Neurological complications of varicella zoster virus reactivation

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Purpose of review
Varicella zoster virus (VZV) reactivation results in zoster, which may be complicated by postherpetic neuralgia, myelitis, meningoencephalitis, and VZV vasculopathy. This review highlights the clinical features, laboratory abnormalities, imaging changes, and optimal treatment of each of those conditions. Because all of these neurological disorders produced by VZV reactivation can occur in the absence of rash, the virological tests proving that VZV caused disease are discussed.

Recent findings
After primary infection, VZV becomes latent in ganglionic neurons along the entire neuraxis. With a decline in VZV-specific cell-mediated immunity, VZV reactivates from ganglia and travels anterograde to the skin to cause zoster, which is often complicated by postherpetic neuralgia. VZV can also travel retrograde to produce meningoencephalitis, myelitis, and stroke. When these complications occur without rash, VZV-induced disease can be diagnosed by detection of VZV DNA or anti-VZV antibody in cerebrospinal fluid and treated with intravenous acyclovir.

Summary
Awareness of the expanding spectrum of neurological complications caused by VZV reactivation with and without rash will improve diagnosis and treatment.

Keywords
neurological complications, varicella zoster virus, zoster

INTRODUCTION

Varicella zoster virus (VZV) is an exclusively human neurotropic, double-stranded DNA alphaherpesvirus. Primary infection causes varicella (chickenpox), after which virus becomes latent in cranial nerve ganglia, dorsal root ganglia, and autonomic ganglia along the entire neuraxis. With a decline in VZV-specific cell-mediated immunity in elderly and immunocompromised individuals, VZV reactivates to cause herpes zoster (shingles), which is often complicated by postherpetic neuralgia (chronic pain), VZV vasculopathy, meningoencephalitis, meningoradiculitis, cerebellitis, myelopathy, and ocular disease. VZV reactivation also causes zoster sine herpete (chronic radicular pain without rash). In fact, all the neurological disorders listed above can develop in the absence of rash. Finally, rapidly accumulating evidence links VZV with giant cell arteritis (GCA). Because more than 95% of the world population is infected with VZV and 50% will develop zoster by 85 years of age, the neurological complications of VZV will continue to be problematic.

HERPES ZOSTER

Herpes zoster, the most common manifestation of VZV reactivation, is characterized by a vesicular eruption on an erythematous base in one to three dermatomes, usually accompanied by severe, sharp, and lancinating radicular pain. Often, itching and unpleasant sensations (dysesthesias) produced by touch (allodynia) occur. Rash and pain usually develop within a few days of each other, although pain can precede rash by weeks to months. After reactivation from cranial nerve, dorsal root, or autonomic ganglia, VZV can travel anterograde to produce rash in the corresponding dermatome. Thus, zoster develops anywhere on the skin, most often in

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KEY POINTS

- The most common complication of herpes zoster is postherpetic neuralgia, pain that persists months to years after rash resolves.
- VZV reactivation can produce meningoencephalitis, meningoradiculopathy, cerebellitis, myelitis, VZV vasculopathy, including a variant presenting as giant cell arteritis, ocular inflammatory disease, and zoster sine herpete.
- All the neurological and ocular complications of VZV reactivation can occur without rash.
- The best test for diagnosis of neurologic disease produced by VZV without rash is detection of intrathecal synthesis of anti-VZV antibody in CSF, or less often VZV DNA.
- Treatment is with intravenous acyclovir.

the thoracic region (>50%), but also in ophthalmic, cervical, and lumbosacral regions.

Cardinal pathologic features of zoster are inflammation and hemorrhagic necrosis with associated neuritis, localized leptomeningitis, unilateral segmental poliomyelitis, and degeneration of related motor and sensory roots [1]. Demyelination may be seen in areas with mononuclear cell infiltration and microglial proliferation. Intranuclear inclusions, viral antigen, and herpesvirus particles have been detected in acutely infected ganglia [2,3]. MRI may show enhancement of ganglia and the affected nerve roots [4].

The annual incidence of zoster in the United States is 3.2 cases per 1000 [5]. Zoster occurs most frequently in the elderly as VZV-specific cell-mediated immunity declines. Other groups at risk include patients taking immunosuppressive or immunomodulatory drugs as well as patients with AIDS. Zoster in an otherwise healthy young individual may be the first manifestation of HIV infection; on the other hand, early reactivation occurs in individuals who developed varicella before the age of 4 years.

