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Benign convulsions associated with mild gastroenteritis: A multicenter clinical study

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KEYWORDS
Afebrile seizures;
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Antiepileptic drugs;
Ictal EEG

Summary:
Purpose: To assess the clinical characteristics and the outcome of benign convulsions associated with mild gastroenteritis (CwG) in Italian children.
Methods: We studied clinical and EEG features of 128 children with CwG who were hospitalized between January 2004 and February 2008 and then followed for at least 12 months in 14 Italian centers.
Results: Age at onset ranged from 6 to 60 months. The seizures were generalized in 73 cases (57%), only focal in 16 (12.5%), and secondarily generalized in 39 (30.5%). The duration of the seizures was under 5 min in 97 patients (75.8%), between 5 and 30 min in 26 (20.3%), and longer than 30 min in 5 (3.9%). Seventy-three participants (57%) had 2 or more seizures, which recurred within 24—48 h. In the acute phase, antiepileptic drugs were used in 72 patients (56.3%). Although interictal abnormalities were present in EEG of 28 children (21.9%), these reverted to normal. During the follow up period, only 6 patients (4.7%) suffered from recurrence of CwG, 7 (5.5%) suffered from simple febrile seizures, and 3 (2.3%) developed epilepsy.
Conclusions: Recognition of CwG in children allows pediatricians to avoid extensive evaluations and continuous antiepileptic therapy and to reassure parents regarding the lack of long-term complications.

Introduction

Benign convulsions associated with mild gastroenteritis (CwG) are defined as afebrile, brief, apparently generalized seizures accompanying symptoms of gastroenteritis without clinical signs of dehydration or electrolyte derangement. CwG can occur in healthy children within the first 5 days of gastroenteritis and are associated with frequent detection of Rotavirus antigen in the stool. Seizures characteristically occur in cluster over a 24-h period. The seizure and psychomotor developmental outcome of patients who suffered from CwG are reported to be excellent (Verrotti et al., 2009).

Since their first description in Japan (Morooka, 1982), CwG have been well documented in the Far East (Komori et al., 1995; Wong, 2001; Uemura et al., 2002; Hung et al., 2003), while they seem to be overlooked in the United States and Europe (Uemura and Okumura, 2005). Thus, the aim of this study is to assess the clinical characteristics and outcome of a large sample of children with CwG from the pediatric departments of 14 centers in Italy.

Patients and methods

The study included 128 patients with CwG who were hospitalized between January 2004 and February 2008 in the following centers: Department of Pediatrics, Chieti ($n = 19$); Department of Pediatrics, Rome ($n = 17$); Department of Child Neuropsychiatry, Sassari ($n = 16$); Department of Child Neuropsychiatry, Mantova ($n = 12$); Department of Child Neuropsychiatry, Naples ($n = 9$); Department of Child Neuropsychiatry, Pavia ($n = 9$); Department of Pediatrics, Udine ($n = 8$); Department of Child Neuropsychiatry, Bologna ($n = 7$); Department of Pediatrics, Siena ($n = 7$); Department of Child Neuropsychiatry, Ancona ($n = 6$); Department of Pediatrics, Ragusa ($n = 6$); Department of Pediatrics, Pavia ($n = 5$); Department of Child Neuropsychiatry, Trieste ($n = 5$); and Division of Child Neurology and Psychiatry, Cagliari ($n = 2$). All 128 patients were followed for at least 12 months in order to fully evaluate their evolution. Informed consent was obtained from the parents/guardians of the recruited children, and the study was approved by the Ethics Committee of each institution.

The following inclusion criteria for CwG were applied: seizures associated with gastroenteritis, absence of clinical signs of severe dehydration or electrolytic derangement, and a body temperature of less than 38.0 °C 24 h before and after the seizures. We used a clinical definition of gastroenteritis as diarrheal disease of rapid onset, with or without accompanying symptoms and signs such as nausea, vomiting, or abdominal pain. Children with mental or neurological deficits or patients with meningitis, encephalitis, encephalopathy associated with a viral infection, and children with apparent personal history of epilepsy were excluded from the study even though they had symptoms similar to those of CwG. We ruled out Sandifer Syndrome in patients with tonic posture and several episodes of vomiting, performing gastric ultrasonography.

