Review Article

Benign convulsions in children with mild gastroenteritis

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Abstract

Background: Benign convulsions with mild gastroenteritis (CwG) is a clinical condition characterized by convulsions occurring in otherwise healthy children, usually in the absence of fever and in the presence of mild acute gastroenteritis. Until now, CwG had not been fully recognized as an epileptic syndrome, and several aspects of this condition are not clearly defined, especially its pathogenesis.

Methods: The main aim of this paper is to discuss after the review of the literature what is known about CwG to facilitate its recognition and treatment.

Results: CwG is a benign condition that has several clinical and prognostic similarities with febrile seizures. The disease occurs in infants and in children who are 1 month to 3 years old, during the winter and early spring when rotavirus and norovirus are circulating. In most cases, seizures follow gastrointestinal symptoms. In a minority of patients, the seizures and gastrointestinal symptoms occur before or simultaneously with the development of diarrhoea. Even if convulsions are mostly described as generalized tonic-clonic, the ictal recordings have always demonstrated a focal origin. Electroencephalography, lumbar punctures, and radiological examinations are not useful because they are normal in these patients; and when alterations are present, they disappear in a relatively short time. Only prolonged seizures, which are usually not common, require antiepileptic treatments in the acute phase.

Conclusion: Knowledge of CwG characteristics is essential for paediatricians to avoid useless hospitalization, examinations and, above all, drug administration, as the drugs have potential side effects.

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1. Introduction

Acute gastroenteritis (AGE) is a very common and clinically important disease in paediatrics. It is the third most common cause of death in children <5 years of age in the developing world. In patients living in industrialized countries, only a few deaths from AGE occur, but the disease has a considerable impact on the health system and the quality of life of children and their families. In a number of cases, AGE is associated with convulsions. Several factors may explain the development of seizures in subjects with AGE (Table 1). Electrolyte abnormalities and dehydration due to the severe loss of electrolytes and water in stools or vomitus may induce neurological symptoms. A high fever (>39 °C) that sometimes accompanies diarrhoeal syndromes may induce convulsions, particularly in infants and toddlers who are highly susceptible to febrile stimuli due to the immaturity of their central nervous system (CNS). Infectious pathogens or fragments of these pathogens may breach the blood-brain barrier and cause significant CNS damage, leading to seizures. Finally, in patients with a disease called benign convulsions with mild gastroenteritis (CwG), convulsions may be observed. This clinical condition, identified more than 30 years ago, was later repeatedly reported, and has been defined as a syndrome characterized by afebrile convulsions occurring in otherwise healthy children with mild AGE who do not have central nervous system infections, dehydration, or electrolyte imbalances and who have a benign prognosis.

Based on these characteristics, it has been suggested that CwG might be termed as situation-related seizures and be classified as an epileptic syndrome within benign infantile seizures in the classification set by the International League Against Epilepsy (ILAE). However, until now, CwG has not been fully recognized as an epileptic syndrome by ILAE. On the other hand, several aspects of this condition are not clearly defined, especially its pathogenesis. The main aim of this paper is to discuss what is known about CwG to facilitate its recognition and treatment.

