal upset, bone marrow toxicity, alopecia, hemorrhagic cystitis, teratogenicity, sterilization, and increased risk of infection and secondary malignancy. Prehydration with intravenous fluids prior to intravenous treatment and maintaining a high fluid intake (oral or intravenous therapy) are important precautions to help avoid hemorrhagic cystitis. Urinalysis and CBCs are monitored closely (every 1–2 weeks at the onset of therapy and then at least monthly). The dose of cyclophosphamide should be decreased if the WBC decreases below 4000/mm^3. Cyclophosphamide is held if the WBC declines below 3000/mm^3, the absolute neutrophil count falls below 1000/mm^3, or there is evidence of hematuria. It can be restarted at a lower dose once the leukopenia has resolved, but we do restart the medication in patient with hematuria.

CHLORAMBUCIL

Chlorambucil is uncommonly used because of the significant side effects, which include bone marrow suppression, increased risk of cancer, infection, hepatotoxicity, Stevens–Johnson syndrome, and gastrointestinal disturbance. However, there are a few reports about chlorambucil being used to treat PM and DM.[215,229,230] CBCs and LFTs need to be monitored closely in patients treated with chlorambucil.

CYCLOSPORINE AND TACROLIMUS

Cyclosporine (2.5–10 mg/kg/d) may be effective in some patients with DM and PM, including childhood DM.[92,231–238] Improvement in strength may be seen within 2–6 weeks, and it may also serve as a steroid-sparing agent. However, the cost and potential side effects have limited its use in most patients with myositis. Tacrolimus has also been reported to help patients with refractory myositis.[239] Side effects of cyclosporine and tacrolimus are renal toxicity, hypertension, electrolyte imbalance, gastrointestinal upset, hypertrichosis, gingival hyperplasia, oncogenicity, tremor, and risk of infection.

We start cyclosporine at a dose of 3.0–4.0 mg/kg/d in two divided doses and gradually increase to 6.0 mg/kg/d as necessary.[15,82] The cyclosporine dose should initially be titrated to maintain trough serum cyclosporine levels of 50–200 ng/mL. Blood pressure, electrolytes and renal function, and trough cyclosporine levels need to be monitored closely.

Tacrolimus is started at a dose of 0.1 mg/kg and increased up to 0.2mg/kg (in two divided doses daily). The doses in titrated to maintain a trough level of 5–15 mg/mL. Blood pressure, electrolytes, and renal function need to be monitored closely and doses adjusted should renal insufficiency develop. With both of these agents, patients should be given a list of drugs to avoid that may increase the risk of renal toxicity.

INFLIXIMAB AND ETANERCEPT

These agents block TNF-α and are effective treatments in rheumatoid arthritis and other autoimmune disorders. A few small reports suggest that these medications may be effective in PM and DM.[68,240–243]

RITUXIMAB

A small open-label study of patients with DM suggested that rituximab could be an effective therapy,[244] and a large prospective, double-blind trial is currently underway. We have used it in a number of refractory patients, some of whom responded quite favorably. The dose is 750 mg per meter-squared (up to 1 g) intravenously with a repeat course one or two weeks later. Rituxan is a monoclonal antibody directed against CD20+ B-cells, which it depletes for 6 months or more.

PLASMAPHERESIS AND LEUKOPHERESIS

Uncontrolled series have reported improvement in DM, PM, and IBM with plasmapheresis or leukopheresis.[212,245,246] However, a controlled trial of 36 patients with DM

and PM comparing plasmapheresis with leukopheresis and with sham apheresis demonstrated no improvement with either plasmapheresis or leukopheresis over the sham apheresis.[247]

TOTAL BODY IRRADIATION

There are a few case reports of refractory cases of DM and PM improving following total body irradiation.[248–250] Others have not found total body irradiation to be effective in PM.[251] Total body irradiation is ineffective in IBM and may actually aggravate the disease.[252]

THYMECTOMY

Thymectomy has been performed on a small number of patients with PM and DM with improvement.[213]

▶ SUMMARY

DM, PM, and IBM are clinically, histologically, and pathogenically distinct categories of idiopathic inflammatory myopathy. Features of DM and PM can overlap with those of other autoimmune connective tissue diseases. Other types of inflammatory myopathy are much less common but are clinically and histologically distinguishable. DM is an immune mediated microangiopathy, perhaps due to overexpression of type 1 interferons that may be directly toxic to muscle fibers as well. PM is a T-cell-mediated disorder directed against muscle fibers. The pathogenesis of IBM is unknown. DM and PM are responsive to immunosuppressive therapy, in contrast to IBM, which is generally refractory to therapy. Prospective, double-blind, placebo-controlled trials are necessary to determine prognostic features for treatment responsiveness and the best treatment options for the different disorders.

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CHAPTER 31

Myopathies Associated with Systemic Disease

Myopathies can occur in the setting of a variety of neuromuscular disorders. Previous chapters have discussed inflammatory myopathies that can occur in the setting of connective tissue diseases (e.g., systemic lupus erythematosus, mixed connective tissue disease, Sjogren syndrome, and rheumatoid arthritis) and systemic infections (e.g., HIV). Myopathies occurring as complications of medications (toxic myopathies) are also dealt with elsewhere in the book. In this chapter we will focus on myopathies related to endocrine disturbances, electrolyte imbalance, nutritional deficiency, and amyloidosis.

▶ ENDOCRINE MYOPATHIES

Myopathies can complicate various endocrinopathies.[1,2] In this section, we review myopathies associated with thyroid, parathyroid, adrenal, pituitary, and pancreatic disorders.

THYROID DISORDERS

Myopathies can develop in patients who either are hyperthyroid or hypothyroid. In addition, polyneuropathy and neuromuscular junction disorders can occur with dysthyroid states and these need to be differentiated from one another.

THYROTOXIC MYOPATHY

Clinical Features

The mean age of onset of thyrotoxicosis is in the fifth decade. The severity of the myopathy does not necessarily relate to the severity of the thyrotoxicosis. Muscle symptoms usually appear several months after the onset of other clinical symptoms associated with mild hyperthyroidism.[3] Interestingly, thyrotoxicosis is more common in females; however, thyrotoxic myopathy occurs more commonly in men. Anywhere from 61–82% of patients with thyrotoxicosis have some degree of detectable weakness on examination, but only about 5% of patients with thyrotoxicosis present with muscle weakness as their chief complaint.[1,3–5]

Thyrotoxic myopathy is characterized by proximal muscle weakness and atrophy.[2–4,6,7] Some individuals have severe shoulder girdle atrophy and scapular winging.[2] Distal extremity weakness can be the predominant feature in approximately 20% of patients.[4] Myalgias and fatigue are common. Some patients develop dysphagia, dysphonia, and respiratory distress due to involvement of bulbar, esophageal-pharyngeal muscles, and ventilatory muscles.[8,9] Weakness of extraocular muscles and proptosis occur in the setting of Grave disease but the sphincters are spared in hyperthyroidism. Rarely, rhabdomyolysis with myoglobinuria can develop in severe thyrotoxicosis.[10]

Muscle stretch tendon reflexes are often brisk. In addition, fasciculations and myokymia are occasionally seen which probably reflects thyrotoxicosis-induced irritability of anterior horn cells or peripheral nerves.[11–13] An association of hyperthyroidism with peripheral neuropathy is quite rare, but a demyelinating polyneuropathy has been reported.[11]

Other manifestations of hyperthyroidism include nervousness, anxiety, psychosis, tremor, increased perspiration, heat intolerance, palpitations, insomnia, diarrhea, increased appetite, and weight loss. Common signs include goiter, tachycardia, atrial fibrillation, widened pulse pressure, as well as warm, thin, and moist skin.

Myasthenia gravis can develop in association with Grave disease. It can be challenging while trying to distinguish which neuromuscular symptoms are related to Grave disease and which are related to myasthenia gravis. Muscle weakness associated with hyperthyroidism does not fluctuate or significantly improve with anticholinesterase inhibitors.

Thyrotoxicosis is also associated with an unusual form of hypokalemic periodic paralysis. Thyrotoxic periodic paralysis appears to occur sporadically, although there may be an autosomal dominant inherited susceptibility. It has been commonly reported in Asians, but it is not restricted to this population.[2,5] Thyrotoxic periodic paralysis is also more common in males. The attacks of weakness are similar in onset, frequency, duration, and pattern familial hypokalemic periodic paralysis (see Chapter 29). While most cases of hypokalemic periodic paralysis occur within the first three decades of

life, onset of thyrotoxic periodic paralysis can develop later in adult life. Serum potassium levels tend to be low during the attacks of weakness, but levels can be normal. Muscle strength returns with treatment and normalization of thyroid function. Beta-adrenergic blocking agents also improve the myopathy.

Laboratory Features

The serum creatine kinase (CK) levels are usually normal in hyperthyroidism and can even be on the low side. Thyroid stimulating hormone (TSH) level is low while the thyroxine (T4) level and occasionally only the triiodothyronin (T3) level is elevated. In thyrotoxic periodic paralysis serum potassium levels are also decreased. Routine motor and sensory nerve conduction studies (NCS) are normal.[96] Electromyography (EMG) is usually normal, although fasciculation potentials and couplets may be evident due to motor nerve hyperactivity.

Histopathology

Routine muscle biopsies are usually unremarkable, however, mild fatty infiltrate, muscle fiber atrophy (types 1 and 2), variability in muscle fiber size, scattered isolated necrotic fibers, decreased glycogen, and increased internal nuclei can be noted.[12,14–16] Non-specific ultrastructural findings on electron microscopy (EM) may be seen including Z-band streaming, focal swelling of the T-tubules, elongated mitochondria, decreased mitochondria, and subsarcolemmal glycogen deposition.[17]

In patients with thyrotoxic periodic paralysis, muscle biopsies reveal changes similar to that seen in familial hypokalemic periodic paralysis: Vacuoles can be appreciated, on routine light microscopy while sarcolemmal blebs filled with glycogen and dilated terminal cisternae of the sarcoplasmic reticulum may be apparent on EM.

Pathogenesis

The thyroid gland produces T4 that is converted to the more active T3 hormone in the periphery. These thyroid hormones are largely bound to plasma proteins. Free thyroid hormones bind to cytoplasmic receptors on target cells and are internalized into the nucleus, where they regulate the transcription of specific genes. Type 1 muscle fibers have a greater density for these thyroid receptors than do type 2 fibers.[18]

The pathogenic basis of thyrotoxic myopathy is unknown but is thought to be due to enhanced muscle catabolism. There is an increase in the basal rate with enhanced mitochondrial consumption of oxygen, pyruvate, and malate.[18] Glucose uptake and glycolysis are stimulated in muscle independent of insulin.[19] This can lead to an insulin-resistant state with fasting hyperglycemia and glucose intolerance and subsequent depletion of glycogen and reduced ATP production. Insulin resistance also may interfere with insulin's anabolic effect on amino acid and protein metabolism.[20] There is an inadequate level of protein synthesis to meet the demands of accelerated breakdown which in turn may be driven by increased lysosomal protease activity.[21,22]

Thyrotoxic periodic paralysis may be the result of muscle membrane inexcitability. Thyroid hormones increase potassium efflux from muscle, which can leads to an increased number and activity of sodium-potassium ATPase pumps.[23] This in turn leads to a partial depolarization of the muscle membrane rendering it less excitable. Diminished muscle membrane excitability may also be secondary to depolarization-induced sodium-channel inactivation[6] and impaired propagation of the action potential across altered T-tubules.[24]

Treatment

Muscle strength improves gradually over several months with treatment of the hyperthyroidism.[2] Propranolol can prevent and lessen the attacks of thyrotoxic periodic paralysis. Unlike the familial form of hypokalemic periodic paralysis, acetazolamide is ineffective in preventing attacks of weakness associated with thyrotoxicosis.

Extraocular muscle weakness associated with Grave's disease can persist for months or years after treatment. Artificial tears and ophthalmic ointments may be beneficial in preventing drying of the cornea and exposure keratitis that can result from severe lid retraction. Immunosuppression with corticosteroids and cyclosporine can be helpful in some patients but are associated with significant side effects.[25]

HYPOTHYROID MYOPATHY

Clinical Features

Approximately one-third of individuals with hypothyroidism develop proximal arm and leg weakness along with myalgias, cramps, and generalized fatigue.[2,7,26] Some patients rarely develop muscle hypertrophy; rhabdomyolysis may occur. Further, ventilatory muscles may be affected in severe cases.[27]

Delayed relaxation of the muscle stretch reflexes may be demonstrated, particularly at the ankle. This finding is best appreciated by having the patient kneel on a chair or bench while striking the Achilles' tendon. Myoedema refers to painless and electrically silent mounding of muscle tissue when firmly percussed and is observed in approximately one-third of affected individuals.[28] Myasthenia gravis can also occur in association with hypothyroidism.[29]

Laboratory Features

The serum CK levels are elevated as much as 10–100 times of normal. In primary hypothyroidism, serum T4 and T3 levels are low while TSH levels are elevated. The motor and sensory NCS are usually normal unless they

have a concomitant polyneuropathy. Needle EMG is also usually normal, although short duration, low-amplitude polyphasic motor unit action potentials (MUAPs) may be appreciated in severely affected muscles.[30–34]

Histopathology

Muscle biopsies reveal nonspecific abnormalities: Variability in muscle fiber size with atrophy of type 2 and occasionally type 1 fibers, hypertrophic muscle fibers, rare necrotic fibers, increased internal nuclei, ring fibers, glycogen accumulation, vacuoles, and increased connective tissue.[15,35,36] Mitochondrial swellings and inclusions, myofibrillar disarray with central core-like changes, autophagic vacuoles, glycogen accumulation, excess lipid, dilated sarcoplasmic reticulum, and T-tubule proliferation may be appreciated on EM.[35]

Pathogenesis

Hypothyroidism leads to reduced anaerobic and mitochondrial aerobic metabolism of carbohydrates and fatty acids which decreases ATP production.[37,38] Hypothyroidism also impairs adrenergic function and produces a concomitant insulin-resistant state. Protein synthesis and catabolism are reduced.

Treatment

The myopathy improves with treatment of the hypothyroidism. However, some degree of weakness can persist even 1 year after return to a euthyroid state.

PARATHYROID DISORDERS

Myopathies are common in disorders of calcium and phosphate homeostasis. The regulation of calcium and phosphate levels requires a complex interaction of intestinal, renal, hepatic, endocrine, skin, and skeletal functions.[2] Vitamin D regulates calcium absorption in the intestines. There are several forms of vitamin D: (1) vitamin D3 or cholecalciferol, which is derived from the skin; (2) vitamin D2 or ergocalciferol, which is dietary and absorbed through the intestines; and (3) 25-hydroxy-vitamin D, which is made in the liver and converted to the more potent metabolite 1,25-dihydroxy-vitamin D in the kidneys. Parathyroid hormone (PTH) assists in the regulation of serum calcium levels by promoting bone resorption, increasing renal calcium absorption and phosphate excretion, and enhancing 1,25-vitamin D conversion. Diet, intestinal absorption, and renal excretion contribute to serum phosphate levels. Increased PTH leads to increased levels of 1,25-dihydroxy-vitamin D, hypercalcemia, and hypophosphatemia. Persistently elevated PTH results in resorption of minerals within bone and replacement by fibrous tissue, a condition termed "osteitis fibrosa" or "osteitis fibrosa cystica" in severe forms.[2]

HYPERPARATHYROIDISM AND OSTEOMALACIA

Clinical Features

Muscle weakness is very common in osteomalacia, occurring in as many as 72% of patients,[39] but develops in only 2–10% of patients with isolated hyperparathyroidism.[39,40] The earlier diagnosis and treatment of hyperparathyroidism and osteomalacia have led to fewer and less severe neuromuscular complications than appreciated in the past.[39–44]

The myopathy associated with primary hyperparathyroidism or osteomalacia is characterized by symmetric proximal weakness and atrophy which are worse in the lower extremities. Concomitant bone pain is common place due to associated microfractures. Involvement of the neck extensor muscles can lead to the so-called "dropped head syndrome." There are rare reports of hoarseness, dysphagia, ventilatory involvement, and spasticity[40,45–47] but it is unclear whether these cases had incidental hyperparathyroidism and amyotrophic lateral sclerosis.[48]

Muscle stretch reflexes are often brisk but plantar responses are flexor. As many as 50% of patients complain of cramps and paresthesia. In addition, in 29–57% of patients there is stocking-glove loss of pain or vibratory sensation and decreased muscle stretch reflexes suggestive of an underlying peripheral neuropathy.[40] Finally, hypercalcemia can be associated with neurobehavioral abnormalities (memory loss, poor concentration, personality changes, inappropriate behavior, anxiety, and hallucinations).