Treatment for zoster in people under age 50 years is based on symptoms. Analgesics are used to relieve discomfort. Antiviral drugs such as famciclovir, 500 mg orally three times daily, or valacyclovir, 1 g orally three times daily, are not required but speed healing of the rash. At any age, zoster in the distribution of the trigeminal nerve should be treated with famciclovir, 500 mg three times daily. In immunocompetent patients age 50 and older, treatment with both analgesic and antiviral drugs is recommended. We also use prednisone 1 mg/kg body weight orally for 3–5 days with antiviral therapy.

POSTHERPETIC NEURALGIA

Postherpetic neuralgia (PHN) is defined as dermatomal-distribution pain persisting for more than 3 months after zoster. Age is the most important factor in predicting its development. Among persons less than 50 years, the incidence of PHN in zoster patients is 18%; in 80-year-old individuals, the incidence is 33% [6▪]. Overall, 80% of PHN occurs among persons 50 years and older. In addition, more than 40% of zoster patients less than 60 years of age experience chronic pain. Analysis of ganglia from an early case of PHN of 2.5 months' duration revealed diffuse and focal infiltration by chronic inflammatory cells, an observation confirmed by Watson *et al.* [7], who found prominent collections of lymphocytes in ganglia from a patient with PHN of 2 years' duration. The inflammatory response in ganglia raises the possibility of persistent viral infection. Further evidence that PHN may be produced by chronic ganglionitis has come from the detection of VZV DNA and proteins in blood mononuclear cells of many patients with PHN and from the favorable response of some PHN patients to antiviral treatment.

PHN is difficult to manage, and no universal treatment exists. The same medications used to treat zoster pain are also used for PHN. These include gabapentin, pregabalin, divalproex sodium, opioid analgesics, tramadol, tricyclic antidepressants, antiepileptics, and topical lidocaine patches or capsaicin (both cream and 8% patches) [8]. Medical interventions are often used in combination.

VARICELLA ZOSTER VIRUS VASCULOPATHY

VZV vasculopathy is caused by productive virus infection of cerebral arteries, resulting in pathological vascular remodeling [9] and ischemic or hemorrhagic stroke. VZV vasculopathy should be suspected in a patient with a recent history of zoster or varicella who presents with a transient ischemic attack, stroke, chronic headache or altered mental status, as well as in patients with vasculopathy in whom a specific cause has not been determined, particularly among HIV+ and immunocompromised patients. Importantly, the absence of a rash should not deter the clinician from pursuing a diagnostic evaluation for VZV, because one-third of patients with virologically verified VZV vasculopathy have no preceding rash [10].

Features of VZV vasculopathy include a mononuclear pleocytosis in cerebrospinal fluid (CSF) and MRI findings consistent with an ischemic or hemorrhagic lesion, particularly at gray–white matter junctions. A study of 30 individuals with

virologically confirmed VZV vasculopathy [10] revealed rash in 63%, CSF pleocytosis in 67%, and imaging abnormalities in 97% of individuals. Angiography revealed abnormalities in 70% of individuals, with large and small arteries involved in 50%, small arteries only in 37%, and large arteries only in 13%. The CSF of 30% of individuals contained VZV DNA, whereas 93% had anti-VZV IgG antibody in CSF with a reduced serum/CSF ratio of anti-VZV IgG that confirmed intrathecal synthesis of anti-VZV IgG. Detection of anti-VZV IgG antibody is the best diagnostic test [11]; viral DNA can be detected by PCR in early disease but disappears shortly thereafter and is often not present in chronic and protracted VZV vasculopathy. Importantly, diagnosis of this treatable cause of stroke is often missed because one-third of individuals have no history of zoster rash, one-third of individuals have normal CSF, and there is an average 4.2-month delay from zoster to neurological symptoms and signs, with VZV DNA often absent in CSF [10].

Immunocompetent patients with VZV vasculopathy should be treated with intravenous acyclovir, 10–15 mg/kg three times daily for 14 days. Immunocompromised patients or those with recurrent VZV vasculopathy may need a longer course. Since virus-infected arteries typically contain inflammatory cells [12], we give oral prednisone, 1 mg/kg daily for 5 days without taper, in conjunction with intravenous acyclovir. Patients with renal disease must be monitored closely when treated with intravenous acyclovir.