2. The epidemiology and pathogenesis of CwG

The epidemiologic characteristics of CwG can help us understand which factors are potentially associated with the development of this disease and suggest, at least for some of the cases, its pathogenesis. CwG has been described in children aged 1 month to 6 years, and the disease peaks in 1- to 2-year-olds. This finding seems to indicate that, in terms of febrile seizures (FS), an immature CNS may favour the occurrence of CwG. Moreover, although some cases have been reported in Europe and America, CwG has been more frequently described in East Asian countries, mainly in Japan, South Korea, Taiwan and Hong Kong where it occurs in approximately 1% of all AGE cases. This finding suggests that the genetic characteristics of the host may play a role in the development of CwG. However, most of the CwG cases occur during the winter and early spring months. This is the period of the year during which viruses, such as rotavirus (RV), norovirus (NV), and adenovirus, have the largest circulation and are the most common cause of AGE in temperate countries. Enteric viruses have been detected in a number of stool specimens from children with CwG. Consequently, we cannot exclude the fact that these infectious agents might induce seizures by directly stimulating the CNS. A number of findings, unfortunately only for RV, support this hypothesis. Before the introduction of RV vaccines, RV was the most common virus associated with CwG in all of the studies. Moreover, RV antigens and RV RNA have been detected in the cerebrospinal fluid (CSF) of a number of children with AGE, and an association between meningitis, meningoencephalitis, acute cerebellitis, flaccid paralysis, and Reye or Reye-like syndrome and RV AGE has been repeatedly reported. In some cases, the CNS lesions in children with RV AGE and seizures have been found to be reversible as evidenced in cases with transient lesions in the splenium of the corpus callosum or transient bilateral basal ganglia lesions. Finally, particular attention has been paid to NSP4, the RV enterotoxin that causes brain damage. NSP4 is a glycosylated protein that is important for viral replication, morphogenesis, and pathogenesis. During AGE, NSP4 is responsible for intestinal secretion by altering calcium...
homeostasis in infected intestinal epithelial cells. Moreover, it has also been demonstrated that NSP4-mediated Ca$^{2+}$ mobilization may trigger the release of amines and peptides from intestinal endocrine cells as well as the release of cytokines, prostaglandins, and nitrous oxide from enterocytes. It has been proposed that, when RV reaches the CSF, all of these functions may cause neurotoxicity and neurotransmitter dysregulation. All of these findings support the hypothesis that RV causes different degrees of CNS lesions. Among the CNS lesions, those observed in children with CwG are the mildest because CwG does not induce persistent damage. On the other hand, it was recently demonstrated that the concentration of neurotransmitter amino acids (i.e., glutamate, glycine, and taurine) in the CSF of children with RV infection and CNS involvement were significantly higher in patients who had experienced prolonged seizures with encephalopathy than in those with CwG.

On the contrary, the hypothesis that particular RV genotypes could be the cause of CwG is debated. Choi et al. detected the P9G2 genotype at a higher frequency than other genotypes in children with CwG. Yang et al. reported that the P9G3 RV genotype was dominant in CwG patients, but the difference was not statistically significant.

Unfortunately, similar pathogenetic explanations cannot be proposed for all cases of CwG that occur in association with infections due to enteric viruses other than RV. The introduction of the RV vaccine has significantly reduced the total number of seizures associated with RV infection. However, in the geographic areas where NV, rather than RV, is the most common cause of AGE, the incidence of CwG was found to be significantly increased. This finding highlights the importance of these infectious agents and suggests that the pathogenetic mechanisms are different from those observed in RV and could play a role in favouring the development of CwG.

There is a lack of definitive knowledge regarding the pathogenesis of CwG. In addition, the convulsions associated with AGE have the same general characteristics as those observed in afebrile CwG. Whether these convulsions should be considered a part of atypical CwG cases or considered common febrile seizures (FS) is not known. Some studies have attempted to answer this question, but the results were conflicting. Lee and Chung compared CwG cases with and without fever and found that the mean age, family history, seizure semiology, and frequency of seizures were not significantly different between the two groups. However, a greater number of patients in the afebrile group experienced ≥ 2 seizures/day compared to the febrile group (63% vs. 38%, p = 0.051). The febrile patients had a tendency of experiencing prolonged seizures lasting ≥ 5 min compared to the afebrile group (34% vs. 11%, p = 0.063). Prior febrile seizures were noted in 5 of the 32 patients (15.6%) in the febrile group, whereas none of the 27 patients in the afebrile group had a similar history (p = 0.056). Considering these differences, the authors suggested that the two conditions could not be considered to be different aspects of the same disease but, rather, that afebrile CwG had to be observed as a distinct condition. Similar conclusions were reached by Kang et al., who examined the medical charts of 17 children with febrile AGE and 42 subjects diagnosed with AGE without fever. These authors reported that FS associated with AGE developed earlier during the course of the illness compared to afebrile seizures. Moreover, seizure episodes were more common in afebrile patients as were the focal seizures with or without secondary generalization. In contrast, a different theory was put forth by Ueda et al. in a recent study. They performed a retrospective analysis of 293 consecutive paediatric patients with viral AGE, among whom 18 developed seizures; 8 of the cases did not develop a fever and 10 developed a fever. Almost all of the children with fever presented with seizures at an early stage of AGE and had more episodes of clustered seizures. However, all of the patients, independent of the presence of fever, presented with generalized tonic-clonic seizures, complex partial seizures or both and responded poorly to diazepam (DZP) and very well to carbamazepine (CBZ) treatment. A comparison of the clinical picture and the response to antiepileptic treatment evidenced in these subjects to children with FS whose underlying cause was different from AGE led to the conclusion that, on the whole, the clinical features of FS during viral AGE may closely resemble those of afebrile CwG than those in FS. The frequency of clustered seizures and the drug responses were significantly more similar between the two forms of seizures with AGE than between each of these forms of seizures and FS due to other causes. Consequently, febrile and afebrile CwG may, at least in part, have a common pathogenetic mechanism distinct from that of FS due to other causes. On the other hand, attempts to identify the same genetic abnormalities in children with CwG and FS to explain the response to low doses of CBZ have failed. Until the reasons for why CwG develops are completely clarified, it will be difficult to understand whether febrile CwG and afebrile CwG are different aspects of the same disease or two different conditions. Further studies are needed to solve the problem.