Secondary hyperparathyroidism and muscle weakness can develop in patients with chronic renal failure.[49] Muscle necrosis and myoglobinuria due to calcification of the arteries (calcifiphylaxis) can develop in this setting.[50,51] Calciphylaxis can also occur in patients with renal failure without overt hyperparathyrodism.[52]

Laboratory Features

Serum CK levels are usually normal in primary and secondary hyperparathyroidism and osteomalacia. In primary hyperparathyroidism, serum calcium levels are usually elevated and serum phosphate levels are low, while urinary excretion of calcium is low and excretion of phosphate is high. In patients with concurrent hypoalbuminemia, serum calcium levels may be normal, so it is imperative to measure the ionized calcium levels which are typically elevated. Increased urinary excretion of cyclic adenosine monophosphate in the presence of hypercalcemia is also seen in hyperparathyroidism. Serum PTH levels and 1,25-dihydroxy-vitamin D levels are elevated in primary hyperparathyroidism. In contrast, 1,25-dihydroxy-vitamin D levels are low in secondary

hyperparathyroidism due to renal failure. Noninvasive imaging techniques, such as ultrasound, thallium/technetium scintigraphy, computed tomography, and magnetic resonance imaging (MRI), may be useful in localizing abnormal parathyroid glands.[53]

Serum calcium level is low or normal, serum phosphate is variably low, and 25 OH vitamin D levels are also usually low in patients with osteomalacia. Urinary excretion of calcium is low (except in cases secondary to renal tubular acidosis) while excretion of phosphate is high. In addition, serum alkaline phosphatase levels are elevated in 80–90% of cases of osteomalacia.[54] Skeletal survey reveals decrease bone density along with loss of trabeculae, blurred of trabecular margins, and variably thinned cortices.[41] EMG and NCS are normal unless the patients have a neuropathy related to their renal failure.

Histopathology

Muscle biopsies usually demonstrate nonspecific myopathic features with atrophy predominantly of type 2 fibers, but occasionally also of type 1 fibers.

Pathogenesis

Primary hyperparathyroidism can be caused by parathyroid adenomas or hyperplasia as well as pituitary adenomas. Secondary hyperparathyroidism usually occurs in the setting of chronic renal failure which results in the reduction of 1,25-dihydroxy-vitamin D conversion. This leads to diminished intestinal absorption of calcium and decreased renal phosphate clearance which promotes secondary hyperparathyroidism and osteomalacia. In addition to acquired forms, there are hereditary forms of primary hyperparathyroidism[55] and of vitamin D deficiency and osteomalacia.[41]

The mechanism(s) of weakness in hyperparathyroidism and osteomalacia are not known. PTH stimulates proteolysis in muscle[56] and impairs energy production, transfer, and utilization.[2,57] In addition, PTH may reduce the sensitivity of contractile myofibrillar proteins to calcium and activate a cytoplasmic protease, thus impairing the bioenergetics of muscle.[1] Calcium and phosphate levels do not correlate well with the clinical severity of muscle weakness.[39,40,58] Vitamin D also has a direct effect on muscle by increasing muscle adenosine triphosphatase concentration, accelerating amino acid incorporation into muscle proteins,[2,59] and enhancing the uptake of calcium by the sarcoplasmic reticulum and mitochondria.[60,61]

Treatment

Hyperparathyroidism is diagnosed earlier than in the past because of routine screening of serum calcium levels. Thus, affected individuals are frequently asymptomatic or only mildly affected when they are diagnosed. Medical therapies and surgery are very effective for improvement of muscle weakness when detected within a few months.[2,40,53,62]

The treatment of choice of symptomatic patients with primary hyperparathyroidism is parathyroidectomy.[53] If a patient has a parathyroid adenoma, the affected gland is removed, while additional glands may be biopsied. Individuals with hyperplasia of all four glands generally have subtotal (three and a half glands) parathyroidectomies. Those who are asymptomatic or have significant perioperative risk may be managed medically.[62] Secondary hyperparathyroidism improves with vitamin D and calcium replacement or renal transplantation, if it is due to end-stage renal failure.[63] Occasionally, subtotal parathyroidectomy may need to be performed in patients with secondary hyperparathyroidism. Likewise, the myopathy associated with osteomalacia responds well to vitamin D and calcium replacement and to treatment of the underlying responsible condition.[39,41–43,54,64,65]

HYPERPARATHYROIDISM AND MOTOR NEURON DISEASE

Some authors have suggested that hyperparathyroidism can cause a neuromuscular syndrome that mimicks amyotrophic lateral sclerosis and that patients may improve following resection of parathyroid adenomas.[40,46] However, we suspect most of these patients who improved with parathyroidectomy did not have a motor neuron disorder, but rather, hyperparathyroid-related myopathy.[48] In our experience, hyperparathyroidism in patients who meet clinical and electrophysiologic criteria for amyotrophic lateral sclerosis is just coincidental, and these patients do not improve with parathyroidectomy.[48]

HYPOPARATHYROIDISM

Clinical Features

Hypoparathyroidism does not typically cause a myopathy, although a few patients do develop mild proximal weakness.[66–68] In addition, painless myoglobinuria without objective weakness or tetany has been reported.[69] On the other hand, paresthesia and tetany can develop in hypoparathyroidism secondary to hypocalcemia. The examiner may be able to demonstrate Chvostek's sign (ipsilateral facial contraction upon tapping the facial nerve at the external auditory meatus) and Trouseau's sign (thumb adduction, metacarpophalangeal joint flexion, and interphalangeal joint extension) in these hypocalcemic patients.

Laboratory Features

Serum CK can be normal or mildly elevated in patents.[70,71] Hypoparathyroidism is associated with low

serum PTH and calcium levels and high serum phosphate levels. Motor and sensory NCS are normal. Needle EMG reveals normal insertional activity but doublets, triplets, or multiplets of MUAPs (single MUAPs repeated firing rapidly in succession with interdischarge intervals between 2 and 20 ms) and fasciculation potentials may be appreciated because of motor nerve hyperexcitability induced by the hypocalcemia.[72–74] Otherwise, MUAP morphology and recruitment are normal.

Histopathology

Muscle biopsies may be normal or demonstrate mild variability in fiber size and increased internalized nuclei that reflect previous muscle damage caused by episodes of tetany.[2,15] Decreased glycogen phosphorylase activity of muscle biopsy specimens has also been described.[1]

Pathogenesis

Hypoparathyroidism is seen in a number of conditions, including osteomalacia, complications of surgery, hypomagnesemia or hypermagnesemia, irradiation, drugs, sepsis, infiltrative diseases of the parathyroid, and autoimmune, hereditary, or developmental disorders of the parathyroid glands.[75] Decreased PTH leads to reduced synthesis of 1,25-dihydroxyvitamin D, hypocalcemia, and hyperphosphatemia.

The pathogenic mechanisms of muscle weakness associated with hypoparathyroidism is poorly understood. Decreased serum calcium concentration causes a shift in the cellular activation potential toward the resting potential.[69,76–78] Therefore, less current is required to elicit an action potential which can lead to tetany. Elevated serum CK and mild histologic abnormalities on muscle biopsy are generally considered secondary to muscle damage from tetany.

Treatment

Muscle weakness improves following correction of the hypocalcemia and hyperphosphatemia with vitamin D and calcium administration.[68]

ADRENAL DISORDERS

The adrenal gland is comprised of three major regions: (1) zona fasciculata, (2) zona glomerulosa, and (3) zona reticularis.[2] The zona fasciculata produces and secretes glucocorticoids, which when produced in excess by a tumor of the adrenal gland can cause a myopathy. Mineralocorticoids such as aldosterone are generated by the zona glomerulosa and when produced in excess can cause hypokalemic which in turn leads to muscle weakness. The zona reticularis generates androgens but excess or deficiency of these hormones do not result in a muscle weakness. In contrast, these so-called anabolic steroids may increase muscle strength and mass. In the following section we discuss myopathies associated with excess or deficiency of glucocorticoids.

STEROID MYOPATHY

Steroid myopathy is the most common endocrine-related myopathy. An excess of glucocorticooids may arise from pituitary or adrenal tumors and iatrogenic sources (corticosteroid medications).

Clinical Features

Approximately 50–80% of patients with Cushing disease develop some degree of proximal weakness prior to treatment.[2,79] Distal extremity, oculobulbar, and facial muscles are spared. Patients classically have an increase in truncal adipose tissue and hyperpigmentation of the skin (i.e., the so-called Cushingoid appearance).

The incidence of iatrogenic steroid myopathy is not at all clear. Women appear to be more at risk for developing a steroid myopathy than men, approximately 2:1 but the reasons are unclear. An increased risk of the myopathy is seen with prednisone doses of 30 mg/d or more (or equivalent doses of other corticosteroids).[2] Fluorinated corticosteroids have a greater propensity for producing muscle weakness than the non-flourinated compounds (e.g., risk for myopathy: Triamcinolone > betamethasone > dexamethasone).[80] Alternate day therapy may reduce the risk of corticosteroid-induced weakness but this has never been proven in a clinical trial. Weakness can develop within several weeks of starting high doses of corticosteroids but more typically develops after chronic administration. In addition, an acute onset of severe generalized weakness can occur in patients receiving high dosages of intravenous corticosteroids with or without concomitant administration of neuromuscular blocking agents (see section on acute quadriplegic myopathy/critical illness myopathy in Chapter 32).

Laboratory Features

Serum CK is normal. Serum potassium can be low and sodium may be elevated. Motor and sensory NCS and EMG are normal.

Histopathology

Muscle biopsy characteristically reveals preferential atrophy of type 2B fibers (Fig. 31–1).[15,81] Milder degrees of atrophy and increased lipid deposition of type 1 muscle may be seen as well.

Pathogenesis

Corticosteroids bind to receptors on target cells and are subsequently internalized into the nuclei where they

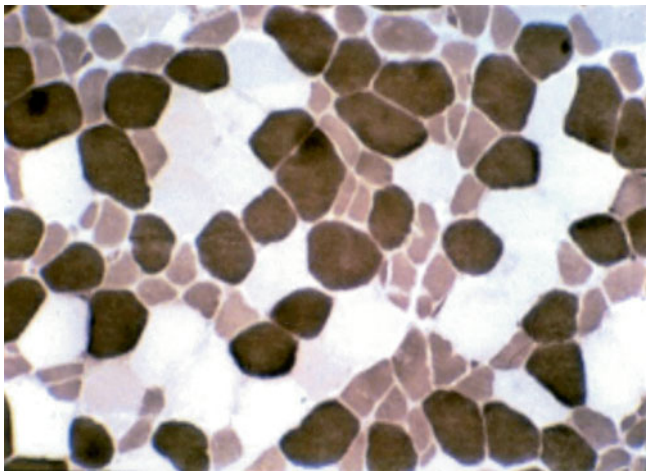


Figure 31–1. Steroid Myopathy. Atrophy of type 2B fibers, which are intermediate staining, are appreciated on ATPase 4.5.

regulate the transcription of specific genes. It is not known how corticosteroids lead to muscle dysfunction. Corticosteroids may result in diminished protein synthesis, increased protein degradation, altered carbohydrate metabolism, impaired mitochondrial function, or decreased sarcolemmal membrane excitability (i.e., in the setting of acute quadriplegic myopathy).[1,2] In addition, hypokalemia associated with excess corticosteroid can also cause muscle weakness.

Treatment

In cases of adrenal tumors, treatment is surgical when possible. In patients with iatrogenic steroid myopathy, treatment requires reduction in the corticosteroid dose, switching to an alternate day regimen, and encouraging exercise to prevent concomitant disuse atrophy.[2] Experimental studies suggest that insulin-like growth factor-1 may have a prophylactic effect on preventing steroid myopathy.[82]

A common dilemma that physicians face is renewed or exacerbated weakness in a patient receiving corticosteroids for treatment of an immune-mediated neuromuscular disorder (e.g., inflammatory myopathy, inflammatory neuropathies, or myasthenia gravis).[83,84] Following an initial improvement in their strength with corticosteroid treatment, some patients later experience a subsequent decline in muscle function. The question then arises: Is this a relapse/exacerbation of the disease or a steroid myopathy? Several clinical and laboratory features may be helpful in these situations. If the weakness developed while the patient was tapering the corticsteroids, a relapse of the underlying disease process should be considered. In contrast, if weakness occurred while the patient was on a chronic high doses of steroids, a steroid myopathy is then perhaps more likely. In the case of an inflammatory myopathy, an increasing serum CK would point to an exacerbation of the myositis.[85] An EMG can be useful in that it is usually normal in steroid myopathy, while abnormal insertion and spontaneous activity along with early recruitment of myopathic MUAPs would be expected in an exacerbation of an inflammatory myopathies. Abnormally increased signal on STIR images of skeletal muscle MRI scans would also favor active myositis. Likewise, in myasthenia gravis, one might expect to find fluctuation of clinical deficits on examination (ptosis and ophthalmoplegia are not seen in steroid myopathy) and an increase in decrement with repetitive stimulation tests, or increased jitter and blocking on single fiber EMG if there was a flare in the myasthenia gravis. Deterioration in the strength of only proximal muscles in patients with chronic inflammatory demyelinating neuropathy would favor a steroid myopathy as distal muscles are preferentially affected in this neuropathy. However, sometimes it is impossible to state with certainty whether the new weakness is related to a relapse of the underlying disease or secondary to the corticosteroid treatment. In such cases, the best approach is to taper the corticsteroid medication and closely observe the patient. If improvement in strength follows, one can assume the patient had a steroid myopathy. If the patient deteriorates, the worsening weakness is more likely related to the underlying autoimmune neuromuscular disorder and they may require increased doses of corticosteroids or other immunosuppressive medication.

ADRENAL INSUFFICIENCY

Adrenal insufficiency can result from adrenal or pituitary dysfunction and may be associated with subjective weakness and fatigue.[2] Objective weakness is usually the result of electrolyte disturbances (e.g., hyperkalemia) or concurrent endocrinopathies.[2] Serum CK levels, EMG, and muscle biopsies are usually normal. Symptoms improve with proper replacement of adrenal hormones.

▶ PITUITARY DISORDERS

ACROMEGALY

Clinical Features

Patients with acromegaly may develop slowly progressive proximal arm and leg weakness without muscle atrophy.[2,86] If anything, muscle hypertrophy is appreciated. Acromegaly can cause bony overgrowth leading to nerve root and spinal cord compression. In addition, there is a predisposition for developing multiple entrapment neuropathies such as carpal tunnel and cubital tunnel syndromes. Degenerative joint changes can produce

pain that limits activity which may result in disuse muscle atrophy as well.

Laboratory Features

Serum CK levels can be normal or mildly elevated. Motor and sensory NCS can be normal or demonstrate features of a mononeuropathy (i.e., carpal tunnel syndrome).[87–89] Short duration and low amplitude MUAPs may be detected on EMG of proximal muscles of the arms and legs owing to the myopathy.[86] Additionally, the EMG can reveal neurogenic features of involved muscle groups if a patient has a mononeuropathy or radiculopathy related to their acromegaly.

HISTOPATHOLOGY

Muscle biopspies reveal variation in muscle fiber size with hypertrophy and atrophy of all fiber types.[90,91] Hypertrophy of satellite cells is often appreciated. In addition, rare necrotic fibers may be seen. Myofibrillar loss and abnormal glycogen accumulation may be found on EM.