For each patient, the pediatric neurologists evaluated the following aspects: gender, age at onset of seizures, personal and family history of epileptic disorders, psychomotor development, seizure duration and manifestation, frequency of seizures, EEG features, laboratory data, brain imaging findings, efficacy of AED (antiepileptic drug) treatment, and recurrence of CwG or other epileptic disorders during the follow up period. AED was regarded as effective when seizures stopped after the administration of the drug. Seizure types were judged based upon feedback from parental interview as well as pediatrician's observations and classified using the International League Against Epilepsy (ILAE) terminology (Commission on Classification and Terminology of the International League Against Epilepsy, 1981).

EEGs were performed while awake and asleep within a week of the seizures. Electrodes were placed according to the international 10—20 system.

General intelligence was measured with the Wechsler Intelligence Scale for Children-Revised (WISC-R).

Serum samples were drawn for analysis of hemogram, serum electrolytes (sodium, chlorine, potassium, calcium, and magnesium), glucose, urea, creatinine, alanine aminotransferase, aspartate aminotransferase, and standard C-reactive protein. Fecal specimens were collected in order to test for the presence of Rotavirus and Adenovirus antigens via commercially available immunochromatographic kits. Bacterial fecal cultures for Salmonella, Shigella, and Campylobacter were also evaluated. Analysis of cerebrospinal fluid (CSF) and brain imaging (CT and/or MRI) were performed when the pediatric neurologists judged necessary.

Clinical and electrical details of all patients were reviewed and unanimously agreed upon by all authors.

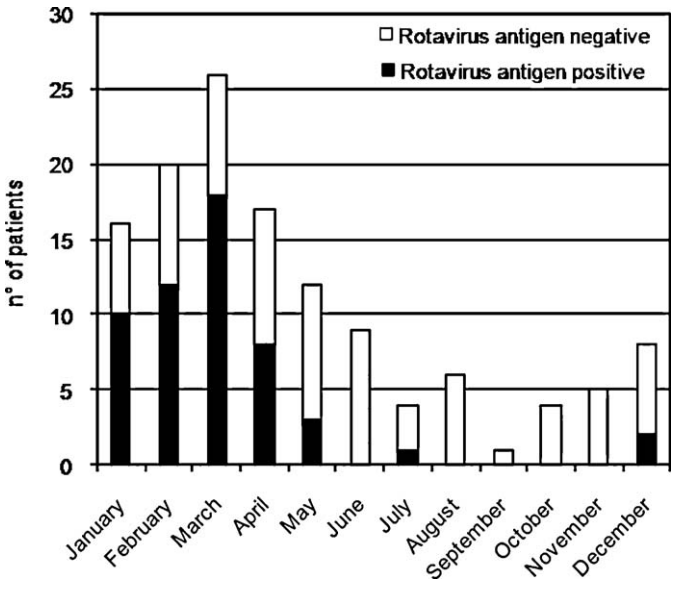

Figure 1 Seasonal distribution of CwG and rate of Rotavirus antigen-positive patients.

Results

Gender and age at onset

Over a 4-year period, 128 (64 male and 64 female) patients suffering from CwG were identified. The age at onset ranged from 6 to 60 months (median 24.0 months), peaking between 13 and 24 months. The highest incidence was in winter/spring (Fig. 1). All patients had a normal psychomotor development and no significant prior medical problems. None of the 128 children had received Rotavirus vaccine.

Personal and family history of epileptic disorders

Nineteen children (14.8%) had suffered from simple febrile seizures on previous occasions. Out of 128 patients, 41 (32%) and 21 (16.4%) patients had a family history of simple febrile seizures and of epilepsy in the first and second-degree relatives. One child reported a family history of CwG.

Clinical characteristics

The interval between the onset of gastroenteritis and the onset of convulsions ranged from 0 to 4 days.

Diarrhea lasted from 3 to 6 days; children had 3—7 watery or loose stools daily. Diarrhea occurred on the same day as the seizures in 45 children (35.1%), while preceded it by 1, 2, 3, and 4 days in 39 (30.5%), 20 (15.6%), 9 (7%), and 7 (5.5%) patients, respectively. Eight children (6.3%) had the seizures 12—24 h before the onset of diarrhea.