3. Clinical manifestations

It must be highlighted that in most of the cases of afebrile CwG, the seizures follow gastrointestinal symptoms; however, in a minority of patients, the seizures occur before or simultaneously with the development of diarrhoea. Uemura et al. studied 114 consecutive episodes of CwG and reported that the average interval between the onset of gastroenteritis and seizures was 2.3 ± 1.1 days (range, 1–6 days). However, 8 (6.3%) and 45 (35.1%) of the 128 children studied by Verrotti et al. experienced seizures 12–24 h before the onset of diarrhoea and on the same day, respectively.

Even if convulsions are mostly described as generalized tonic-clonic, the ictal recordings have always demonstrated a focal origin. Komori et al. observed focal features, such as hemiconvulsions or a lateral gaze, in 10 out of 19 CwG episodes. Moreover, ictal EEGs have shown that the majority of the seizures in patients with CwG tended to evolve into secondary generalized manifestations. The most common site of origin was found in the temporal area for complex partial seizures and the parietal or occipital area for secondary generalized seizures. An interictal EEG was normal in most of the patients, although in some cases slight abnormalities, such as slow waves and epileptiform discharges, were observed. The duration can vary significantly. The majority of patients have seizures lasting only seconds or a few minutes, but in some cases the seizures can persist much longer.
longer. Verrotti et al. reported that 87.7% of children had seizures lasting less than 5 min and 12.3% between 5 and 10 min. A cluster of several seizures during a single diarrhoeal episode is common. In the study by Uemura et al., 2 or more seizures occurred in 86 (75%) of the 114 episodes.

As previously reported, in afebrile CwG blood electrolytes, other blood chemistry values, and CSF characteristics were always found to be normal. This means that the systematic examination of the CSF in children with CwG is not necessary. The same is true for radiological examinations. Neither computed tomography nor magnetic resonance is useful because typically no lesion is detected and, even if present, lesions are transient.

Anticonvulsant therapy is not necessary if the patient has seizures of minimal duration, even if they occur in clusters. Prolonged seizures usually respond to conventional therapy, but drug-resistant cases have been described. Okumura et al. retrospectively investigated the effect of antiepileptic treatment in 110 consecutive episodes in 103 patients with CwG. They found that the first-line drug DZP/bromazepam (BZP) was effective in 38% of cases; phenobarbital (PB) was effective in 40% of the cases, and lidocaine (LD) was effective in 100% of the cases. As second-line drug, the effectiveness of DZP/BZP, PB, and LD was 42%, 69% and 100%, respectively. As third-line drug, PB was effective in 70%. The results were not substantially different from those reported by Verrotti et al. Benzo-diazepines, such as DZP, midazolam, and PB were effective in stopping the seizures in only 37.7%, 0.0% and 28.6% of cases, respectively. These authors indicated CBZ to be the most effective drug and suggested the administration of 5 mg/kg/die of this drug as the best solution to treat prolonged seizures. However, there is no consensus concerning the drug of choice to treat CwG because different authors have reported different results with the same therapeutic scheme. Nevertheless, all of the experts agree on the exclusion of benzodiazepines in routinely treating patients with CwG.