Pathogenesis

The development and severity of muscle weakness correlates with the duration of acromegaly rather than the levels of serum growth hormone.[86,92] Growth hormone increases protein synthesis within muscle fibers and may lead to muscle fiber hypertrophy.[93,94] However, the pathogenic basis for the muscle weakness that develops despite increased muscle bulk is not known. Studies have demonstrated that the respiratory quotient of resting forearms muscles of patients with acromegaly is lower than normal (0.68 vs. 0.76).[95] Adminstration of growth hormone increases fatty acid oxidation and decreases glucose utilization.[96] It appears that growth hormone causes muscle to preferentially metabolize lipid as opposed to carbohydrates and this could alter dynamic muscle activity and fatigue. In addition, growth hormone may reduce myofibrillar ATPase activity.[97] In addition, muscle membranes are slightly depolarized compared to normal resting activity which would make them less excitable.[1]

Treatment

Surgical resection of the pituitary adenoma with subsequent reduction of the growth hormone levels leads to improved muscle strength.[86]

PANHYPOPITUITARISM

Pituitary failure in adults commonly leads to muscle weakness and fatigue, probably due to secondary deficiencies of thyroid and glucocorticoid hormones.[98] The myopathy improves with replacement of these hormones. Prepubertal panhypopituitarism is associated with dwarfism and lack of sexual and muscular development. Deficiency of growth hormone may contribute to muscle weakness in this condition as administration of only thyroid and adrenal hormones does not result in improved strength unless growth hormone is also replaced.[99] However, it is less clear if growth hormone deficiency can contribute to muscle weakness in adults with panhypopituitarism.

DIABETES MELLITUS

Neuromuscular complications of diabetes are usually referable to peripheral neuropathies (see Chapter 19). The only myopathic disorder clearly associated with diabetes is muscle infarction.

DIABETIC MUSCLE INFARCTION

Clinical Features

Diabetic muscle infarction usually occurs in the setting of poorly controlled diabetes. Most patients have other evidence of end-organ damage (retinopathy, nephropathy, neuropathy).[100–105] Patients most commonly present with acute pain and swelling in one thigh. Occasionally, the calf is affected. A tender mass may be palpated in the quadriceps (most often the vastus lateralis), biceps femoris, or thigh adductors, and occasionally in the gastrocnemius muscle. The focal swelling and MRI changes often lead to a misdiagnosis of a sarcoma or focal myositis. Muscle biopsy should be avoided, if possible, because of the risk of subsequent hemorrhage into the tissue.[52]

Laboratory Features

Serum CK levels are usually normal. MRI or CT of the leg demonstrates signal abnormalities in areas of infracted muscle. EMG demonstrates fibrillation potentials and positive sharp waves as well as small, polyphasic MUAPs with early recruitment in the involved muscles.[101]

Histopathology

Muscle biopsies demonstrate large areas of necrosis, edema, hemorrhage, and inflammatory infiltrate consistent with muscle infarction (Fig. 31–2). This infarcted area is later replaced by connective and adipose tissue. Thickening of the basement membranes, hyperplasia of the media, and lumens occluded by fibrin, calcium, and lipid of small and medium sized blood vessels may be appreciated.[52]

Pathogenesis

Ischemic damage and secondary hemorrhagic infarction result from long-standing, diabetic vasculopathy.

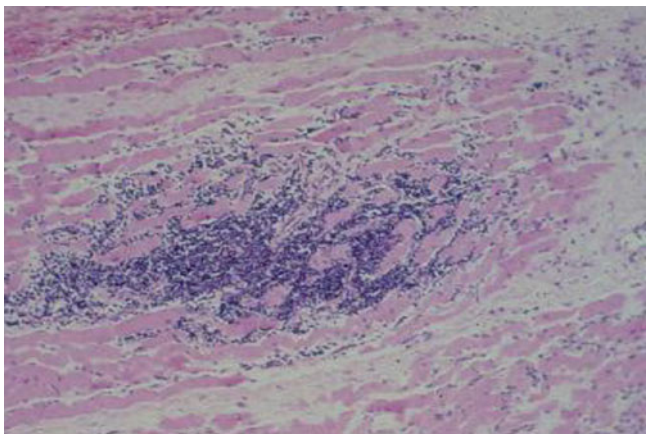


Figure 31–2. Diabetic Muscle Infarct. Quadriceps muscle biopsy reveals widespread necrosis and endomysial inflammatory cell infiltrate. Paraffin section, stained with hematoxylin and eosin.

Treatment

The muscle pain and swelling resolves after several weeks, although symptoms may recur in the contralateral leg. Treatment consists of immobilization and pain control. Sometimes we give a short course of prednisone to help with the pain by reducing edema and release of cytokines. However, one must closely monitor the serum glucose levels in such cases.

▶ MYOPATHIES ASSOCIATED WITH ELECTROLYTE IMBALANCE

DISORDERS OF POTASSIUM (HYPOKALEMIA)

Clinical Features

Hypokalemia is the most common electrolyte abnormality that causes muscle weakness.[106] Clinical, laboratory, and electrophysiological features are similar to familial hypokalemic periodic paralysis (see Chapter 29). Patients must be evaluated for other etiologies of hypokalemia (Table 31–1) before assuming a diagnosis of family hypokalemic periodic paralysis. Patients usually present with symmetric proximal or generalized weakness, although asymmetric muscle weakness can be seen. Weakness is often accompanied by complaints of myalgias and cramps. A severe complication of hypokalemia is rhabdomyolysis with myoglobinuria and secondary renal failure.

Laboratory Features

Usually the potassium levels need to be less than 2.5 mEq/l before any muscle breakdown and weakness occur. Serum CK levels are usually elevated in patients with hypokalemic myopathy. NCS are normal. EMG of weak muscles may demonstrate fibrillation potentials and positive sharp waves as well as early recruitment of small duration, low-amplitude MUAPs. The EKG may demonstrate bradycardia, flattened T waves, prolonged PR and QT intervals, and notable U waves.

▶ **TABLE 31–1. ETIOLOGIES OF SECONDARY HYPOKALEMIC AND HYPERKALEMIC PARALYSES**

Hypokalemic Paralysis
Thyrotoxic periodic paralysis
Renal tubular acidosis
Villous adenoma
Bartter's syndrome
Hyperaldosteronism
Chronic or excessive use of diuretics, corticosteroids, licorice
Amphotericin B toxicity
Alcoholism
Toluene toxicity
Barium poisoning
Hyperkalemic Paralysis
Addison disease
Hypoaldosteronism (hyporenemic)
Isolated aldosterone deficiency
Excessive potassium supplementation
Potassium-sparing diuretics (e.g., spironolactone, triamterene)
Chronic renal failure
Rhabdomyolysis

Histopathology

Biopsies of very weak muscles may demonstrate vacuoles and scattered necrotic fibers.

Pathogenesis

The mechanism of muscle fiber destruction and weakness is not fully known. Reduced extracellular potassium concentration may render the muscle membrane less excitable. Hypokalemia may also diminish blood flow and suppress the synthesis and storage of glycogen in muscles.

Treatment

Muscle strength returns with correction of the hypokalemia. The patients need a medical work-up to elucidate the underlying cause of the hypokalemia.

HYPERKALEMIA

Clinical Features

Hyperkalemia can also cause generalized muscle weakness. In addition, there is evidence of increased neuronal or muscle membrane excitability as manifested by the presence of Chvostek's sign or myotonic lid lag. There

are a number of causes of hyperkalemia and these need to be excluded before concluding a patient has familial hyperkalemic periodic paralysis (Table 31–1).

Laboratory Features

Most patients with severe generalized weakness have serum potassium levels greater than 7 mEq/L. Renal insufficiency and acidosis may accompany the hyperkalemia but serum CK levels are usually normal. EKG may demonstrate tall, peaked T-waves.

Routine NCS are normal. EMG may demonstrate early recruitment of small "myopathic" MUAPs, but fibrillation potentials and positive sharp waves are not typically seen. Unlike, familial potassium-sensitive periodic paralysis, myotonic discharges are never seen in the acquired forms of hyperkalemic myopathy.

Histopathology

Muscle biopsies are typically normal.

Pathogenesis

Hyperkalemia causes a prolonged depolarization of the muscle membrane that in turn inactivates the sodium channel inactivation reduces the excitability of the muscle membrane.

Treatment

Muscle strength returns with correction of hyperkalemia. The underlying cause of the hyperkalemia must be elucidated and treated.

DISORDERS OF CALCIUM

Muscle weakness secondary to hypercalcemia and hypocalcemia was discussed in the section regarding parathyroid myopathies.

DISORDERS OF PHOSPHATE

Hypophosphatemia

Hypophosphatemia can occur in diabetic ketoacidosis, acute alcohol intoxication, hyperalimentation with phosphate-poor preparations, severe diarrhea, and in patients taking phosphate-binding antacids. Serum phosphate levels less than 0.4 mM/L may lead to generalized muscle weakness, rhabdomyolysis, and myoglobinuria.[107] Some patients develop paresthesiae and diminished muscle stretch reflexes. Detailed electrophysiological studies or histopathologic descriptions are lacking in hypophosphatemia-induced muscle weakness. Symptoms resolve with correction of the serum phosphate levels.

DISORDERS OF MAGNESIUM

Hypermagnesemia most often occurs secondary to over usage of magnesium-containing laxatives, particularly if the patient has renal insufficiency.[108] It can also develop during treatment of eclampsia with magnesemia sulfate. Severe generalized and ventilatory muscle weakness may ensue but resolve with correction of the serum magnesium levels.

Muscle and nerve hyperexitability as characterized by Chovstek's and Trousseau's signs and tetany may be seen in hypomagnesemia. However, hypocalcemia and other electrolyte disturbances typically accompany hypomagnesemia and therefore, it is difficult to attribute the neuromuscular abnormality solely to the low serum magnesium levels.

▶ MYOPATHIES ASSOCIATED WITH MALIGNANCY

Patients with malignancies frequently develop generalized weakness, although most do not have a true paraneoplastic syndrome. Muscle weakness in patients with cancer are much more likely related to impaired nutrition, increased catabolic state induced by the tumor, disuse atrophy, and perhaps toxic effects of chemotherapeutic agents. There are a few well-defined paraneoplastic syndromes, including sensory neuronopathies or sensorimotor neuropathies (e.g., anti-Hu syndrome as discussed in Chapter 17) and Lambert-Eaton syndrome (see Chapter 23), resulting in generalized weakness. Inflammatory and necrotizing myopathies can occur in the setting of cancer (as discussed in more detail in Chapter 30). Rarely, patients with malignancy can have spread of the tumor into a region of muscle.[109,110] Any muscle group can be invaded by resulting in pain, swelling, and weakness in the local region. EMG of the affected muscles may reveal membrane instability and MUAPs with short duration and low amplitudes. Muscle biopsy can demonstrate evidence of tumor emboli.

▶ OTHER MYOPATHIES SECONDARY TO SYSTEMIC DISEASE

AMYLOID MYOPATHY

Clinical Features

Amyloid myopathy usually occurs in the setting of primary amyolidosis (light-chain amyloidosis).[111–118] and is less frequent with familial amyloidosis.[119,120] Amyloid myopathy does not occur in secondary amyloidosis (AA).

With primary and familial amyloidosis, cardiac muscle, peripheral nerves, skin, kidneys, and other organs

can also be affected in addition to skeletal muscle. In fact, most patients present with non-muscle related symptoms. Approximately 20% of patients have a co-existent generalized peripheral neuropathy; mononeuropathies such as carpal tunnel syndrome and ulnar neuropathy also occur.[116] Amyloid myopathy usually manifests with an insidious onset of progressive proximal weakness, although distal muscles can also be affected.[116,118] The distal muscle weakness may be in-part related to a superimposed amyloid myopathy. Hypertrophy of involved muscle groups can be appreciated; the tongue is often involved with notable macroglossia. However, other patients develop atrophic muscles; again this could be related to the associated neuropathy. Ventilatory failure can occur due to involvement of the diaphragm muscle and phrenic nerves. Muscle induration, stiffness, and pain are also variably present.

Laboratory Features

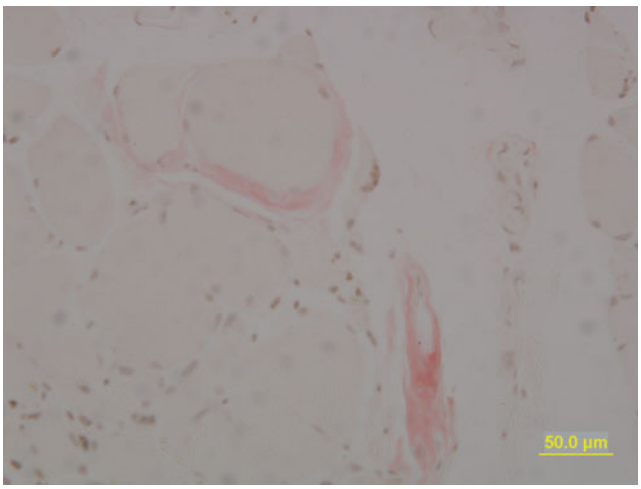
Serum CK is usually elevated 2 to 5 fold but has been as high as 70-fold in a patient with familial amyloidosis due to gelsolin mutation FA.[116] AL is associated with monoclonal light chain immunoglobulins (λ greater than κ) in the serum or urine. Renal insufficiency and proteinuria can arise due to amyloid deposition in the kidneys.

Nerve conduction studies are abnormal in patients with coexistent peripheral neuropathy. They often reveal reduced motor and sensory amplitudes and mild slowing of conduction velocities.[113,115–117] Superimposed carpal tunnel syndrome is a common finding. EMG reveals muscle membrane irritability with frequent fibrillation potentials and positive sharp waves, particularly in the paraspinal and proximal extremity muscles.[111,113–118,121] Complex repetitive discharges and myotonic discharges may also be appreciated. Early recruitment of short duration, low amplitude, polyphasic MUAPs is present in weak proximal muscles. In addition, patients with superimposed amyloid neuropathy often have decreased recruitment of long duration, large-amplitude potentials MUAPs in distal muscles.

Histopathology

Muscle biopsies demonstrate variability in fiber size with an admixture of hypertrophic and atrophic fibers.[116] Scattered necrotic and regenerating fibers, and increased internalized nuclei may be seen. Group atrophy related to denervation may be appreciated. Amyloid deposition is best visualized using rhodamine optics on Congo-red stained section (Fig. 31–3).[116] After employing this technique in the routine evaluation of all muscle specimens, the Mayo Clinic demonstrated a 10-fold increase in the diagnosis of amyloid myopathy, suggesting it is probably an underdiagnosed entity.[116]

The amyloid deposits are best appreciated surrounding small arterioles and venules. In addition, muscle fibers are also partially or completely encased by amyloid deposits. In primary amyloidosis, immunohistochemical studies reveal that the amyloid deposits are composed of λ or κ light chains.[116] Immunohistochemistry employing antibodies directed against gelsolin and transthyretin are useful in excluded familial amyloidosis. Membrane attack complex may co-localize with amyloid deposition. ApoE was deposited in all patients regardless of the type to systemic amyloidosis in one large series of patients.[116] EM confirms the deposition of short,



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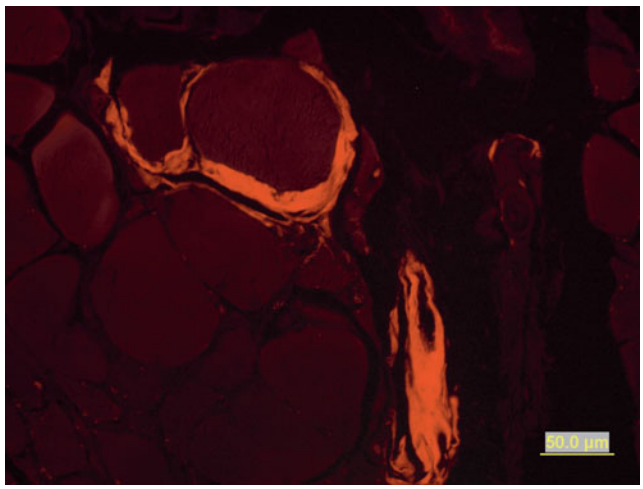

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Figure 31–3. Amyloid myopathy. Amyloid deposition is appreciated surrounding blood vessels and occasionally encasing individual muscle fibers on Congo red staining. The deposits are pink on routine light microscopy (Figure 31–3A) and bright red using rhodamine optics (Figure 31–3B).

non-branching 10 nm amyloid filaments around small blood vessel and muscle fibers.

Pathogenesis

The exact mechanism by which amyloid deposition causes muscle fiber damage is not known. Ischemic damage may arise due to deposition of amyloid in blood vessel walls. Encasement of muscle fibers by the amyloid may interfere with the transport of oxygen, nutrients, and wastes into and out of muscle fibers. There may also be mechanical interference of muscle contraction secondary to amyloid infiltration. Alternatively, the amyloid may interfere with electrical conduction along the sarcolemma.