Fifty-five patients (43%) had only single seizures, whereas 73 (57%) had 2 or more seizures with the same semiological characteristics within 24—48 h. Seventy-three patients (57%) showed generalized seizures: tonic ($n = 19$; 14.8%), atonic ($n = 6$; 4.7%), and tonic-clonic ones ($n = 48$; 37.5%); the seizures were focal in 16 (12.5%) and focal with secondary generalization in 39 (30.5%). The duration of the seizures was under 5 min in 97 cases (75.8%), between 5 and 30 min in 26 (20.3%), and longer than 30 min (status epilepticus) in 5 (3.9%).

EEG features

Ictal EEG was recorded in 9 children (7%) (Table 1) (Figs. 2 and 3). Interictal EEG was normal in 100 patients (78.1%), while some abnormalities (slow focal activity and widespread epileptiform discharges) were observed in 28 (21.9%).

Treatment

AEDs were administered in 72 patients (56.3%) during the acute phase. Cluster of seizures did not stop after the administration of the first AED in 46 of treated children (63.9%). The AEDs used and their respective efficacy are summarized in Fig. 4. A continuous AED therapy was carried out in 6 children for 2 years.

Laboratory findings

Serum electrolytes, glucose, urea, creatinine, alanine aminotransferase, and aspartate aminotransferase were normal in all children. White cell count and C-reactive protein were slightly increased in 15 (11.7%)

Table 1 Ictal EEG and seizure semiology.

No.	Origin of ictal discharge	Seizure evolution	Clinical manifestation
1	Right occipital	Focal → Generalized	Left lateral gaze → GTCS
2	Right occipital	Focal → Generalized	Clonic movements of the left hand → GTCS
3	Right parietal	Focal → Generalized	Clonic movements of the left hand → GTCS
4	Right parieto-occipital	Focal → Generalized	Loss of responsiveness, left lateral gaze → GTCS
5	Left parietal	Focal → Generalized	Loss of responsiveness, right lateral gaze → GTCS
6	Left frontal	Focal → Generalized	Right lateral gaze → GTCS
7	Bilateral frontal	Focal → Generalized	Upward gaze → GTCS
8	Right frontal	Focal	Left lateral gaze
9	Left frontal	Focal	Staring, clonic movements of the right limbs

GTCS, generalized tonic-clonic seizure.

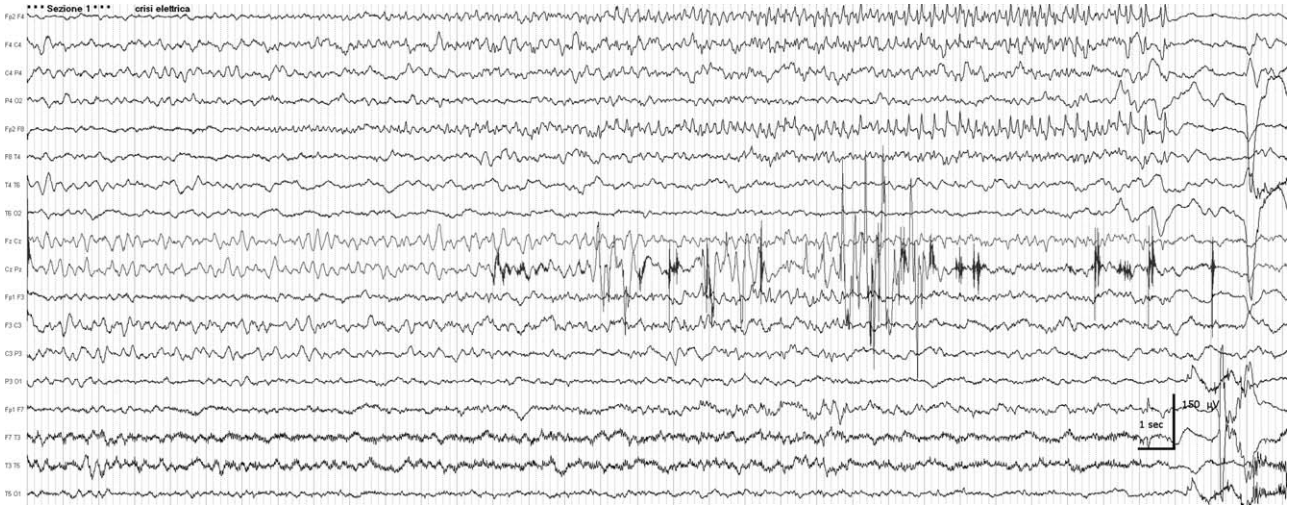

Figure 2 Electrical seizure characterized by a small amplitude theta activity on the right frontal region, progressively replaced by high amplitude spikes. The seizure ends abruptly after 25 s.