ASSOCIATION OF MULTIFOCAL VARICELLA ZOSTER VIRUS VASCULOPATHY AND TEMPORAL ARTERY INFECTION WITH GIANT CELL ARTERITIS

Recently, a new variant of VZV vasculopathy, that is, multifocal VZV vasculopathy with temporal artery infection, was described in three case reports with features similar to those of GCA [13,14▪,15▪]. All three patients presented with ischemic optic neuropathy, one of whom subsequently developed acute retinal necrosis, and VZV infection of the ipsilateral temporal artery was confirmed in all three patients. Importantly, these patients experienced symptoms, signs, and laboratory abnormalities characteristic of GCA, a vasculitis of unclear etiology that is treated with corticosteroids; however, histopathological examination of the temporal arteries was negative for GCA. These cases raise the possibility that patients with suspected GCA but whose arteries are pathologically negative for GCA have multifocal VZV vasculopathy with temporal artery infection.

To further address the incidence of VZV infection in GCA biopsy-negative patients, 24 temporal arteries from patients with clinically suspect GCA, but biopsy-negative, were examined by immunohistochemistry for the presence of VZV antigen [16▪]; the temporal arteries from 5 of 24 (21%) patients, all of whom had presented with clinical and laboratory features of GCA and early visual disturbances, contained VZV antigen. Thirteen normal temporal arteries did not contain VZV antigen. In another GCA-negative temporal artery, detection of VZV antigen and VZV DNA in multiple regions (skip areas), as well as in skeletal muscle adjacent to the infected artery, led to additional pathological analysis of sections contiguous with those containing VZV antigen. Remarkably, inflammation involving the arterial media and abundant multinucleated giant cells were seen, resulting in a change in pathological diagnosis from GCA-negative to GCA-positive [17]. Overall, multifocal VZV vasculopathy with temporal artery infection can present with the full spectrum of clinical features and laboratory abnormalities characteristically seen in GCA. The role of VZV as a major cause of GCA is under intense study.

VARICELLA ZOSTER VIRUS MENINGOENCEPHALITIS, MENINGORADICULITIS, AND CEREBELLITIS

Aside from VZV vasculopathy, VZV can reactivate and infect the meninges, brain parenchyma, and nerve roots to produce a VZV meningoencephalitis [18,19], and meningoradiculitis [20,21]. In addition, VZV can cause cerebellitis [22,23]. All of these complications can occur in the absence of rash. Diagnosis is confirmed by the detection of VZV DNA or anti-VZV antibody in CSF. Treatment is intravenous acyclovir as for VZV vasculopathy.

VARICELLA ZOSTER VIRUS MYELOPATHY

There are several forms of VZV myelopathy involving a postinfectious process, direct infection of the spinal cord, or VZV vasculopathy. Postinfectious VZV myelopathy presents as a self-limiting, monophasic spastic paraparesis, with or without sensory features and sphincter problems, and usually occurs in immunocompetent patients days to weeks after acute varicella or zoster. VZV myelopathy can also present as an insidious, progressive, and, sometimes, fatal myelitis, mostly in immunocompromised individuals, such as patients with AIDS or on immunomodulatory therapy [24,25]. MRI reveals longitudinal serpiginous enhancing lesions.

Diagnosis is confirmed by the presence of VZV DNA or anti-VZV IgG or both in CSF [26]. Pathological and virological analyses of the spinal cord from fatal cases have revealed frank invasion of VZV in the parenchyma [27] and, in some instances, spread of virus to adjacent nerve roots. Early diagnosis and aggressive treatment with intravenous acyclovir have been helpful, even in immunocompromised patients [28]. Rarely, VZV myelitis recurs, even in immunocompetent patients [29]. VZV can also produce spinal cord infarction, identified by diffusion-weighted MRI and confirmed virologically [30]. Thus, VZV vasculopathy (see above) can cause stroke in the spinal cord as well as in the brain. Treatment is intravenous acyclovir.

OCULAR DISEASE

VZV infection can produce acute retinal necrosis or progressive outer retinal necrosis (PORN). Although VZV is the most common cause of PORN, herpes simplex virus and cytomegalovirus can also cause this syndrome. Most cases occur in AIDS patients with CD4 T-cell counts less than 10 cells/μl of blood, but also in other immunosuppressed individuals. PORN may be preceded by retrobulbar optic neuritis and aseptic meningitis [31], central retinal artery occlusion or ophthalmic-distribution zoster [32], and may occur together with multifocal vasculopathy or myelitis. PORN patients treated with ganciclovir alone or in combination with foscarnet had a better final visual acuity than those treated with acyclovir or foscarnet alone. Like all neurological disorders caused by VZV, ocular disease caused by VZV can also occur in the absence of rash.