Treatment

There is no proven effective medical therapy for the myopathy secondary to systemic amyloidosis.

CRITICAL ILLNESS MYOPATHY/ACUTE QUADRIPLEGIC MYOPATHY

This entity is usually associated with high dose steroids with or without non-depolarizing neuromuscular agents and is discussed in detail in Chapter 32 regarding Toxic Myopathies.

▶ ILL-DEFINED DISORDERS

POLYMYALGIA RHEUMATICA

Clinical Features

Polymyalgia rheumatica usually occurs in patients over the age of 50 years (peak incidence of 70–79 years).[7,122,123] The prevalence is approximately of 1 case for every 133 people over the age of 50 years.[124] There is a female predilection for development of polymyalgia rheumatic. Patients usually complain of an insidious or acute onset of diffuse nonarticular pain beginning about the neck and shoulder region but other muscle groups can be affected. A low-grade fever and malaise may accompany the myalgias. Affected individuals may complain of feeling weak or fatigued but on manual muscle testing their strength should be normal. Approximately 16% of patients develop temporal arteritis which can be complicated by acute vision loss.[122] Temporal-artery biopsy should be performed on all such patients with headaches or visual disturbances to look for evidence in giant-cell arteritis.

Laboratory Features

The erythrocyte sedimentation rate (ESR) is usually abnormal and elevated; typically over of 40 mm/hr. Serum CK should be normal. Likewise, EMG and NCS should be normal.

Histopathology

The muscle biopsies should be normal, but mild nonspecific findings (e.g., type 2 fiber atrophy, fiber size variation, and moth-eaten fibers) have been reported.[123] Also note there is no evidence of significant inflammation in the muscle or overlying fascia.

Pathogenesis

The exact pathogenic basis for polymyalgia rheumatic is unclear. The elevated ESR and excellent response to corticosteroids suggests an immunologic mechanism. Some cases are clearly associated with arteritis/vasculitis but it is not usually related to a true myositis or faciitis.

Treatment

The administration of corticosteroids results in considerable symptom relief within a few days.

FIBROMYALGIA

Fibromyalgia and myofascial pain syndrome are commonly diagnosed disorders that are controversial in regard to their nature because of the lack of objective evidence of organic disease.[125,126] Fibromyalgia is often dominated by subjective complaints of generalized muscle pain in addition to other somatic complains including headaches, fatigue, and abdominal cramps. In this regard, it shares many features with the somatoform disorders and the equally dubious chronic fatigue syndrome.[127,128]

There is no "gold standard" for diagnosing fibromyalgia. Fibromyalgia may be diagnosed if a sufficient number of "tender points" at specific locations on the body are found.[129] Unfortunately, the study by which these criteria were based is scientifically flawed.[125,126] The investigators predetermined that tender points were necessary for diagnosis and they each received training in how to identify such tender points. Patients diagnosed with fibromyalgia based on the presence of tender points were then evaluated by other investigators to confirm their presence. The fact that these tender points were reproducible (good intra-observer reliability), served as a validation of the diagnosis for the investigators. Skeptics criticized the study for confirming the established bias of the investigators.[125,126,130] Detecting tender points is dependent on the patient's subjective input and is in no way a truly objective marker. The neurological examination including muscle strength testing and laboratory evaluation is otherwise normal in fibromyalgia.

Likewise, serum CK, nerve conduction studies, and electromyography (even of in the areas of tender points) are normal. Finally, there is no difference in the frequency of abnormal histologic findings compared to control populations.

Myofacial pain syndrome (MPS) is similar to fibromyalgia but the pain is described as being more focal or regional as opposed to generalized.[125,126] Rather than tender points, advocates of the disorder suggest patients have "trigger points." These trigger points have been associated with "taut bands," "nodules," and "local twitch responses." However, a blinded, controlled studies have demonstrated a low sensitivity and specificity of this so-called diagnostic marker of MPS.[131] One study described abnormal "spontaneous EMG" activity in the area of the trigger points.[132] However, review of the published figures suggest this was just normal end plate spike activity. The majority of electromyographers, including ourselves, have not been able to verify the presence of any abnormalities in MPS.[125,126] As with fibromyalgia, the clinical examination, serum CK, EMG and NCS, and muscle biopsies are normal.

Regardless of the organicity of the pain related to fibromyalgia or MPS, the patients' symptoms are often quite distressing and disabling to them. We often recommend treatment with tricyclic antidepressant medications, pregabalin, or gabapentin as we do with other chronic pain syndromes. patients may also benefit from physical therapy program to increase their endurance and tolerance.

▶ SUMMARY

Many systemic disorders can be associated with a myopathy. The myopathy may be a direct effect of the systemic process or may be toxic related to drugs used to treat the underlying condition. Sometimes the myopathy improves with treatment of the systemic disorder, thus the importance of a detailed evaluation in patients referred for possible myopathy.

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CHAPTER 32

Toxic Myopathies

Many drugs can cause a myopathy.[1–9] The pathophysiological mechanisms for myotoxicity are diverse and, in many instances, unclear. Medications can have either a direct or an indirect adverse effect on muscle. The direct effect can be focal, as might occur secondary to a drug being injected into tissue, or generalized. Indirect toxic effects may result from the agent creating an electrolyte imbalance or inducing an immunological reaction. Muscle fibers may undergo necrosis as a result of the drug directly disrupting the sarcolemma, nuclear or mitochondria function, or that of other organelles. We try to classify the toxic myopathies according to their presumed pathogenic mechanisms (Table 32–1).

▶ NECROTIZING MYOPATHIES

A number of drugs can cause a generalized necrotizing myopathy. Affected individuals may complain of myalgias or weakness or they might just have asymptomatic elevations of their serum creatine kinase (CK) levels. Severe necrotizing myopathy may be complicated by myoglobinuria and renal failure. The degree of serum CK elevation is proportionate to the amount of muscle damaged.

CHOLESTEROL-LOWERING DRUGS

Cholesterol-lowering medications including 3-hydroxy-3methyl-glutaryl-coenzyme A (3-HMG-CoA) reductase inhibitors,[10–18] fibric acid derivatives,[15,19–29] niacin,[30,31] and ezetimibe[32–35] can cause a toxic myopathy. Most patients just have mild elevations in serum CK without any symptoms. Others have myalgias and less frequently weakness. Myoglobinuria is a rare event but can be complicated by death. With discontinuation of the offending agent, the myalgias, weakness, and elevated serum CK levels tend to completely resolve but it may take several days to months. However, rarely these agents may trigger an immune-mediated inflammatory myopathy, usually necrotizing, that requires treatment with immunosuppressive medications.

HMG-CoA Reductase Inhibitors

Clinical Features

Statin agents inhibit 3-HMG-CoA reductase, the rate controlling enzyme in cholesterol synthesis (Fig. 32–1). Adverse side effects including asymptomatic hyper-CK-emia, myalgias, proximal weakness, and, less commonly, myoglobinuria occur with all of the major HMG-CoA reductase inhibitors: lovastatin,[12,15,17,18,31,36,37] simvastatin,[11,13,14,37,38] provastatin,[16,37] atorvastatin,[10,37,39] fluvastatin,[37] and cerivastatin.[37,40,41] The nomenclature regarding statin-induced toxic myopathies in the published literature is unfortunately quite unsatisfactory, listing "myalgias," "myositis," and "myopathy" as three independent types of muscle disorders caused by statin use, when in fact the definitions of these three subtypes may just reflect the spectrum of severity of the myopathy.[42–44]

Reviews discussing statin myopathies cite a 2–7% incidence of myalgias and 0.1–1.0% incidence of weakness or elevated CK, and myoglobinuria developing in <0.5% of patients.[1,42,45,46] The National Heart Lung and Blood Institute advisory panel estimated the incidence of severe myopathy to be approximately 0.08% for lovastatin, simvastatin, and pravastatin.[43] The risk of toxic myopathy increases with the concomitant use of fibric acids,[17,18,26,30,31,39] niacin,[31] erythromycin,[47] cyclosporine,[17,18] and ezetimibe,[32–35] as do renal insufficiency, and hepatobiliary dysfunction. In this regard, 5% of patients taking both lovastatin and gemfibrozil developed a severe myopathy,[26] while a severe myopathy complicated as many as 30% of patients receiving both lovastatin and cyclosporine.[12,17,18]

Although the term "myositis" has been used to denote cases associated with markedly elevated serum CK levels, histopathological confirmation is lacking in most cases. "Myositis" denotes an autoimmune attack on muscle. Rare cases of myositis, particularly dermatomyositis, have been described in association with statin use.[16,48–55] An immune-mediated necrotizing myopathy may rarely develop in the setting of statin use. In some cases the weakness continued to progress for 6 month or more after discontinuation of the statin and only improved once the patients were treated with immunosuppressive agents. Whether the statins in such cases were

▶ TABLE 32–1. TOXIC MYOPATHIES

Pathogenic Classification	Drug	Clinical Features	Laboratory Features	Histopathology
Necrotizing myopathy	Cholesterol-lowering agents Cyclosporine Labetolol Propofol Alcohol	Acute or insidious onset Proximal weakness Myalgias	Elevated serum CK EMG: fibs, PSWs, myotonia (statins, cyclosporine), and myopathic MUAPs	Many necrotic muscle fibers No evidence of endomysial inflammatory cell infiltrate invading non-necrotic muscle fibers
Amphiphilic	Chloroquine Hydroxylchloroquine Amiodarone	Acute or insidious onset Proximal and distal weakness Myalgias Sensorimotor neuropathy Hypothyroid (amiodarone)	Elevated serum CK EMG: fibs, PSWs, myotonia (choroquine), and myopathic MUAPs NCS: axonal sensorimotor neuropathy	Autophagic vacuoles and inclusions are apparent in some muscle fibers and in Schwann cells
Antimicrotubular	Colchicine Vincristine	Acute or insidious onset Proximal and distal weakness Myalgias Sensorimotor neuropathy	Normal or elevated CK EMG: fibs, PSWs, Myotonia (colchicine), and myopathic MUAPs NCS: axonal sensorimotor neuropathy	Autophagic vacuoles and inclusions are evident in some muscle fibers; nerve biopsies demonstrate axonal degeneration
Mitochondrial myopathy	Zidovudine Other HIV-related antiretrovirals	Acute or insidious onset Proximal weakness Myalgias Rhabdomyolysis Painful sensory neuropathy	Normal or elevated CK EMG: normal or myopathic NCS: axonal sensory neuropathy/ neuronopathy	Muscle biopsies reveal ragged red fibers, COX-negative fibers May also see inflammatory cell infiltrates, cytoplasmic bodies, and nemaline rods
Inflammatory myopathy	L-Tryptophan D-Penicillamine Cimetidine L-Dopa Phenytoin Lamotrigine Alpha-interferon Hydroxyurea Imatinib Possibly cholesterol-lower agents	Acute or insidious onset Proximal weakness Myalgias	Elevated serum CK EMG: fibs, PSWs, and myopathic MUAPs	Perivascular, perimysial, or endomysial inflammatory cell infiltrates
Hypokalemic myopathy	Diuretics Laxatives Amphotericin Toluene abuse Licorice Corticosteroids Alcohol abuse	Acute proximal or generalized weakness Myalgias	Serum CK may be elevated Low serum potassium	May see scattered necrotic fibers and vacuoles
Critical illness myopathy	Corticosteroids Nondepolarizing neuromuscular blocking agents	Acute generalized weakness including respiratory muscles	Serum CK can be normal or elevated NCS: low-amplitude CMAPs with relatively normal SNAPs EMG: fibs, PSWs, myopathic MUAPs, or no voluntary MUAPs	Atrophy of muscle fibers, scattered necrotic fibers Absence of myosin thick filaments

(*continued*)

▶ **TABLE 32–1. (CONTINUED)**

Pathogenic Classification	Drug	Clinical Features	Laboratory Features	Histopathology
Unknown	Omeprazole	Acute or insidious onset Proximal weakness Myalgias Sensorimotor neuropathy	Normal or slightly elevated serum CK EMG: myopathic MUAPs NCS: axonal sensorimotor neuropathy	Type II muscle fiber atrophy may be seen
	Isotretinoin	Acute or insidious onset Proximal weakness Myalgias	Normal or slightly elevated CK	Atrophy of fibers
	Finasteride		Serum CK is normal EMG: myopathic MUAPs	Variability in fiber size, type II fiber atrophy, and increased internalized nuclei
	Emetine	Acute or insidious onset Proximal weakness Myalgias	Serum CKs mild to moderately elevated	Myofibrillar myopathy

CK, creatine kinase; EMG, electromyography; NCS, nerve conduction study; fibs, fibrillation potentials; PSW, positive sharp waves; COX, cytochrome oxidase; MUAP, motor unit action potential.
Modified from Amato AA, Dumitru D. Acquired myopathies. In Dumitru D, Amato AA, Zwarts MJ (eds). Electrodiagnostic Medicine, 2nd Edn. Philadelphia: Hanley & Belfus, 2002, pp. 1371–1432.

coincidental or triggered the autoimmune attack is unclear.

Laboratory Features

Asymptomatic elevation of serum CK is common in patients taking statin medications. Marked elevations of CK occur in patients with severe weakness and myoglobinuria. Routine motor and sensory nerve conduction studies (NCS) are normal. Fibrillation potentials, positive sharp waves, and myotonic discharges with early recruitment of small-duration motor unit action potentials (MUAPs) are apparent in weak muscles.[56] Electromyography (EMG) in patients with asymptomatic serum CK elevations is often normal.

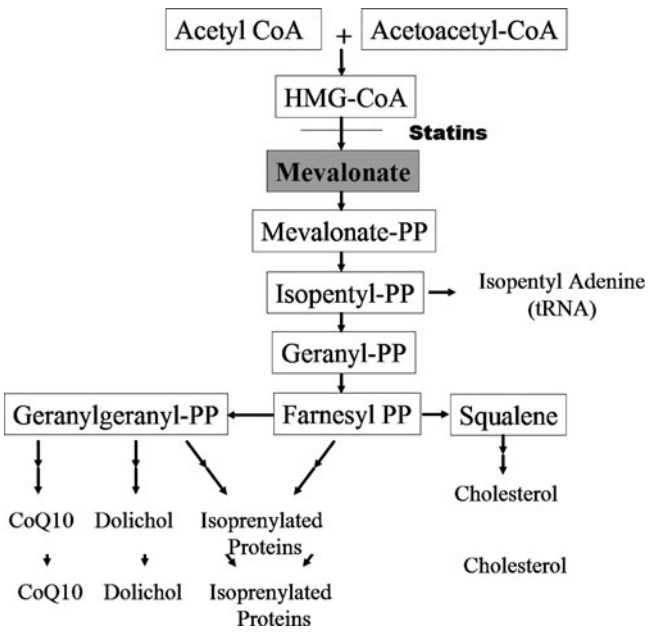


Figure 32–1. Hydroxy-3methyl-glutaryl-coenzyme A pathway. (With permission from Greenberg SA, Amato AA. Statin myopathies. Continuum 2006;12(3): 169–184.)

Histopathology

Muscle biopsies reveal muscle fiber necrosis with phagocytosis and small regenerating fibers in patients with elevated serum CKs and weakness or myalgias (Fig. 32–2).

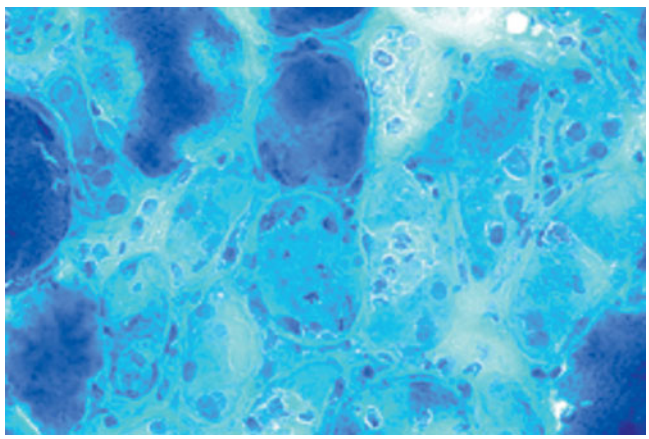


Figure 32–2. Statin myopathy. Muscle biopsy demonstrates scattered necrotic muscle fibers. Modified Gomori trichrome.