(range = 16,300—18,700/mm^3) and 19 patients (14.8%) (range = 1.42—5.62 md/dL), respectively. Rotavirus antigen was detected in the stools of 54 children (42.2%). All stool specimens were negative for Adenovirus antigen. All patients had negative bacterial stool cultures.

Analysis of CSF was performed in 7 patients (5.5%) and showed no abnormalities.

Imaging studies

Neuroimaging studies (25 MRIs and 13 CTs) were performed in 38 patients (29.7%) and revealed no abnormalities.

Long-term evaluation

The follow up period was between 12 and 60 months (median: 35 months). At the last evaluation, neurological examination and psychomotor development were normal in all children, even in those with status epilepticus at presentation. The interictal EEG abnormalities, which were found in 28 cases (21.9%), reverted to normal both in the patients who received continuous AED therapy and in the patients who did not receive this treatment. Out of the 128 patients, 6 (4.7%) suffered from recurrence of CwG, 7 (5.5%) suffered from simple febrile seizures, and 3 (2.3%) developed epilepsy. These 3 children have had no interictal EEG abnormalities during the acute phase; after the subsequent

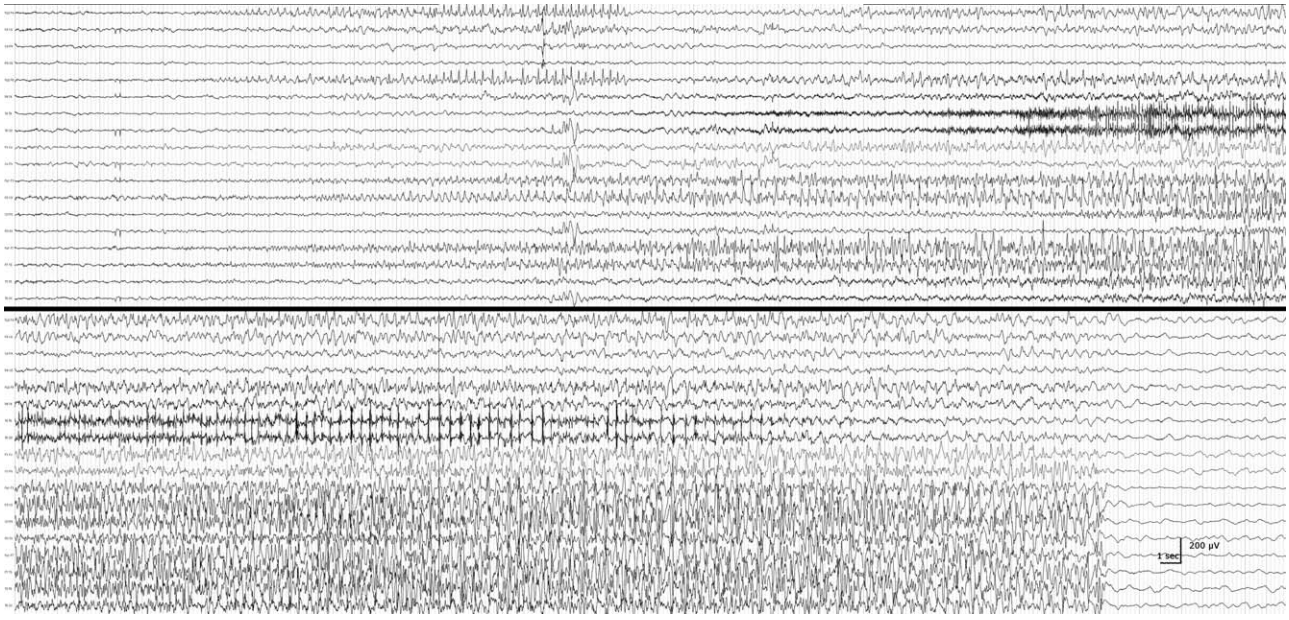

Figure 3 Focal seizure lasting 2 min. Note a recruiting discharge starting on the right frontal region and ending after 25 s. An independent seizure starts from the left frontal region and involves subsequently the vertex and the whole left hemisphere.