Moreover, there is no consensus regarding the need for therapy after a seizure of short duration to prevent further episodes in between episodes when the child has no signs and symptoms of neurologic involvement. Cusmai et al. withheld drug treatment during the interval between one seizure and another because the children were clinically healthy and the authors did not find any further problems in psychomotor development in the children enrolled in the study.

All of the studies that have evaluated the outcome of children with CwG have shown that this clinical condition generally has a good prognosis. Neurodevelopmental sequelae are very rare regardless of the severity at presentation. In the study by Verrotti et al. in which the clinical features of 81 subjects with CwG were followed-up for a mean period of 9.8 years, the neurological examination and cognitive level at the last evaluation were found to be normal in all the patients, and only a mild attention deficit was detected in three cases (3.7%). Intercital EEG abnormalities returned to normal during the follow-up period in all of the studies. In both children who had received continuous antiepileptic therapy and in those who did not receive any drug, these abnormalities returned to normal. These findings highlight that drugs are not effective and that long-term therapy is not appropriate for these children. The development of epilepsy later on has rarely been described and is not considered to be a consequence of CwG. However, CwG can recur during new episodes of gastroenteritis in 3–20% of the cases. Moreover, 2.5–6.7% of children with CwG can subsequently suffer from FS and, more rarely, from unprovoked afebrile seizures without the development of epilepsy later on.

### Table 2: Main characteristics of benign convulsions with mild gastroenteritis (CwG).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age range</strong></td>
<td>From 1 month to 6 years</td>
</tr>
<tr>
<td><strong>Epidemiology</strong></td>
<td>Although described in Europe and America, it is mainly reported in Japan, south Korea, Taiwan and Hong Kong</td>
</tr>
<tr>
<td><strong>Seasonality</strong></td>
<td>Winter and early spring</td>
</tr>
<tr>
<td><strong>Microbiological findings</strong></td>
<td>Frequent detection of rotavirus and norovirus</td>
</tr>
<tr>
<td><strong>Seizure onset</strong></td>
<td>Usually after gastrointestinal symptoms</td>
</tr>
<tr>
<td><strong>Seizure pattern</strong></td>
<td>Mostly generalized, tonic-clonic convulsions lasting seconds or a few minutes</td>
</tr>
<tr>
<td><strong>Fever</strong></td>
<td>Usually absent</td>
</tr>
<tr>
<td><strong>Gastrointestinal symptoms</strong></td>
<td>Diarrhoea ± vomiting without dehydration</td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td>Usually favourable</td>
</tr>
<tr>
<td><strong>Ictal electroencephalography</strong></td>
<td>Focal findings followed by secondary manifestations</td>
</tr>
<tr>
<td><strong>Blood chemistry</strong></td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Cerebrospinal fluid</strong></td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Radiological examinations</strong></td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Anticonvulsant therapy</strong></td>
<td>Usually not needed (required only for prolonged seizures)</td>
</tr>
</tbody>
</table>

Table 2 summarizes the characteristics of CwG. CwG is a benign condition that has several clinical and prognostic similarities with FS. Interestingly, CwG is associated with AGE and possibly has a different pathogenesis. As CwG is completely benign with normal interictal EEG in the large majority of the cases, its clinical relevance is reduced. Only prolonged seizures, which are usually not common, require antiepileptic treatments in the acute phase. Even when clusters are observed, the administration of drugs appears to be useless unless the duration of a single convulsion episode is particularly long. Similarly, long-term prophylaxis is not necessary; EEGs, lumbar punctures, and radiological

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4. **Conclusions**

Table 2 summarizes the characteristics of CwG. CwG is a benign condition that has several clinical and prognostic similarities with FS. Interestingly, CwG is associated with AGE and possibly has a different pathogenesis. As CwG is completely benign with normal interictal EEG in the large majority of the cases, its clinical relevance is reduced. Only prolonged seizures, which are usually not common, require antiepileptic treatments in the acute phase. Even when clusters are observed, the administration of drugs appears to be useless unless the duration of a single convulsion episode is particularly long. Similarly, long-term prophylaxis is not necessary; EEGs, lumbar punctures, and radiological
examinations are also not useful. The findings on these tests are usually normal and, when alterations are present, they disappear in a relatively short time. Knowledge of all of these characteristics is essential for paediatricians to avoid useless hospitalization, examinations and, above all, drug administration because these drugs have potential side effects.

Conflict of interest
None.

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