Lipid-filled vacuoles within myofibers and cytochrome oxidase-negative myofibers may be appreciated, but these are not consistent findings.[57]

Pathogenesis

The pathogenesis of the myopathy secondary to HMG-CoA reductase inhibitors is unclear, as several pathways may potentially be interrupted downstream (Fig. 32–1).[1,58] Mevalonate is the immediate product of HMG-CoA reductase metabolism. Subsequently, mevalonate is metabolized to farnesol, which is converted to either squalene or geranylgeraniol. Squalene is the first metabolite committed to the synthesis of cholesterol. In contrast, geranylgeraniol is important in the biosynthesis of coenzyme Q_{10} (a mitochondrial enzyme important in the production of adenosine triophosphate [ATP]), dolichol (important in glycoprotein synthesis) and isopentyladine (a component of tRNA) and in the activation of regulatory proteins (G-proteins). It is possible that statins could diminish cholesterol within muscle membranes, thereby predisposing the muscle fibers to rhabdomyolysis. However, the depletion of metabolites of geranylgeraniol, and not the inhibition of cholesterol synthesis, may be the primary cause of myotoxicity. In this regard, HMG-CoA reductase inhibitors decrease the levels of coenzyme Q, which could impair energy production.

There are several reports of patients treated with statins who developed dermatomyositis[50–52,54,55] or polymyositis.[16,48,49,53] The most common myositis which we have seen in patients on a statin medication is an necrotizing myopathy. Unlike what is seen in muscle biopsies of polymyositis, we find many necrotic fibers without much in the way of endomysial inflammation except around and within the necrotic fibers. In many instances, the myositis does not improve following discontinuation of the statin medication (after 6 months or more) and only improves after treatment with an immunosuppressant medication. In addition, the myopathy may worsen after discontinuation of the immunosuppressant agent and improve once again upon reinstituting immunotherapy. Thus, we feel that these cases did not just represent delayed improvement of a "toxic" myopathy. Further, we certainly have seen occasional patients develop DM when on a statin medication or a flare of their DM when started on a statin medication. Whether or not the dermatomyositis or necrotizing was coincidental or triggered by statin medication is unclear at this point.

FIBRIC ACID DERIVATIVES

Clinical Features

Clofibrate and gemfibrozil are branched-chain fatty acid esters, which are used to treat hyperlipidemia. These fibric acid derivatives can cause a myopathy that typically presents within 2 or 3 months after starting the drug.[15,19–29,39] However, the toxic myopathy may develop up to 2 years following initiation of treatment. Affected individuals may complain of generalized weakness, myalgias, and cramps. Myoglobinuria is also a rare complication. Patients with renal insufficiency, those taking both clofibrate and gemfibrozil, and especially also those receiving an HMG-CoA inhibitor, are particularly at increased risk of developing a severe myopathy.

Laboratory Features

Elevated serum CK levels are usually noted. Motor and sensory NCS are normal.[21,23,27] Needle EMG demonstrates fibrillation potentials, positive sharp waves, complex repetitive discharges, myotonic discharges, and short-duration, small-amplitude polyphasic motor unit action potentials (MUAPs) in affected muscle groups.[19,20,24,28,59]

Histopathology

Muscle biopsies demonstrate scattered necrotic muscle fibers. In animal models, clofibrate is also known to result in a noninflammatory necrosis of muscle tissue with fiber size variation and groups of small atrophic muscle fibers.[60]

Pathogenesis

The pathogenic mechanism of the myopathy associated with fibric acid derivatives is not known. These medications might somehow destabilize the lipophilic muscle membrane leading to muscle fiber degeneration.[26]

NIACIN

Rarely, niacin use is complicated by myalgias and cramps.[30] Serum CK levels can be elevated as much as 10-fold. The symptoms improve and CK levels normalize after discontinuation of niacin. Electrodiagnostic studies and muscle biopsies have not been reported in detail. In most cases, rhabdomyolysis occurred in patients who were also taking a statin agent.[31] Of note, niacin can inhibit HMG-CoA reductase; therefore, the pathogenic mechanism of the myopathy is likely similar to that of the statins.

EZETIMIBE

Ezetimibe is a newer class of lipid-lowering drugs, the 2-azetidinones, which selectively inhibit the absorption of intestinal cholesterol. There are a few reports of ezetimide-induced myopathy.[32–35] Similar to other cholesterol-lowering agents, patients may develop hyper-CK-emia with or without myalgias or weakness. Most cases occur in patients who are already on a statin

agent, but some occur with Ezetimibe monotherapy. The toxic myopathy usually resolves within a few weeks after the medication is discontinued. However, we have also seen rare cases of what appear to be an immune-mediated necrotizing myopathy as discussed in the statin section in which the myopathy improved only after the affected patients were treated with immunosuppressive agents.

IMMUNOPHILINS: CYCLOSPORINE AND TACROLIMUS

Clinical Features

The immunophilins (i.e., cyclosporine and tacrolimus) are commonly used as immunosuppressive agents, especially in patients requiring transplantation.[61] Rarely, generalized myalgias and proximal muscle weakness develop within months after starting these medications.[61–66] Myoglobinuria can also occur, particularly in patients receiving cyclosporine or tacrolimus concurrent with cholesterol-lowering agents or colchicine.[17,18,67–70] Tacrolimus has also been associated with hypertrophic cardiomyopathy and congestive heart failure.[71] Myalgias, muscle strength, and cardiac function improve with reduction or discontinuation of the offending cyclophilin.

Laboratory Features

Serum CK is usually elevated. NCS are normal. EMG is remarkable for evidence of increased muscle membrane instability with fibrillation potentials, positive sharp waves, and myotonic potentials.[63] Early recruitment of small-amplitude, short-duration MUAPs may be demonstrated in weak muscle groups.

Histopathology

Muscle biopsies demonstrate necrosis, vacuoles, and type 2 muscle fiber atrophy.

Pathogenesis

The pathogenic basis of immunophilin-induced myopathy and cardiomyopathy is not known. Perhaps, the agents destabilize the lipophilic muscle membrane leading to muscle fiber degeneration, similar to the cholesterol-lowering agents. In this regard, cyclosporine itself has a cholesterol-lowering effect. This may explain the increased risk of myopathy in patients receiving cyclosporine and the more classic lipid-lowering agents (e.g., fibric acid derivatives and statins).

LABETOLOL

Clinical Features

There are a few reports of necrotizing myopathy associated with the use of the antihypertensive agent, labetolol.[72,73] Patients can develop acute or insidious onset of proximal weakness or myalgias, which resolved following discontinuation of the medication.

Laboratory Features

Serum CK can be markedly elevated. EMG demonstrates increased insertional and spontaneous activity with fibrillation potentials and positive sharp waves. Short-duration, small-amplitude, polyphasic MUAPs, which recruit early, are evident.

Histopathology

Routine light microscopy can be normal[72] or can reveal necrotic and regenerating fibers.[73] Electron microscopy (EM) revealed subsarcolemmal vacuoles in one case.[72]

Pathogenesis

The pathogenic etiology for the muscle necrosis seen is not known.

PROPOFOL

Clinical Features

Propofol is an anesthetic agent that is frequently used for sedating patients who are mechanically ventilated and sometimes for treatment of status epilepticus. Myoglobinuria, metabolic acidosis, hypoxia, and myocardial arrest are rare adverse events associated with the use of propofol.[74–76] Propofol does not appear to be associated with malignant hyperthermia. Acute quadriplegic myopathy (AQM) in the intensive care unit (ICU) has also developed in patients treated with propofol in combination with high-dose intravenous corticosteroids.[77] The myopathy in these individuals could be explained by the high-dose corticosteroids rather than the use of propofol. It remains to be determined if propofol is an independent risk factor for the development of AQM.

Laboratory Features

Serum CK levels are markedly elevated. Electrophysiologic studies have not been performed or were not reported in the cases associated with rhabdomyolysis in children. The adult patients with AQM have low-amplitude compound muscle action potentials (CMAPs), profuse fibrillation potentials, positive sharp waves, and early recruitment of short-duration, small-amplitude polyphasic MUAPs.[77]

Histopathology

Muscle biopsies reveal necrosis of skeletal and cardiac muscle.[74–76] Patients with AQM, may have prominent necrosis and loss of thick filaments.[77]

Pathogenesis

The mechanism for muscle destruction is unknown.

Treatment

Propofol should be discontinued and supportive therapy instituted for myoglobinuria, metabolic acidosis, hyperkalemia, and renal failure.

AMPHIPHILIC DRUG MYOPATHY (DRUG-INDUCED AUTOPHAGIC LYSOSOMAL MYOPATHY)

Amphiphilic drugs contain separate hydrophobic and hydrophilic regions, which allow the drugs to interact with the anionic phospholipids of cell membranes and organelles. In addition to a myopathy, these agents can also cause a toxic neuropathy that is even more severe than the direct toxicity on the muscle myotoxicity.

CHLOROQUINE

Clinical Features

Chloroquine, a quinoline derivative, is used to treat malaria, sarcoidosis, systemic lupus erythematosus, and other connective tissue diseases.[7,8,78–81] Some patients develop slowly progressive, painless, proximal weakness and atrophy, which are worse in the legs than in the arms. A cardiomyopathy can also occur. Sensation is often reduced as are muscle stretch reflexes, particularly at the ankle, secondary to a concomitant neuropathy. This "neuromyopathy" usually does not occur unless patients take 500 mg for a year or more but has been reported with doses as low as 200 mg/d. The neuromyopathy improves after chloroquine discontinuation.

Laboratory Features

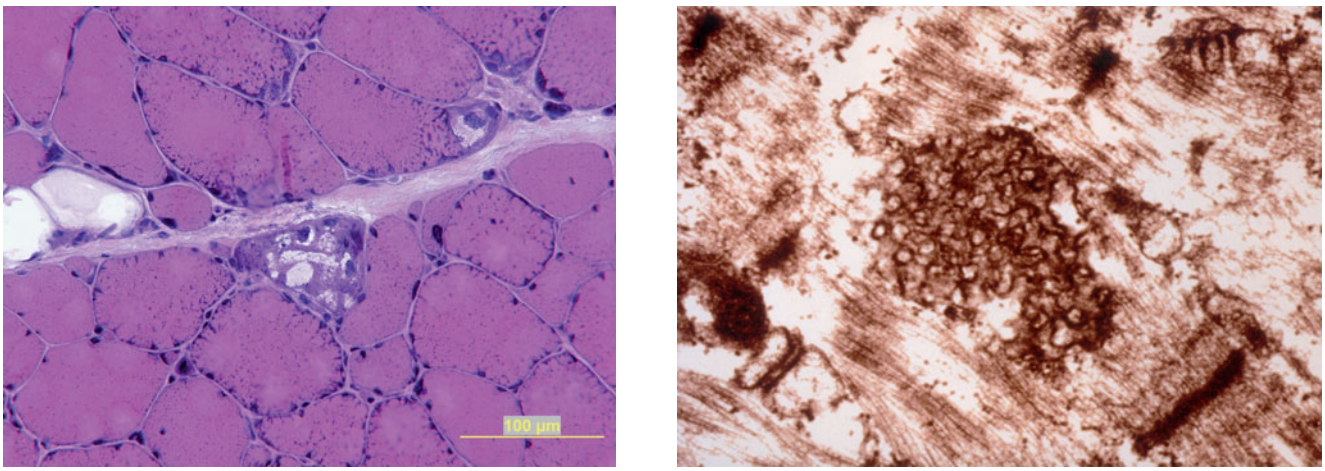
Serum CK levels are usually elevated. Motor and sensory NCS reveal mild-to-moderate reduction in the amplitudes with slight slow velocities in patients with a superimposed neuropathy.[79,81] Individuals with only the myopathy usually have normal motor and sensory studies.[78] Increased insertional activity in the form of positive sharp waves, fibrillation potentials, and myotonic discharges are seen primarily, but not exclusively, in the proximal limb muscles.[78,79,81] Early recruitment of small-amplitude, short-duration polyphasic MUAPs are appreciated in weak proximal muscles. Neurogenic appearing units and reduced recruitment may be seen in distal muscles that are more affected by the toxic neuropathy.

Histopathology

Autophagic vacuoles are evident in as many as 50% of skeletal and cardiac muscle fibers (Fig. 32–3).[7,8,78–81] Type 1 fibers appear to be preferentially affected. The vacuoles stain positive for acid phosphatase, suggesting lysosomal origin. On EM, the vacuoles are noted to contain concentric lamellar myeloid debris and curvilinear structures. Autophagic vacuoles are also evident in nerve biopsies.

Pathogenesis

Chloroquine is believed to interact with lipid membranes, forming drug–lipid complexes that are resistant to digestion by lysosomal enzymes. This results in the



A B

Figure 32–3. Chloroquine myopathy. Chloroquine can cause a vacuolar myopathy (A), hematoxylin and eosin (H&E). Electron microscopy reveals a bundle of dilated tubules (B).(Reproduced with permission from Wasay M, Wolfe GI, Herrold JM, Burns DK, Barohn RJ. Chloroquine myopathy and neuropathy with elevated CSF protein. Neurology 1998;51:1226–1227.)

formation of the autophagic vacuoles filled with myeloid debris.

HYDROXYCHLOROQUINE

Hydroxychloroquine is structurally similar to chloroquine and can cause a neuromyopathy.[79] The myopathy is usually not as severe as seen in chloroquine. Vacuoles are less appreciated on routine light microscopy, but EM still usually demonstrates the abnormal accumulation of myeloid and curvilinear bodies.

AMIODARONE

Clinical Features

Amiodarone is an antiarrhythmic medication that can also cause a neuromyopathy.[82–86] The neuromyopathy is characterized by severe proximal and distal weakness along with distal sensory loss and reduced muscle stretch reflexes. The legs are more affected than the arms. Some patients develop a tremor or ataxia. Amiodarone can also cause hypothyroidism, which may also contribute to proximal weakness. Patients with renal insufficiency are predisposed to developing the toxic neuromyopathy. Muscle strength gradually improves following discontinuation of amiodarone.

Laboratory Features

Serum CK levels are elevated. Motor and sensory NCS reveal reduced amplitudes and slow conduction velocities particularly in the lower extremities.[85,86] EMG demonstrates fibrillation potentials and positive sharp waves in proximal and distal muscles. In proximal muscles, MUAPs are typically polyphasic, short in duration, and small in amplitude and recruit early. Distal muscles are more likely to have large-amplitude, long-duration polyphasic MUAPs with decreased recruitment.

Histopathology

Muscle biopsies demonstrate scattered fibers with autophagic vacuoles. In addition, neurogenic atrophy can also be appreciated, particularly in distal muscles. EM reveals myofibrillar disorganization and autophagic vacuoles filled with myeloid debris. Myeloid inclusions are also apparent on nerve biopsies. These lipid membrane inclusions may be evident in muscle and nerve biopsies as long as 2 years following discontinuation of amiodarone.

Pathogenesis

The pathogenesis is presumably similar to other amphiphilic medications (e.g., chloroquine).

▶ ANTIMICROTUBULAR MYOPATHIES

COLCHICINE

Clinical Features

Colchicine is commonly prescribed for individuals with gout. Colchicine can also cause a generalized toxic neuromyopathy. It is weakly amphiphilic, but its toxic effect is believed to arise secondary to its binding with tubulin and prevention of tubulin's polymerization into microtubular structures.[5,8,9] The neuromyopathy usually develops after chronic administration, but it can also develop secondary to acute intoxication.[5,87–89] Chronic renal failure and age over 50 years are risk factors for the development of neuromyopathy. Patients usually manifest with progressive proximal muscle weakness over several months. Clinical myotonia has been described.[90] A superimposed toxic neuropathy leads to distal sensory loss as well as diminished reflexes. The neuromyopathy weakness typically resolves within 4–6 months after discontinuing the colchicine.

Laboratory Features

Serum CK level is elevated up to 50-fold in symptomatic patients. Serum CK may also be mildly elevated in asymptomatic patients taking colchicine.

Electrophysiologic Findings

Nerve conduction studies reveal reduced amplitudes, slightly prolonged latencies, and mildly slow conduction velocities of motor and sensory nerves in the arms and legs.[87–89,91] Needle EMG demonstrates positive sharp waves, fibrillation potentials, and complex repetitive discharges, which are detected with ease in all muscle regions. Myotonic discharges may also be seen.[90] The myopathic MUAP abnormalities can be masked in the distal limb muscles secondary to the superimposed peripheral neuropathy.