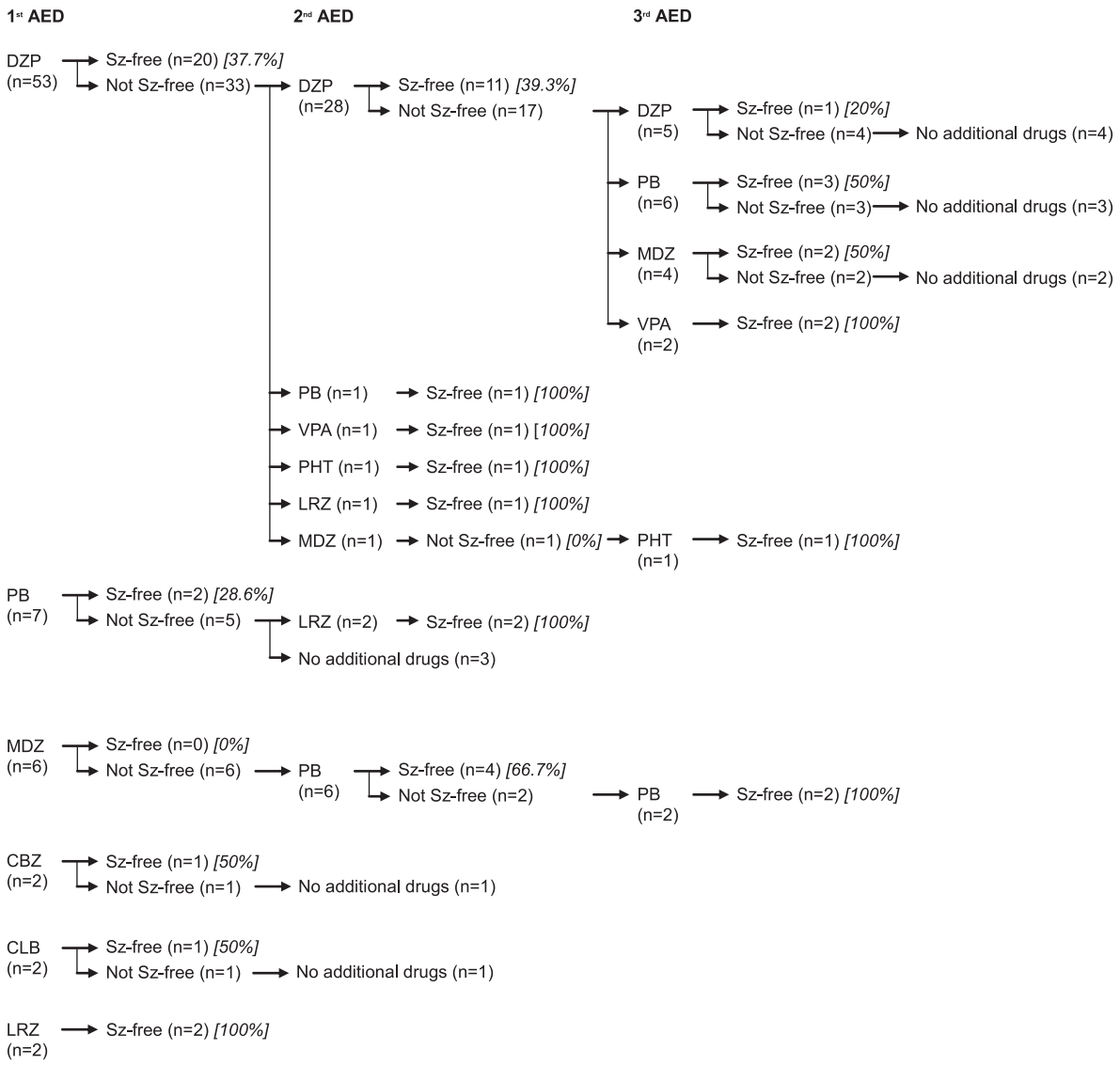

Figure 4 AEDs administered to patients with CwG. AED, antiepileptic drug; Sz, seizure; CBZ, carbamazepine; CLB, clobazam; DZP, diazepam; MDZ, midazolam; LRZ, lorazepam; PB, phenobarbital; PHT, phenytoin; VPA, valproate. In parentheses: efficacy of AED.

unprovoked seizures, interictal EEG showed abnormalities in one child (medium-voltage sharp waves and spikes localized mainly in the temporo-parietal regions and rarely in the fronto-temporal areas), while remained normal in 2.