ZOSTER SINE HERPETE: RADICULAR PAIN IN THE ABSENCE OF RASH

Zoster sine herpete was first described in multiple patients with dermatomal distribution radicular pain in areas distinct from pain with rash in zoster [33]. The first two virologically confirmed cases of zoster sine herpete were verified by detection of VZV DNA in CSF [26]. A third case of thoracic-distribution zoster sine herpete, in which electromyography of paraspinal muscles demonstrated frequent fibrillation potentials restricted to chronically painful thoracic root segments, was confirmed by detection of VZV DNA in blood mononuclear cells and anti-VZV IgG antibody in CSF [34]. Blumenthal *et al.* [35] recently described a patient with zoster sine herpete whose CSF did not contain amplifiable VZV DNA but did reveal anti-VZV IgG and reduced serum/CSF ratios of anti-VZV IgG indicative of intrathecal synthesis. Perhaps the most compelling evidence that persistent radicular pain without rash can be caused by chronic active VZV ganglionitis came from analysis of two cases. In the first, a trigeminal ganglionic mass was removed from an immunocompetent adult who had experienced chronic trigeminal-distribution pain for more than 1 year; pathological and virological analyses of the ganglionic mass revealed active VZV ganglionitis [36]. In the second case, pathological and virological analysis of the trigeminal ganglia at autopsy of a patient who experienced chronic trigeminal-distribution pain for months before death revealed active VZV ganglionitis [37].

CONCLUSION

In addition to zoster, VZV reactivation causes multiple neurological and ocular diseases, including VZV vasculopathy with a variant presenting as GCA, meningoradiculitis, cerebellitis, myelopathy, ocular disease, and zoster sine herpete. It is important to remember that all of these complications can occur without rash. The best test for diagnosis is the presence of intrathecal synthesis of anti-VZV antibodies, whereas the best treatment is intravenous acyclovir, which may need to be prolonged in immunosuppressed individuals or in extended duration of disease.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Head H, Campbell AW. The pathology of herpes zoster and its bearing on sensory localization. Brain 1900; 23:353–523.
2. Nagashima K, Nakazawa M, Endo H. Pathology of the human spinal ganglia in varicella-zoster virus infection. Acta Neuropathol 1975; 33:105–117.
3. Worrell JT, Cockerell CJ. Histopathology of peripheral nerves in cutaneous herpesvirus infection. Am J Dermatopathol 1997; 19:133–137.
4. Berrettini S, Bianchi MC, Segnini G, *et al.* Herpes zoster oticus: correlations between clinical and MRI findings. Eur Neurol 1998; 39:26–31.
5. Insinga RP, Itzler RF, Pellissier JM, *et al.* The incidence of herpes zoster in a United States administrative database. J Gen Intern Med 2005; 20:748–753.
6. Yawn BP, Gilden D. The global epidemiology of herpes zoster. Neurology ■ 2013; 81:928–930.

This is an excellent updated review of zoster epidemiology in the vaccine era.

7. Watson CP, Deck JH, Morshead C, *et al.* Postherpetic neuralgia: further postmortem studies of cases with and without pain. Pain 1991; 44:105–117.

8. Mou J, Paillard F, Turnbull B, *et al.* Qutenza (capsaicin) 8% patch onset and duration of response and effects of multiple treatments in neuropathic pain patients. Clin J Pain 2014; 30:286–294.
9. Nagel MA, Traktinskiy I, Azarkh Y, *et al.* Varicella zoster virus vasculopathy: analysis of virus-infected arteries. Neurology 2011; 77:364–370.
10. Nagel MA, Cohrs RJ, Mahalingam R, *et al.* The varicella zoster virus vasculopathies: clinical, CSF, imaging, and virologic features. Neurology 2008; 70:853–860.
11. Nagel MA, Forghani B, Mahalingam R, *et al.* The value of detecting anti-VZV IgG antibody in CSF to diagnose VZV vasculopathy. Neurology 2007; 68:1069–1073.
12. Nagel MA, Traktinskiy I, Stenmark KR, *et al.* Varicella zoster virus vasculopathy: immune characteristics of virus infected arteries. Neurology 2013; 80:62–68.
13. Salazar R, Russman AN, Nagel MA, *et al.* Varicella zoster virus ischemic optic neuropathy and subclinical temporal artery involvement. Arch Neurol 2011; 68:517–520.
14. ■ Nagel MA, Russman AN, Feit H, *et al.* VZV ischemic optic neuropathy and subclinical temporal artery infection without rash. Neurology 2013; 80:220–222.

This study shows that VZV vasculopathy without rash can present as biopsy-negative GCA.

15. ■ Mathias M, Nagel MA, Khmeleva N, *et al.* VZV multifocal vasculopathy with ischemic optic neuropathy, acute retinal necrosis and temporal artery infection in the absence of zoster rash. J Neurol Sci 2013; 325:180–182.