Histopathology

Muscle biopsy demonstrates acid phosphatase-positive autophagic vacuoles containing membranous debris. In addition, nerve biopsies can reveal evidence suggestive of a mild axonal neuropathy.

Pathogenesis

The abnormal assembly of microtubules most likely disrupts intracellular movement or localization of lysosomes, leading to the accumulation of autophagic vacuoles.[88]

VINCRISTINE

Clinical Features

Vincristine is a chemotherapeutic agent, which disrupts gene transcription and also promotes the polymerization of tubulin into microtubules.[8] The dose limiting side effect of vincristine is a toxic axonal sensorimotor polyneuropathy that is associated with distal muscle weakness and sensory loss. Proximal muscle weakness and myalgias are less common.[92]

Laboratory Features

Serum CK levels have not been reported in patients suspected of having a superimposed myopathy. NCS demonstrate markedly reduced amplitudes of SNAPs and CMAPs, while the distal latencies are slightly prolonged and conduction velocities are mildly slow.[92] Needle EMG demonstrates positive sharp waves, fibrillation potentials, and neurogenic appearing MUAPs in the distally located muscles of the upper and lower extremities.

Histopathology

Biopsies of distal muscles demonstrate evidence of neurogenic atrophy and, occasionally, the accumulation of lipofuscin granules. Proximal muscle biopsies reveal scattered necrotic fibers.[92] On EM, there is prominent myofibrillar disarray and subsarcolemmal accumulation of osmiophilic material. In addition, some myonuclei contain membrane-bound inclusions. Autophagic vacuoles with spheromembranous debris have been noted in research animals[93,94] but have not been appreciated in humans.[92]

Pathogenesis

The pathogenic basis of the neuromyopathy is presumably similar to that of colchicine.

▶ DRUG-INDUCED MITOCHONDRIAL MYOPATHY

ZIDOVUDINE (AZIDOTHYMIDINE)

Clinical Features

Patients with azidothymidine (AZT) myopathy usually present with an insidious onset of progressive proximal muscle weakness and myalgias.[95–105] However, these clinical features do no help distinguish AZT myopathy from other HIV-related myopathies. Such myopathies related to HIV infection are heterogeneous and include inflammatory myopathy, microvasculitis, noninflammatory necrotizing myopathy, type 2 muscle fiber atrophy secondary to disuse or wasting due to their chronic debilitated state, and a toxic myopathy secondary to AZT.[96,99,101,103–113] Furthermore, weakness in an HIV-infected patient can also be secondary to peripheral neuropathy (e.g., chronic inflammatory demyelinating polyneuropathy) or myasthenia gravis. Clinically, AZT myopathy and the other myopathic disorders associated with HIV infection are indistinguishable, compounding the diagnostic difficulty. Regardless of etiology of the myopathy, patients manifest with progressive proximal muscle weakness and myalgias. In addition, muscle weakness may be multifactorial: An individual patient can have an HIV-associated myositis, nemaline rod myopathy, AZT-induced mitochondrial myopathy, and type 2 muscle fiber atrophy (not to mention an HIV-related or drug-induced peripheral neuropathy).

Laboratory Features

Serum CK levels are normal or only mildly elevated in AZT myopathy. However, similar elevations are evident in other forms of HIV-related myopathy. A markedly elevated serum CK (e.g., greater than five times the upper limited of normal) is more suggestive of an HIV-associated myositis. Motor and sensory NCS are normal unless there is a concomitant peripheral neuropathy. Needle EMG may demonstrate positive sharp waves and fibrillation potentials and early recruitment of short-duration, small-amplitude polyphasic MUAPs.[103,108,111,114] In addition, small polyphasic MUAPs with early recruitment but no abnormal spontaneous activity was reported in patients with AIDS, with ultrastructural mitochondrial abnormalities but no inflammation or nemaline rods on biopsy.[101]

Histopathology

Muscle biopsies are remarkable for the presence of ragged red fibers, suggesting mitochondrial abnormalities in AZT myopathy (Fig. 32–4). The number of

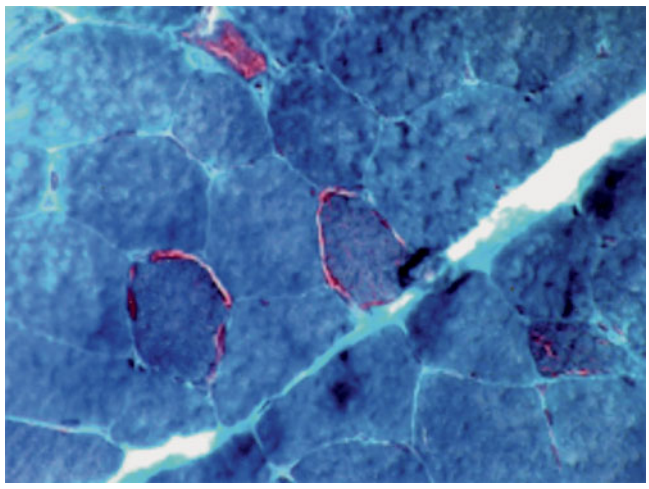


Figure 32–4. Azidothymidine myopathy. Ragged red fibers suggestive of abnormal mitochondria are evident on modified Gomori trichrome stain.

ragged red fibers correlates with the cumulative dose of AZT.[99,100] In addition, necrotic fibers, cytoplasmic bodies, nemaline rods, and fibers with microvacuolation may be seen in addition to ragged red fibers.[96,99,115] In contrast to HIV-associated inflammatory myopathy, significant endomysial inflammation with or without invasion of non-necrotic fibers should not be present in cases of pure AZT myopathy. EM reveals abnormalities of the mitochondria and myofilaments.

Pathogenesis

AZT acts as a false substitute for the viral reverse transcriptase, thereby inhibiting its enzymatic activity and replication of the HIV virus. However, AZT also inhibits the activity of mitochondrial DNA polymerase, which probably accounts for the mitochondrial abnormalities. When treated with AZT, patients with HIV have a decrease in quantity of mitochondrial DNA and decline in respiratory chain enzymatic activity, compared to untreated infected patients.[100,116] The histological and molecular abnormalities on repeat muscle biopsies resolve coinciding with clinical improvement following discontinuation of AZT.[117] Although, AZT is responsible for at least some of the mitochondrial abnormalities evident on muscle biopsy, the contribution of these mitochondrial abnormalities to the muscle weakness remains controversial.

Treatment

Anywhere from 18% to 100% of patients with "AZT" myopathy improve following discontinuation of the medication.[96,99,101,103,105,108,109] The major drawback of discontinuing AZT is the possible increase in HIV replication. In patients with normal or only mildly elevated serum CK and normal or only slightly increased spontaneous activity on EMG, it is impossible to distinguish AZT myopathy from other HIV-associated myopathies. One approach is starting a nonsteroidal anti-inflammatory drug with or without decreasing the dose of AZT.[96] If there is no significant improvement in strength, one should consider discontinuation of AZT.[118] If there is still no objective improvement, patients should undergo a muscle biopsy and be considered for immunomodulating therapy (e.g., intravenous immunoglobulin [IVIG]) or corticosteroid treatment, if there is histological evidence of an inflammatory myopathy. Patients can be rechallenged with AZT, particularly if there are no ragged red fibers on biopsy.

OTHER ANTIVIRAL AGENTS

The risk of mitochondrial myopathy with other nucleoside reverse transcriptase inhibitors (e.g., lamivudine), zalcitabine, didanosine is probably less than that of AZT.[119,120] However, these agents are clearly associated with mitochondrial toxicity, and patients may develop associated hyperlactemia and hepatic steatosis on these medications. The AIDS Clinical Trial group randomized 2467 patients to receive one of four single or combination regimens with AZT, didanosine, zalcitabine, and their respective placebo.[112] Approximately 10% of patients had myalgias prior to treatment and 7% developed myalgia during treatment. There was no significant difference between treatment arms and the rate of myalgia or muscle weakness in any group. Five patients (0.5%) had elevated serum CK (>4× normal) prior to treatment, and 52 (5%) developed increased CK during treatment. Serum CK levels were significantly higher in the AZT-zalcitabine group, but this did not correlate with symptoms of myopathy. Unfortunately, there was no comment on muscle biopsies, and thus it is unclear whether the myopathies were secondary to mitochondrial toxicity or myositis.

The main treatment of HIV infection currently is with highly active antiretroviral therapy (HAART) consisting of a combination of nucleoside reverse transcriptase inhibitors and protease inhibitors. Rare cases of rhabdomyolysis and myoglobinuria occur in patients taking other HAART medications including tenofovir[121] and ritonavir.[122] A review of 563 patients receiving HAART in Essen, Germany, between 1995 and 1998 demonstrated a prevalence of "HIV-associated myopathy" in 1.5% of patients treated with HAART.[80] It was not clearly stated how the myopathy was defined (e.g., clinical symptoms or signs, elevated serum CK, EMG, or biopsy). Further, it is unclear if the myopathy was felt to be due to mitochondrial toxicity, myositis, or wasting syndrome.

▶ DRUG-INDUCED INFLAMMATORY MYOPATHIES

CHOLESTEROL LOWER AGENTS

As discussed in the Necrotizing Myopathies section, dermatomyositis, polymyositis, and in particular, an immune-mediated necrotizing myopathy rarely occur in patients taking statin medications and occasionally the other cholesterol lowering agents. These inflammatory myopathies do not improve with the discontinuation of the cholesterol lower agent. Rather, patients need to be treated with immunotherapy.

L-TRYPTOPHAN/EOSINOPHILIA-MYALGIA SYNDROME

Clinical Features

Eosinophilia-myalgia syndrome was described in the late 1980s and early 1990s and was found to be caused by a contaminant used in the production of L-tryptophan.[123–129] The clinical, laboratory, electrophysiologic,

and histopathological features were similar to that seen in diffuse fasciitis with eosinophilia (Shulman syndrome).[130] Patients developed a subacute onset of generalized muscle pain and tenderness with variable degrees of weakness. Onset could have been within a few weeks or several years after starting tryptophan. Numbness, paresthesias, arthralgias, lymphadenopathy, dyspnea, abdominal pain, mucocutaneous ulcers, and an erythematous rash were also common. Some patients developed a severe generalized sensorimotor polyneuropathy mimicking Guillain–Barre syndrome[128,131] or multiple mononeuropathies suggestive of a vasculitis.[132]

Laboratory Features

The serum CK level were normal or elevated. Autoantibodies were absent and ESR was usually normal. The absolute eosinophil count was elevated ($>1 \times 10^9$ cells/L). Decreased amplitudes of compound muscle and sensory nerve action potentials with normal or mildly reduced conduction velocities were evident in patients with a polyneuropathy.[128,133] A few patients with severe Guillain–Barre syndrome had electrophysiologic studies showing multifocal conduction block and slowing of conduction velocities.[131] Needle EMG revealed muscle membrane instability in the form of fibrillation potentials, positive sharp waves, and complex repetitive discharges.[126,128,131] Small and large polyphasic MUAPs with early recruitment were seen as a result of the chronic myopathy.[126,128] Large polyphasic MUAPs with decreased recruitment were seen in patients with severe neuropathy.[128] The electrophysiological abnormalities improve with discontinuation of tryptophan.

Histopathology

Muscle biopsies demonstrated diffuse or perivascular inflammatory infiltrate in the fascia, perimysium, and, to a lesser extent, in the endomysium.[128] The majority of inflammatory cells were CD8+ T cells and macrophages, while eosinophils and B cells comprised <3% of the infiltrating cells. Unlike DM, there was no deposition of membrane attack complex on small blood vessels. Nerve biopsies showed predominately perivasular inflammatory infiltrate, mainly mononuclear, with occasional eosinophils in the epineurium, endoneurium, and/or perineurium with axonal degeneration.[126,128,131,133,134]

Pathogenesis

The disorder was caused by a contaminant(s) in the manufacture of tryptophan. Two trace adulterants have been identified as the possible toxins: 3-phenylaminoalanine and 1,1′-ethylidenebis tryptophan.[135] The mechanism by which this contaminant resulted in the disorder is unknown, but the eosinophilia and eosinophilic infiltrate in tissues suggest some form of allergic reaction.

Treatment

Discontinuation of L-tryptophan and treatment with high-dose corticosteroids were usually effective. Some patients experienced relapses upon withdrawal of steroids.

TOXIC OIL SYNDROME

The toxic oil syndrome was quite similar to the eosinophilia-myalgia syndrome associated with tryptophan.[136] This condition was restricted to a single epidemic in Spain and has not recurred since 1981. The disorder was linked to the ingestion of illegally marked, denatured rapeseed oil as a cooking substitute for olive oil. Interestingly, the toxic contaminant in the rapeseed oil, 3-phenylamino-1, 2-propanediol, is chemically similar to 3-phenyla-minoalanine, the adulterant in tryptophan causing the eosinophilia-myalgia syndrome.[135]

D-PENICILLAMINE

D-Penicillamine is rarely used nowadays to treat Wilson disease, rheumatoid arthritis, and other connective tissue disorders. Approximately 0.2–1.4% of patients treated with D-penicillamine developed an inflammatory myopathy reminiscent of polymyositis or dermatomyostis.[137–140] Discontinuation of the drug results in resolution of the symptoms. The medication may be restarted at a lower dosage without recurrence of the inflammatory myopathy.

CIMETIDINE

Rare cases of inflammatory myopathy have been reported with cimetidine, a histamine H_2 receptor antagonist.[141] One patient developed generalized weakness and myalgias associated with CK elevations up to 40,000 U/L and interstitial nephritis. The muscle biopsy revealed perivascular inflammation, predominantly consisting of CD8+ lymphocytes. No deposition of immunoglobulin or complement on small blood vessels was noted, nor did the patients have a cutaneous rash to suggest dermatomyositis. However, cases of cutaneous vasculitis have been described with cimetidine use.[142]

PROCAINAMIDE

Proximal muscle weakness and myalgias rarely occur with procainamide usage.[40,143] Serum CK levels are elevated, and EMG have been reported as being consistent with a "patchy" myopathy. Muscle biopsies demonstrate perivascular inflammation and rare necrotic muscle

fibers. The pathogenesis may be related to lupus-like vasculitis, which can occur in patients treated with procainamide. The myopathy resolves following withdrawal of procainamide.

L-DOPA

A single case of proximal muscle weakness and myalgias has been reported in a patient with Parkinson disease treated with L-Dopa.[144] The patient developed the muscle symptoms after treatment with L-Dopa for over 4 years. The serum CK was elevated 10-fold. Gastrocnemius and quadriceps muscle biopsies revealed perivascular inflammation and rare necrotic fibers. The authors suggested that the patient developed a hypersensitivity vasculitis to the L-Dopa; however, it is more likely that the myositis occurred incidentally.

PHENYTOIN

Myalgias and weakness may develop in patients treated with phenytoin due to hypersensitivity reactions.[145] Serum CK levels can be elevated, and muscle biopsies show scattered necrotic and regenerating muscle fibers. EMG can reveal increased spontaneous activity with fibrillation potentials and positive sharp waves. Small-amplitude, short-duration, polyphasic MUAPs, which recruit early may be observed. The myopathy improves with discontinuation of the phenytoin and a short course of corticosteroids.

LAMOTRIGINE

We have seen a case of severe myoglobinuria and renal failure associated with a generalized rash, anemia, leukopenia, and thrombocytopenia shortly after the patient was started on lamotrigine. The clinical and laboratory features resemble thrombocytic thrombocytopenic purpura. The patient improved with plasmapheresis and discontinuation of lamotrigine.

ALPHA-INTERFERON

Alpha-interferon is used in the treatment of viral hepatitis and certain malignancies (e.g., chronic myelogenous leukemia [CML] and melanoma). A rare side effect of α-interferon is the occurrence of autoimmune disorders including myasthenia gravis and myositis.[146–148] Further, as discussed in Chapter 30, the overproduction of type 1 interferons, such as alpha-interferon, have been implicated in the pathogenesis of dermatomyositis.