Discussion

CwG were first described in 1982 by Morooka; since then, several case series confirming the relationship between mild gastroenteritis and afebrile convulsions have been published in Japan (Komori et al., 1995; Uemura et al., 2002; Kawano et al., 2007; Motoyama et al., 2009), Hong Kong (Wong, 2001), and Taiwan (Hung et al., 2003; Chen et al., 2009). On the other hand, CwG have been rarely reported in the United States and Europe (Contino et al., 1994; Narchi, 2004; Gómez-Lado et al., 2005; Iglesias Escalera et al., 2005; Zerr et al., 2005; Chalouhi et al., 2006; DiFazio et al., 2007; Iyadurai et al., 2007; Fernández Fernández et al., 2008; Plana Fernández et al., 2008). Recently, however, the clinical features of 2 groups of children with CwG have been described in Argentina and Spain (Caraballo et al., 2009; Durá-Travé et al., 2010). Our study is the first to describe several aspects of CwG in a large group of children enrolled throughout Italy in a homogeneous survey.

As stated previously (Komori et al., 1995; Uemura et al., 2002; Hung et al., 2003; Narchi, 2004; Zerr et al., 2005; Kawano et al., 2007; Chen et al., 2009), our data indicate a distinct winter/spring seasonal distribution of CwG.

With regard to the timing of the seizure episodes, it has been previously demonstrated that the seizures may occur within the first 5 days of gastroenteritis (Komori et al., 1995; Narchi, 2004; Caraballo et al., 2009); in our experience, children presented the convulsions within the 4th day. On the other hand, as reported elsewhere (Komori et al.,