This study shows that VZV vasculopathy without rash can present as biopsy-negative GCA.

16. ■ Nagel MA, Bennett JL, Khmeleva N, *et al.* Multifocal VZV vasculopathy with temporal artery infection mimics giant cell arteritis. Neurology 2013; 80: 2017–2021.

This comprehensive, retrospective study shows VZV in temporal arteries of 5 of 24 patients with biopsy-negative GCAs.

17. Nagel MA, Khmeleva N, Boyer PJ, *et al.* Varicella zoster virus in the temporal artery of a patient with giant cell arteritis. J Neurol Sci 2013; 335:228–230.
18. Habib AA, Gilden D, Schmid DS, Safdieh JE. Varicella zoster virus meningitis with hypoglycorrhachia in the absence of rash in an immunocompetent woman. J Neurovirol 2009; 15:206–208.
19. Bhagat RK, Zieske AW, Kamble RT. Cerebrospinal leukemoid reaction secondary to VZV meninigoencephalitis in an AML patient post allogeneic bone marrow transplantation. Blood 2013; 122:300–301.
20. Gunson RN, Aitken C, Gilden D. A woman with acute headache and sacral dermatomal numbness. J Clin Virol 2011; 50:191–193.
21. Matsumoto H, Shimizu T, Tokushige S, *et al.* Rectal ulcer in a patient with VZV sacral meningoradiculitis (Elsberg syndrome). Intern Med 2012; 51:651–654.
22. Moses H, Nagel MA, Gilden DH. Acute cerebellar ataxia in a 41 year old woman. Lancet Neurol 2006; 5:984–988.
23. Calabria F, Zappini F, Vattemi G, Tinazzi M. Pearls & Oy-sters: an unusual case of varicella-zoster virus cerebellitis and vasculopathy. Neurology 2014; 82:e14–15.
24. Cuello JP, Romero J, de Ory F, de Andres C. Longitudinally extensive varicella-zoster virus myelitis in a patient with multiple sclerosis. Spine 2013; 38:1282–1284.
25. Yeung J, Cauquil C, Saliou G, *et al.* Varicella-zoster virus acute myelitis in a patient with MS treated with natalizumab. Neurology 2013; 80:1812–1813.
26. Gilden DH, Wright RR, Schneck SA, *et al.* Zoster sine herpete, a clinical variant. Ann Neurol 1994; 35:530–533.
27. Kleinschmidt-DeMasters BK, Gilden DH. Varicella-zoster virus infections of the nervous system: clinical and pathologic correlates. Arch Pathol Lab Med 2001; 125:770–780.
28. de Silva SM, Mark AS, Gilden DH, *et al.* Zoster myelitis: improvement with antiviral therapy in two cases. Neurology 1996; 47:929–931.
29. Gilden DH, Beinlich BR, Rubinstien EM, *et al.* Varicella-zoster virus myelitis: an expanding spectrum. Neurology 1994; 44:1818–1823.
30. Orme HT, Smith AG, Nagel MA, *et al.* VZV spinal cord infarction identified by diffusion-weighted MRI (DWI). Neurology 2007; 69:398–400.
31. Franco-Paredes C, Bellehemeur T, Merchant A, *et al.* Aseptic meningitis and optic neuritis preceding varicella-zoster progressive outer retinal necrosis in a patient with AIDS. AIDS 2002; 16:1045–1049.
32. Menerath JM, Gerard M, Laurichesse H, *et al.* Bilateral acute retinal necrosis in a patient with acquired immunodeficiency syndrome. J Fr Ophtalmol 1995; 18:625–633.
33. Lewis GW. Zoster sine herpete. Br Med J 1958; 2:418–421.
34. Amlie-Lefond C, Mackin GA, Ferguson M, *et al.* Another case of virologically confirmed zoster sine herpete, with electrophysiologic correlation. J Neurovirol 1996; 2:136–138.
35. Blumenthal DT, Shacham-Shmueli E, Bokstein F, *et al.* Zoster sine herpete: virologic verification by detection of anti-VZV IgG antibody in CSF. Neurology 2011; 76:484–485.
36. Hevner R, Vilela M, Rostomily R, *et al.* An unusual cause of trigeminal-distribution pain and tumor. Lancet Neurol 2003; 2:567–571.
37. Birlea M, Nagel MA, Khmeleva N, *et al.* Varicella-zoster virus trigeminal ganglioneuritis without rash. Neurology 2014; 82:90–92.