IMATINIB MESYLATE (GLEEVIC)

Imatinib mesylate is a tyrosine kinase inhibitor used to treat patients with CML. Imatinib inhibits the tyrosine kinase activity of the BCR-ABL oncoprotein in CML. Imatinib is well tolerated, but myalgias occur in 21–52% of patients. We reported a patient with CML who developed polymyositis while taking imatinib.[149] CML28 antibodies were detected in the patient's serum. CML28 is identical to hRrp46p, a component of the human exosome, a multiprotein complex involved in processing of RNA. Antibodies directed against hRrp46p and other components of the human exosome (e.g., PM-Scl 100 and PM-Scl 75) have been noted in patients with polymyositis (see Chapter 30). The patient's strength and serum CK normalized with discontinuation of the imatinib and a course of corticosteroids.

Tyrosine kinases are involved in signal transduction, cell growth, and differentiation. The mechanism by which imatinib therapy could cause myositis is unclear. The previous use of an immunomodulatory agent (i.e., alpha-interferon) followed by imatinib leads to rapid apoptosis of leukemic cells. The subsequent release of a large bolus of leukemia antigens may have cross-reactivity with muscle antigens and generate an autoimmune response.

▶ MYOPATHIES SECONDARY TO IMPAIRED PROTEIN SYNTHESIS OR INCREASED CATABOLISM

STEROID MYOPATHY

Clinical Features

Steroid myopathy manifests as proximal muscle weakness and atrophy affecting the legs more than the arms.[150–157] The distal extremities, oculobulbar, and facial muscles are normal as are sensation and muscle stretch reflexes. Most patients exhibit a Cushingoid appearance with facial edema and increased trunkal adipose tissue. Prednisone at doses of 30 mg/d or more (or equivalent doses of other corticosteroids) is associated with an increased risk of myopathy.[154] Any synthetic glucocorticoid can cause the myopathy, but those that are fluorinated (triamcinolone > betamethasone > dexamethasone) are more likely to result in muscle weakness than the nonflourinated compounds.[158] Women appear to be more at risk than men (approximately 2:1) of developing a steroid myopathy. Alternate-day dosing may reduce the risk of corticosteroid-induced weakness.

Muscle weakness can develop within several weeks following the administration of corticosteroids; however, it more commonly occurs as a complication of chronic administration of oral high-dose corticosteroids. Acute

onset of severe generalized weakness can occur in patients receiving high dosages of intravenous corticosteroids with or without concomitant administration of neuromuscular blocking agents or sepsis (see section regarding Acute Quadriplegic Myopathy).

Laboratory Features

Serum CK is normal. Serum potassium can be low as a result of glucocorticoid excess and can cause some degree of weakness. Motor and sensory nerve conductions are normal in steroid myopathy.[159] Repetitive stimulation studies should not demonstrate a significant decrement or increment. Needle EMG is normal as well.

The paucity of abnormalities is understandable, as corticosteroids preferentially affect type 2 muscle fibers. The first recruited motor units are comprised of type 1 muscle fibers. Because these are not affected as severely as type 2 fibers, there is little in the way of electrophysiologic pathology to observe.

Histopathology

Muscle biopsies reveal atrophy of type 2 fibers, especially the fast-twitch, glycolytic type 2B fibers (Fig. 32–5).[153,154,160,161] There may also be a lesser degree of atrophy of type 1 muscle fibers. Lipid droplets are commonly noted in type 1 fibers, and rare mitochondrial abnormalities have been seen on EM.

Pathogenesis

Corticosteroids bind to receptors on target cells and are subsequently internalized into the nuclei, where these regulate the transcription of specific genes. How corticosteroids cause a myopathy is not known, but could be the result of decreased protein synthesis, increased protein degradation, alterations in carbohydrate metabolism, mitochondrial alterations, or reduced sarcolemmal excitability.[153,154]

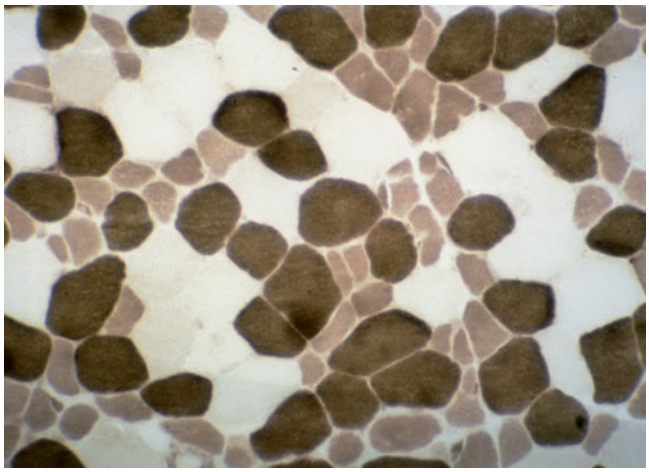


Figure 32–5. Steroid myopathy. Selective atrophy of the intermediately staining type 2B fibers is evident. ATPase pH 4.5.

Treatment

Reduction in the dose, tapering to an alternate-day regimen, or switching to a nonflourinated steroid along with a low carbohydrate diet and exercise to prevent concomitant disuse atrophy are major modes of therapy.[154,158,162]

Of particular concern is to distinguish steroid myopathy from an exacerbation of underlying immune-mediated neuromuscular disorder (e.g., inflammatory myopathy, myasthenia gravis, and chronic inflammatory demyelinating polyneuropathy) in a patient being treated with corticosteroids.[156,162–164] If the weakness occurred while the patient was tapering the corticosteroid, relapse of the underlying disease process would be most likely. In contrast, if weakness developed while the patient was on chronic high doses of steroids, a steroid myopathy should be considered. In the case of an inflammatory myopathy, an increasing serum CK and an EMG with prominent increase in insertional and spontaneous activity would point to an exacerbation of the myositis.[162] In some cases, it is impossible to state with certainty whether the new weakness is related to a relapse of the underlying disease or secondary to the corticosteroid treatment. In such cases, we taper the corticosteroid medication and closely observe the patient. If muscle strength improves presumably, the patient had a steroid myopathy. If patient's strength declines then more likely the weakness is caused by an exacerbation of the underlying autoimmune disease and requires increased doses of corticosteroids or other immunosuppressive medication.

FINASTERIDE

Clinical Features

Finasteride is used to treat benign prostatic hypertrophy. It is a 4-azasteroid that inhibits 5α-reductase, and thus block dihydrotestosterone production and androgen action in the prostate and skin. One patient developed severe proximal greater than distal weakness and atrophy while being treated with finasteride (5 mg qd).[165] Sensation and muscle stretch reflexes were normal.

Laboratory Features

Serum CK levels were normal.

Electrophysiological Findings

Nerve conduction studies were normal, while the EMG demonstrated showed small polyphasic MUAPs.

Histopathology

Muscle biopsy revealed only mild variability in fiber size, type 2 muscle fiber atrophy, and increased central nuclei.

Pathogenesis

The pathophysiologic mechanism for the myopathy is not known. Finasteride is one of the 4-azasteroids and its parent compound, as well as the metabolites, has structural similarity to corticosteroids. Thus, the pathogenic mechanism may be similar to that seen of steroid myopathy.

Treatment

Discontinuation of finasteride was associated with normalization of strength and improvement in EMG abnormalities.

EMETINE (IPECAC)

Clinical Features

Emetine hydrochloride is an emetic agent that has been abused, particularly in patients with anorexia nervosa and bulemia. A severe proximal myopathy and cardiomyopathy can occur with overuse of emetine (500–600 mg/d for over 10 days).[166–168] Patients also complain of muscle pain, tenderness, and stiffness. Muscle stretch reflexes are usually diminished, but the sensory examination is completely normal. The myopathy is reversible following discontinuation of the medication.

Laboratory Features

The serum CK levels may be mildly to moderately elevated. Sensory and motor nerve conduction studies are normal.[166–168] Needle EMG examination can be normal although, positive sharp waves and fibrillation potentials are usually apparent. There is early recruitment of small-amplitude, short-duration MUAPs.

Histopathology

Muscle biopsies reveal scattered necrotic fibers, small atrophic and regenerating fibers as well as many fibers containing cytoplasmic bodies. Oxidative enzyme stains demonstrate targetoid or moth-eaten structures. On EM, there is evidence of myofibrillar degeneration in addition to compacted myofibrillar debris (cytoplasmic bodies). The histological appearance of light and electron microscopy is similar to myofibrillar myopathy.[169,170]

Pathogenesis

The exact pathogenic basis for the disorder is not known, but it is postulated that emetine might inhibit the synthesis of important muscle proteins.

Treatment

The myopathy resolves following discontinued use of emetine.

▶ TOXIC MYOPATHIES WITH MULTIFACTORIAL OR UNKNOWN PATHOGENIC MECHANISMS

ACUTE QUADRIPLEGIC MYOPATHY/ CRITICAL ILLNESS MYOPATHY

Patients in the intensive care unit (ICU) may develop generalized weakness due to critical illness polyneuropathy,[171,172] prolonged neuromuscular blockage,[173,174] or secondary to a myopathic process. The myopathic disorder has been termed AQM, acute illness myopathy, critical illness myopathy, and myopathy associated with thick filament (myosin loss).[77,174–188] It can be difficult to differentiate AQM from critical illness neuropathy or prolonged neuromuscular blockade, and patients can potentially have a combination of the above. Some series of ICU weakness report critical illness neuropathy to be more frequent than AQM,[189,190] while others found the myopathy to be more prevalent.[181,185,191] In the largest series involving 88 patients who developed weakness while in an ICU, AQM was three times as common as critical illness myopathy (42% vs. 13%); prolonged neuromuscular blockade occurred in only one patient who also had AQM.[181] In our experience, AQM is much more common than critical illness neuropathy.

Clinical Features

The first reported case of AQM was a 24-year-old woman with status asthmaticus who developed severe generalized weakness following treatment with high doses of intravenous corticosteroids and neuromuscular blockade.[183] Subsequently, there have been numerous reports of AQM usually developing in patients who received high-dose intravenous corticosteroids and/or nondepolarizing neuromuscular blockers.[77,174–176,179–182,184–188,192–194] The myopathy can also develop in patients with sepsis or multiorgan failure who never received either corticosteroids or nondepolarizing neuromuscular blocking agents.[177,178,187] Recent organ transplantation appear to be at increased risk factor for development of AQM, perhaps because patients undergoing these procedures receive high doses of intravenous corticosteroids for prevention of rejection and neuromuscular blocking agents in the perioperative period. Because of their immunosuppressed state, patients undergoing transplant are also prone to infection and sepsis, which also predisposes to AQM.

The incidence of AQM is uncertain because there have been only a few prospective series published on the subject.[192,195] In a study of 25 consecutive patients

requiring mechanical ventilation for severe asthma, myopathy developed in 9/25 (36%) and elevated serum CK levels in 19/22 (76%) of patients tested.[195] The patients were treated with dexamethasone 10 mg every 8 hours or hydrocortisone 250 mg every 6 hours; 22 of the 25 patients also received vecuronium. Mechanical ventilation lasted an average of 3.1 +/− 3.1 days in patients without myopathy and 12.9 +/− 6.6 days in those with myopathy. In a prospective study of 100 consecutive adult patients undergoing liver transplantation, seven patients developed AQM.[192] Patients were treated with nondepolarizing neuromuscular blocking agents and high-dose steroids in the perioperative period. Three of six patients tested had elevated serum CK levels, as high as 10 times the upper limit of normal 25 days post-op. Four patients had muscle biopsies demonstrating necrosis and selected loss of myosin (see below). Three patients later died from sepsis and multiorgan failure. The remaining patients slowly regained strength and the ability to ambulate over 1–3 months.

Patients with AQM usually exhibit severe generalized weakness of the trunk, extremities, and respiratory muscles and can rarely involve the extraocular muscles.[188,194] The myopathy is usually initially recognized by the inability to wean the patient from the ventilator. Sensory examination is usually normal, but this of course can be difficult to determine in an intubated patient with altered mental status. Muscle reflexes are decreased or absent. The mortality is high, approximately 30% in one large series, secondary to multiple organ failure and sepsis rather than the myopathy.[181] The morbidity and mortality in AQM and critical illness neuropathy appear to be similar.[181] In patients who survive, muscle strength recovers slowly over several months.

Laboratory Features

Serum CK levels can be normal but are moderately elevated in about 50% of patients. Nerve conduction studies reveal marked reduced amplitudes of CMAPs with normal distal latencies and conduction velocities. In contrast, sensory nerve action potential (SNAP) amplitudes should be normal or mildly reduced (>80% of the lower limit of normal) in comparison. Markedly reduced amplitudes of SNAPs should lead to the consideration of critical illness myopathy. However, the SNAPs may be affected if the patient has a baseline (unrelated neuropathy) and many of these patients have illnesses that are associated with neuropathy (diabetes mellitus and renal or liver failure). Thus, reduced SNAP amplitudes in and of itself does not exclude AQM. In our experience, most cases of weakness developing in the ICU is due to AQM and not critical illness neuropathy.

Direct muscle stimulation may help to distinguish AQM from critical illness myopathy, but these studies are fraught with possibility of technical error.[185,186,196] Direct muscle stimulation bypasses the distal motor nerve and neuromuscular junction. In critical illness neuropathy or prolonged neuromuscular blockade, the muscle membranes should retain their excitability, and direct muscle stimulation CMAP (dmCMAP) should be near normal despite a low or absent nerve stimulation-evoked CMAP (neCMAP). In contrast, if the muscle membrane excitability is reduced as seen in AQM, both the neCMAP and the dmCMAP should be very low. Theoretically, the ratio of neCMAP to dmCMAP should be close to 1:1 in a myopathy and should approach zero in a neuropathy or neuromuscular junction disorder. In this regard, absent or reduced amplitudes of the dmCMAP with neCMAP/dmCMAP ratios >0.9 were demonstrated in 11 patients with AQM, while neCMAP/dmCMAP ratios were 0.5 or less in patients with severe neuropathy.[185,186]

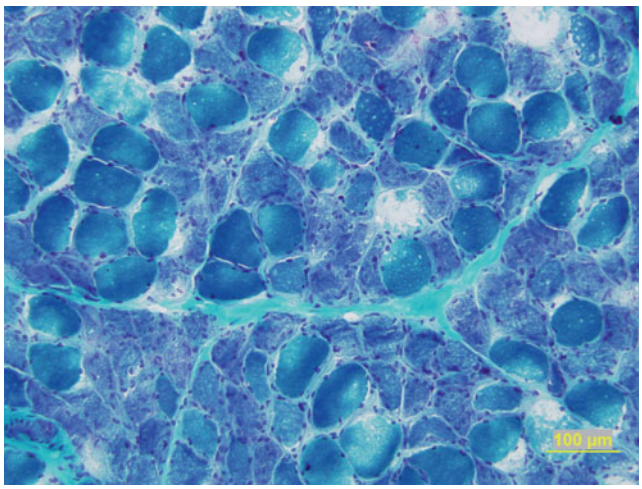
EMG usually demonstrates prominent fibrillation potentials and positive sharp waves; however, abnormal spontaneous activity is not always evident. Early recruitment of short-duration, small-amplitude, polyphasic MUAPs may be seen if the patient has sufficient strength to generate any MUAPs; patients with severe weakness may be unable to volitionally recruit any MUAP. The inability to quantitate MUAP morphology and recruitment can make it difficult to distinguish AQM from critical illness neuropathy in patients who may have abnormal sensory conduction studies incidentally. Sequential EMG studies have reported profuse spontaneous activity and inability to actively recruit MUAPs early, followed by the appearance of small polyphasic MUAPs with early recruitment during the recovery period.[193]

Histopathology

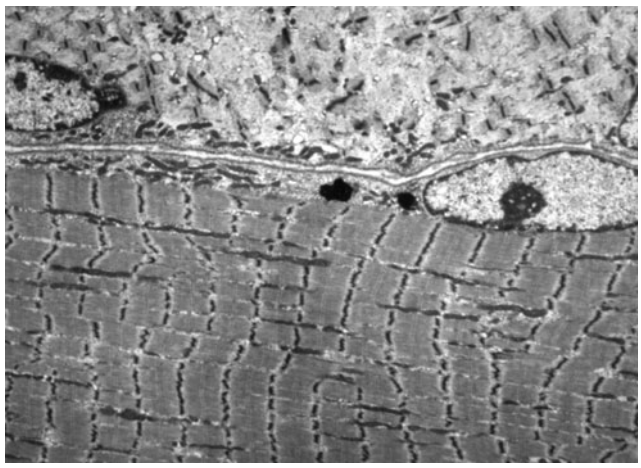
Muscle biopsies reveal a wide spectrum of histological abnormalities (Fig. 32–6). Type 2 muscle fiber atrophy with or without type 1 fiber atrophy is common.[22,174,175,178,179,181,187,188,194] Scattered necrotic muscle fibers may be seen.[181,184,187,192,194] Focal or diffuse loss of reactivity for myosin ATPase activity in type 1 fibers more than type 2 fibers corresponding to the loss of thick filaments (myosin) apparent on EM is typically observed (Fig. 32–6).[22,174,176,177,179–181,187,192] Other structural proteins (actin, titin, and nebulin) are relatively spared.[187]