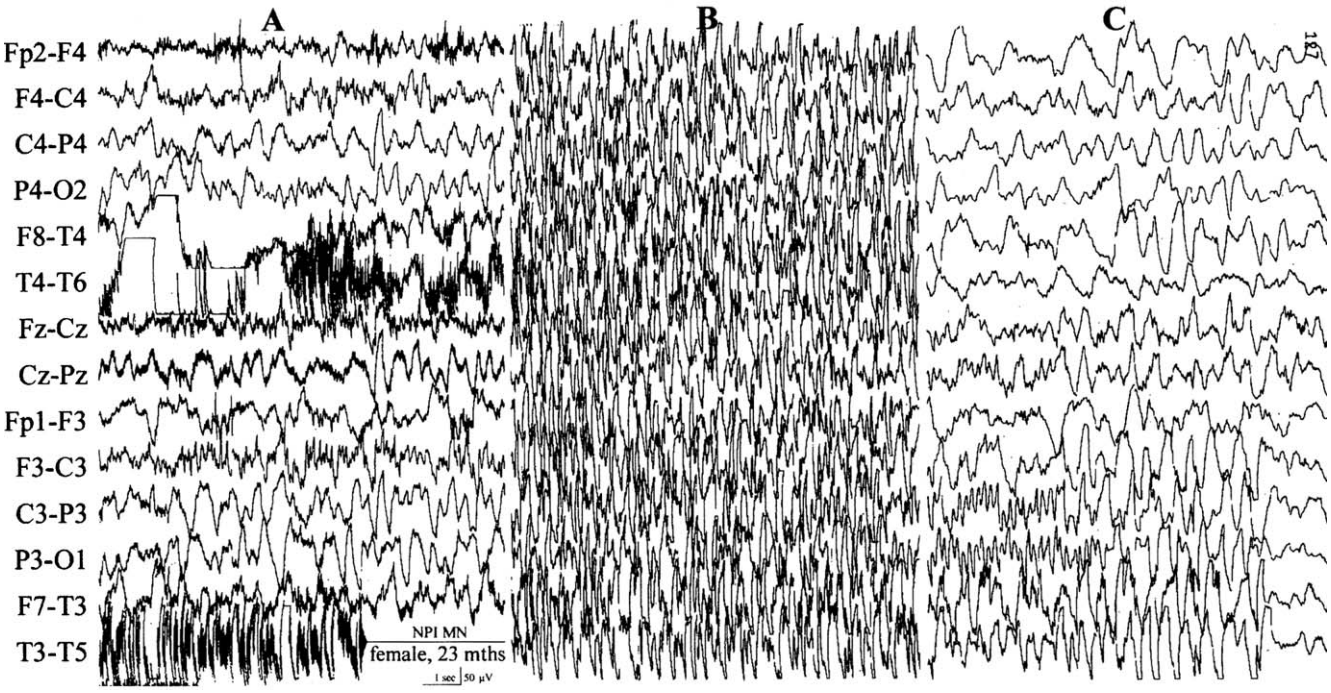

Figure 5 Secondarily generalized focal seizure in a 23-month old infant with total duration of 195 s. She was afebrile, and diarrhea started some hours after this seizure. (A) A focal recruiting discharge is evident on the left centro-parietal region. The discharge is related to clonic jerks of the right hand. (B) A secondary generalization with clonic movements affecting the four limbs is observed 20 s after the seizure onset. (C) A focal discharge on the left parieto-occipital regions is evident at the end of the seizure. (Modified from Capovilla and Vigevano, 2001. J. Child Neurol. 16, 874—881.).

1995; Durá-Travé et al., 2010), in some patients, the seizures started before the onset of diarrhea; for this reason, it may sometimes be difficult to identify CwG in the first phases of the disease.

Rotavirus antigen was detected in the stool specimens of about half of our patients. Rotavirus is the most common agent among the diarrheal viruses that may cause sporadic episodes of CwG. It is postulated that Rotavirus is able to spread beyond the intestine, reach the central nervous system through the bloodstream, and induce encephalitis, encephalopathy, or seizures. This hypothesis is supported by evidence of antigenemia and viremia in affected patients, even in those with diarrhea but with Rotavirus-negative stools (Blutt et al., 2003, 2007; Chiappini et al., 2005; Fischer et al., 2005; Ray et al., 2006; Sugata et al., 2008); besides, Rotavirus RNA has been detected in the CSF of children with seizures (Yoshida et al., 1995; Pang et al., 1996; Liu et al., 2009). However, this mechanism does not explain the pathogenesis in those patients with seizures preceding diarrhea. Probably, other mechanisms are involved, as an increased level of nitric oxide or carnitine in CSF related to Rotavirus infection (Shinawi et al., 1998; Kawashima et al., 2004; Rodríguez-Díaz et al., 2006). Furthermore, it is interesting to note that CwG are not Rotavirus-specific (Abe et al., 2000; Wong, 2001; Lee and Ong, 2004; Kawano et al., 2007; Chen et al., 2009). Indeed, other infectious agents, such as Norovirus, have also been found in the stools of patients with CwG (Abe et al., 2000; Kawano et al., 2007; Chen et al., 2009). This virus was not tested in our patients and might justify the occurrence of CwG in our Rotavirus-negative children.

As in previous studies (Komori et al., 1995; Wong, 2001; Uemura et al., 2002; Hung et al., 2003; Lee and Ong, 2004; Narchi, 2004; Zerr et al., 2005; Tanabe et al., 2006; Kawano et al., 2007; Caraballo et al., 2009; Chen et al., 2009; Motoyama et al., 2009), we mostly observed primarily or secondarily generalized seizures which occurred as a single seizure or in cluster over a 12- to 24-h period. Although the duration of seizures was brief (less than 5 min) in a large number of children, some patients experienced prolonged seizures (5—30 min) or status epilepticus, as described by others authors (Lee and Ong, 2004; Fernández Fernández et al., 2008; Chen et al., 2009; Durá-Travé et al., 2010). These findings indicate that CwG might exhibit variable clinical features.

Ictal recordings suggest a relationship between CwG and benign infantile (familial and non-familial) convulsions. After first description as generalized seizures (Fukuyama, 1963), many observations demonstrated that benign infantile convulsions were focal, with or without secondary generalization, by their nature (Capovilla et al., 1998; Capovilla and Vigevano, 2001). The same concept may be applied to CwG as all ictal recordings revealed a focal onset of the seizures (Fig. 5) (Imai et al., 1999; Maruyama et al., 2007). Moreover, in both types of conditions, the seizures could originate from different cerebral areas, start from one hemisphere and involve subsequently the other one, even in the same patient and in the same recording.