Pathogenesis

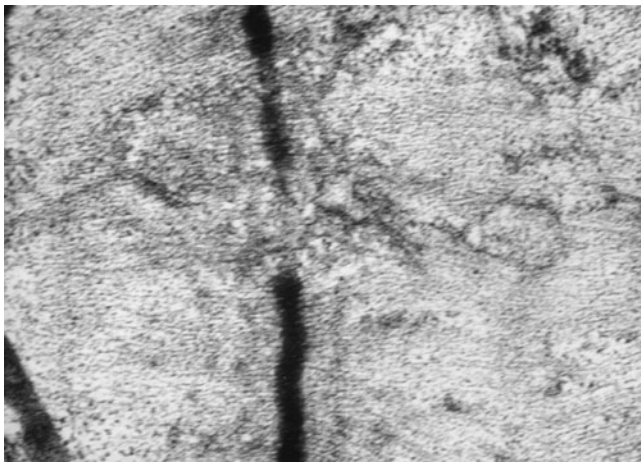
The variable laboratory, histologic, and electrophysiological features suggest that the pathogenesis is multifactorial. Some biopsies demonstrate widespread necrosis, which certainly can account for the muscle weakness observed in patients. The mechanism of muscle fiber necrosis is not known, and, importantly, not all patients have this feature on biopsy. Myosin is selectively lost in some but not all patients. Calcium-activated proteases (calpains) may be responsible for proteolysis of myosin.[187]



A



B



C

Figure 32–6. Critical illness/acute quadriplegic myopathy. Muscle biopsy demonstrates marked degeneration and atrophy of muscle fibers on modified Gomori trichrome (A). Electron microscopy demonstrates a muscle fiber with a preserved sarcomere adjacent to a degenerating muscle fiber (B). Higher power view on EM reveals the preserved Z-disk and thin filaments but the loss of the myosin thick filaments (C).

Perhaps, glucocorticoids, nondepolarizing neuromuscular agents, or the milieu of critical illness induces the expression of calpains. In addition, the enhanced expression of cytokines during sepsis may, in turn, lead to a catabolic state in muscle with breakdown of proteins, glycogen, and lipid.

The reduced muscle membrane excitability may be the result of a combination of several factors: (1) partial depolarization of the resting membrane potential, (2) reduced muscle membrane resistance, and (3) decreased sodium currents.[185,186,196,197] Denervation and neuromuscular blockade normally decrease the resting membrane muscle potential, increase membrane resistance secondary to decreased chloride conductance, and increase the number of sodium channels on the muscle membrane. In denervated rats treated with corticosteroids, the resting membrane potential does not significantly decrease but muscle membrane resistance decreases (rather than increase) as a result of increased chloride conductance. The reduced membrane resistance decreases the depolarization caused by the opening of sodium channels. Additionally, there is diminished sodium current secondary to a reduction in the number of sodium channels, decreased sodium channel conductance, or impaired voltage-dependent gating.

Treatment

Supportive care and treating underlying systemic abnormalities (e.g., antibiotics in sepsis and dialysis in renal failure) are the only modes of therapy. Corticosteroids or nondepolarizing neuromuscular blockers should be discontinued if possible. Patients require extensive physical and occupational therapy to prevent contractures and help regain muscle strength and functional abilities.

OMEPRAZOLE

Clinical Features

Omeprazole inhibits the H^+/K^+ ATPase enzyme system (the proton pump) at the secretory surface of the gastric parietal cell and is used for the treatment of gastric and duodenal ulcers and reflux. Rare cases of neuromyopathy have been reported with the use of omeprazole.[180,198,199] Patients develop proximal weakness and

myalgias along with paresthesias and a stocking distribution of sensory loss, predominantly in the legs. Muscle reflexes are diminished or absent.

Laboratory Features

Serum CK levels are normal or mildly elevated. Nerve conduction studies may be normal or reveal an axonal sensorimotor polyneuropathy.[198] EMG can be normal or show small polyphasic MUAPs.[199]

Histopathology

Muscle biopsies in the two reported patients revealed only type 2 muscle fiber atrophy.[198,199] Superficial peroneal nerve biopsy in one patient demonstrated axonal degeneration.[198]

Pathogenesis

The pathogenic mechanism for the neuromyopathy is unknown.

Treatment

Muscle strength and sensation improve and serum CK levels normalize following discontinuation of omeprazole. Symptoms may recurr if omeprazole is restarted.

ISORETINION

Clinical Features

Isoretinion (Accutane) is used for treatment of severe acne. Exercise induced myalgias are common.[200,201] In addition, rare individuals develop proximal muscle weakness.[202]

Laboratory Features

Serum CK levels can be normal or mildly elevated. Decreased serum carnitine levels may be seen.[200] EMG can demonstrate small polyphasic MUAPs.[202]

Histopathology

Muscle biopsy in a single reported patient demonstrated only atrophy of muscle fibers.[202]

Pathogenesis

The basis for the myopathy is not clear. The diminished carnitine levels and response to L-carnitine in some patients suggest that a perturbation of lipid metabolism may be contributory.

Treatment

The myalgias, weakness, and CK elevations improve with discontinuation of isoretinion. A single, small, unblinded study reported that supplementation with L-carnitine may be beneficial.[200]

DRUG-INDUCED HYPOKALEMIC MYOPATHY

Hypokalemia can be a complication of a variety of medications (e.g., diuretics, laxatives, mineralocorticoids, amphotericin, and lithium). Further, excessive eating of licorice may have an aldosterone-like effect and cause hypokalemia. Hypokalemic myopathy has also been associated with alcohol abuse and inhalation of toluene. The clinical, laboratory, histopathological, and electrophysiologic features of hypokalemic myopathy are similar, regardless of the etiology of the hypokalemia. Affected individuals develop acute or subacute generalized weakness that can resemble Guillain-Barre syndrome. Weakness usually does not occur unless the serum potassium levels are less than 2 meq/L. The serum CK levels are elevated. EMGs can be normal or demonstrate mild irritability in the form of fibrillation potentials and positive sharp waves in severely weakened muscles. Muscle biopsies are not typically performed as the diagnosis is apparent with the appropriate laboratory testing. However, muscle biopsies may demonstrate scattered necrotic and regenerating muscle fibers as well as vacuoles that arise from T-tubules. The weakness improves with correction of the hypokalemia.

▶ MYOPATHIES ASSOCIATED WITH ANESTHETIC AGENTS AND CENTRALLY ACTING MEDICATIONS

MALIGNANT HYPERTHERMIA

Clinical Features

Malignant hyperthermia genetically heterogeneous group of disorders and is characterized by severe muscle rigidity, myoglobinuria, fever, tachycardia, cyanosis, and cardiac arrhythmias precipitated by depolarizing muscle relaxants (e.g., succinylcholine) and inhalational anesthetic agents (e.g., halothane).[203] The incidence of malignant hyperthermia ranges from 0.5% to 0.0005%.[203] At least 50% of patients had previous anesthesia without any problems.[4] The signs of malignant hyperthermia usually appear during surgery but can develop in the postoperative period. Rarely, attacks of malignant hyperthermia have been triggered by exercise, ingestion of caffeine, and stress.[204]

Laboratory Features

Serum CK can be normal or mildly elevated between attacks in patients susceptible to malignant hyperthermia. During attacks of malignant hyperthermia, serum CK levels are markedly elevated and myoglobinuria can develop. Hyperkalemia is also usually present. Metabolic and respiratory acidosis is evident with lactic acidosis,

hypoxia, and hypercarbia. Nerve conduction studies and EMG are usually normal in the interictal periods. However, EMG performed shortly after an attack of malignant hyperthermia may demonstrate increased spontaneous activity and, perhaps, small polyphasic MUAPs recruiting early.

The in vitro muscle contracture test can be performed to assess the susceptibility of malignant hyperthermia in individuals who may be at risk (i.e., family members with history of malignant hyperthermia).[203] However, the test is not routinely available and false positive and false negative tests occur. Varying concentrations of halothane and caffeine are applied to strips of muscle that are stimulated at 0.1–0.2 Hz for 1–5 seconds, while tension is measured by a stain gauge. In patients susceptible to malignant hyperthermia, much lower concentrations of caffeine and halothane produce muscle contractions than needed in normal muscle tissue.

Histopathology

Muscle biopsies demonstrate nonspecific myopathic features including fiber size variability, increased internal nuclei, moth-eaten fibers, and necrotic fibers after an attack of malignant hyperthermia.

Pathogenesis and Molecular Genetics

At least some cases of malignant hyperthermia probably arise secondary to excessive calcium release by the sarcoplasmic reticulum calcium channels. Increased intracytoplasmic calcium leads to excessive muscle contraction, increased use of oxygen and ATP, and overproduction of heat. Why various anesthetic agents and depolarizing muscle relaxants trigger this exaggerated release of calcium from the sarcoplasmic reticulum in predispose individuals is not known.

Malignant hyperthermia susceptibility is genetically very heterogeneic, as families have been linked to different chromosomes and genes. The first mutations were discovered in the ryanodine receptor gene located on chromosome 19q13.1 (MHS1).[132,205,206] The ryanodine receptor bridges the gap between the sarcoplasmic reticulum and the T tubule. Mutations in the ryanodine receptor may result in a functional alteration of the associated calcium channel such that there is an excessive release of calcium into the cytoplasm upon activation. Of note, mutations in this gene also cause the congenital myopathy, the central core disease. Mutations in the ryanodine receptor gene account for only a minority of patients with malignant hyperthermia; other genetic loci have been identified. MHS2 localizes to chromosome 17q11.2–q24 (possibly the gene for the α subunit of the sodium channel).[207] Thus, MHS2 may be allelic to potassium-sensitive periodic paralysis, paramyotonia congenita, and related disorders. MHS3 links to chromosome 7q21–q22 (possibly to a gene encoding a subunit of the calcium channel).[208] MHS4 localizes to chromosome 3q13.1, but the gene has yet to be identified.[209] Mutations in the dihydropteridine receptor gene on chromosome 1q31 (allelic to hypokalemic periodic paralysis) cause MHS5.[210] Linkage to chromosome 5p has been demonstrated in still other families (MHS6).[211] In addition, patients with muscular dystrophies, myotonic dystrophies, mitochondrial myopathies, and other channelopathies are susceptible to developing malignant hyperthermia.[212] Thus, it appears that malignant hyperthermia may occur in various myopathic disorders, affecting the structural proteins of the muscle membrane or ion channels.

Treatment

Individuals at risk of malignant hyperthermia should not be given known triggering anesthetic agents if possible. Malignant hyperthermia is a medical emergency, requiring several therapeutic steps, and fibers with non-rimmed vacuoles.[203] The anesthetic agent must be discontinued, while 100% oxygen is delivered. Dantrolene 2–3 mg/kg every 5 minutes for a total of 10 mg/kg should be administered. The stomach, bladder, and lower gastrointestinal tract are lavaged with iced saline solution, and cooling blankets are applied. Acidosis and hyperkalemia are treated with sodium bicarbonate, hyperventilation, dextrose, insulin, and occasionally calcium chloride. Urinary output must be maintained with hydration, furosamide, or mannitol. The patient must be monitored and treated for cardiac arrhythmias.

▶ MYOPATHIES SECONDARY TO DRUGS OF ABUSE

ALCOHOLIC MYOPATHY

Chronic alcohol abuse is more often attributed to causing neuropathy than myopathy.[9] However, several forms of a toxic myopathy due to alcohol have been described: (1) acute necrotizing myopathy, (2) acute hypokalemic myopathy, (3) chronic alcoholic myopathy, (4) asymptomatic alcoholic myopathy, and (5) alcoholic cardiomyopathy.[2,8,9]

An acute necrotizing myopathy manifests as acute muscle pain, tenderness to palpation, cramping, swelling, and weakness following or during a recent particularly intense binge. The severity of the myopathy is highly variable. Severe cases can be associated with myoglobinuria and acute renal failure. The muscle cramps resolve over the course of several days, while the remainder of symptoms may last several weeks. Serum CK levels are markedly elevated during these attacks. Muscle biopsies reveal widespread muscle fiber necrosis and occasionally fibers with tubular aggregates. Disorganizing of the sarcomeres and degeneration of mitochondria may be appreciated on EM. Patents require

appropriate supportive medical care and nutritional supplementation as many are malnourished.

Alcohol abuse can lead to acute hypokalemia, which can cause generalized weakness. Muscle weakness evolves over the time period of 1 or 2 days. Serum potassium is very low, <2 meq/L, and the CK levels are elevated. Muscle biopsy performed in the acute time frame may reveal vacuoles with the muscle fibers. The myopathy resolves with correction of the serum potassium.

Some alcoholics develop the insidious onset of primarily proximal limb-girdle weakness, especially of the lower limbs, which has been attributed to a chronic alcoholic myopathy. Muscle biopsy may reveal scattered muscle fiber atrophy, necrosis, and regeneration. Whether the muscle weakness is caused by a toxic influence of alcohol on muscle, a toxic peripheral neuropathy, or the malnutrition is unclear.

An asymptomatic alcoholic myopathy has been suggested in some patients on the basis of an elevated serum CK levels found coincidentally. There is no complaint of weakness, and the physical examination does not reveal striking evidence of a myopathic disorder. Histologic findings are not available for this class of patients, and the true nature of this presumed form of alcoholic myopathy is questionable. The elevated serum CK may be related to subclinical necrotizing myopathy, hypokalemia, or muscle trauma.

Laboratory Features

Serum CK levels may be normal or slightly elevated and potassium levels may be reduced or normal. Reduced amplitudes of the sensory and, occasionally, motor nerve conductions studies may be seen if patients have a concomitant alcoholic neuropathy. Needle EMG may reveal positive sharp waves, fibrillation potentials, and early recruitment of short-duration, low-amplitude MUAPs firing at high rates with minimal force production in weak muscles in patients with a necrotizing alcoholic myopathy.[67,213–217]

Pathogenesis

The pathogenic basis for the various forms of alcoholic myopathies is not known. The metabolism of alcohol may lead to the accumulation of toxic metabolites (e.g., acetaldehyde) or free radicals that may be toxic to lipid membranes.[9]

▶ MYOPATHIES SECONDARY TO ILLICIT DRUGS

Illicit drugs and controlled narcotics (e.g., heroin, meperidine, cocaine, pentazocine, piritramide, amphetamines, etc.) may be myotoxic.[2,8,218–221] Muscle injury can be related to direct muscle trauma (e.g., needle injury), rhabdomyolysis secondary to pressure and ischemic necrosis related to prolonged loss of consciousness, ischemia due to vasoconstriction, rhabdomyolysis caused by generalized status epilepticus, or the direct toxic effects of the drugs (or adulterants) on muscle tissue. Serum CK levels should be markedly elevated, and muscle biopsies reveal widespread necrosis in such cases.

Inhalation of volatile agents (e.g., toluene) can also cause generalized muscle weakness and, occasionally, myoglobinuria. Toluene causes distal renal tubular acidosis with associated severe hypokalemia, hypophosphatemia, and mild hypocalcemia. Muscle strength returns after correction of the electrolyte abnormalities and abstaining from inhaling volatile agents.

▶ SUMMARY

Various drugs can cause muscle damage and from a variety of different mechanisms. It is imperative to take a good medical history including current and previous medication history (as well as history of illicit drug use and alcohol abuse), as stopping the offending agent usually leads to improvement of the myopathy. However, continued use can be associated with significant morbidity and even death (e.g., from myoglobinuria). The most common toxic myopathy is associated with statin use, given how frequently these medications are prescribed. That said, most individuals treated with statin medications and other medications known to cause toxic myopathy have no complications.

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