Consistent with many studies (Komori et al., 1995; Uemura et al., 2002; Narchi, 2004; Caraballo et al., 2009), interictal EEG appeared normal in most of our patients. Although 28 children (21.9%) initially presented some EEG

abnormalities, such as slow waves and epileptiform discharges, the EEGs returned to normal during the follow up period. As highlighted by other authors (Wong, 2001; Hung et al., 2003; Isik and Caliskan, 2008; Chen et al., 2009), these findings suggest that abnormal EEGs in patients with CwG are transient and are not absolute indicators for initiating long-term AED treatment.

Analyses of CSF and brain imaging studies, which showed normal results in our tested children, are unnecessary when patients present only afebrile convulsions in association with mild gastroenteritis and without other signs of encephalitis or meningitis (Komori et al., 1995; Uemura et al., 2002; Hung et al., 2003; Narchi, 2004; Kawano et al., 2007; Caraballo et al., 2009; Durá-Travé et al., 2010).

The optimal treatment for clustered seizures in cases of CwG has not yet been defined since these seizures are rather refractory in response to AED treatment; in particular, the efficacy of benzodiazepines and phenobarbital is reported to be low (Uemura et al., 2002; Okumura et al., 2004a). Indeed, in 46 (63.9%) of our treated children, the first-line AED failed to achieve seizure cessation: benzodiazepines, such as diazepam and midazolam, and phenobarbital were effective in stopping the seizures only in 37.7%, 0%, and 28.6% of cases, respectively. Although Japanese neuropediatricians proposed various approaches to treat seizure clusters, such as lidocaine administered continuously in drip infusion (Okumura et al., 2004a), lidocaine tape (Okumura et al., 2004b), oral administration of carbamazepine (Ichiyama et al., 2005; Kawano et al., 2007; Motoyama et al., 2009; Tanabe et al., 2010), and suppository administration of chloral hydrate (Enoki et al., 2007), an intensive AED treatment might be unnecessary since the clusters of seizures did not persist for more than 24 h in the majority of cases. However, treatment may be useful in clusters with several seizures, which frighten parents and physicians. Carbamazepine appears to be the most effective choice reported to date; thus, according to the recent finding of Tanabe et al. (2010), we suggest that 1 day therapy with low-dose of carbamazepine (5 mg/kg/day) could be effective and without side effects. Nevertheless, further randomized controlled studies are needed to clarify the efficacy of these different treatments in patients with CwG.

During the follow up period, a good prognosis as regards the seizures, neurological examination, and psychomotor development was observed in most of children. Recurrence of CwG, together with the possibility of suffering from simple febrile seizure or developing epilepsy, appeared low. In addition, the interictal EEG abnormalities, which were initially found in some children, reverted to normal both in patients who received continuous AED therapy and in patients who did not receive this treatment. For these reasons, we believe that administration of long-term AED treatment is not appropriate in patients with CwG. Others studies have also shown that the clinical outcome following CwG is usually benign and continuous AED therapy is unnecessary (Uemura et al., 2002; Caraballo et al., 2009). However, considering that 3 patients developed subsequent unprovoked seizures, we recommend a long follow up in these children.

To date, CwG have not been categorized by ILAE (Berg et al., 2010); some authors (Capovilla and Vigevano, 2001; Caraballo et al., 2009) consider them as benign infantile seizures precipitated by mild diarrhea, while others (Uemura et al., 2002) believe that CwG are situation-related seizures rather than epilepsy.

Conclusions

Our findings confirm that CwG may be a new clinical entity with a good prognosis, occurring in infancy and early childhood. This condition is not confined in Japan and in the Far East but should be considered a worldwide condition. Patients experience single or clustered seizures during the course of a mild gastroenteritis, which is frequently associated with Rotavirus infection. The seizures are brief in the majority of cases even if prolonged convulsions or status epilepticus may be observed. Although interictal EEG may show some abnormalities, these revert to normal. Irrespective to the nosological location of this entity, it is important to recognize it in order to avoid extensive evaluation and unnecessary AED therapy and to reassure parents about the lack of long-term complications.

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