Infantile convulsions with mild gastroenteritis: a retrospective study of 25 patients

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Background: The aim of this study was to analyze the epidemiologic, clinical, and evoluntional characteristics in patients who presented convulsions with mild gastroenteritis (CwG) to facilitate the diagnosis in daily clinical practice.

Methods: Twenty-five medical records of patients diagnosed with CwG were reviewed, and the epidemiological and clinical features, results of complementary studies, and evoluntional data were collected.

Results: Age of onset ranged between 12 and 24 months in 76% of patients. Female/male ratio was 2.6 (18 women and seven men). Seizures were mostly brief (<5 min) and apparently generalized, and often repetitive occurring in cluster (2.2 seizures per episode). One patient with status epilepticus was recorded. The average interval between the onset of gastroenteritis and seizures was 3.8 days, even though seizure preceded diarrhea in three cases. Mean rectal temperature at the moment of seizure was 37.1°C. Rotavirus antigen was positive in stool in 17 episodes (55.8%). There were no abnormalities in serum biochemistry tests and cerebrospinal fluid studies. Four patients showed anomalies in the interictal electroencephalogram. The period of follow-up was 4.2 years. Five patients (20%) experienced recurrences when suffering a new gastroenteritis episode. One patient developed epilepsy during the follow-up period.

Conclusions: CwG would constitute a well-differentiated convulsive syndrome. Prognosis is excellent, but a relatively important percentage of patients relapse when suffering a new diarrhea episode.

Introduction

Infantile convulsions with mild gastroenteritis (CwG) were first described by Morooka in 1982 in Japan. CwG are characterized by occurring in previously healthy children and in a clinical context of gastroenteritis, mainly of viral etiology, showing neither apparent signs of dehydration nor biochemical and/or hydroelectrolitic alterations. They usually consist of apparently generalized afebrile seizures with normal interictal electroencephalogram (EEG) recording, which generally recur within the same episode of diarrhea and carry good prognosis [1–5].

Several reports have come out in oriental [1–4,6–9] and occidental [10–22] countries since initial description, which has made different authors consider them as a different entity that could be included in the new classification of the International League Against Epilepsy (ILAE) [23], either as an epileptic syndrome within benign infantile seizures [24,25] or as a condition with epileptic seizures that do not require a diagnosis of epilepsy [3–5], as it happens with febrile seizures. Anyway, CwG constitute a quite unknown entity for general pediatrician; in addition, their semiologic peculiarities, specially recurrence and afebrile condition, would explain the trend to accomplish many complementary studies to determine the etiology, as well as to prescribe anticonvulsant drugs.

The aim of this work is to expose and analyze the epidemiologic, clinical, and evoluntional characteristics in a group of patients diagnosed with CwG, to facilitate diagnosis in clinical practice.

Material and methods

Twenty-five clinical records of patients who were diagnosed with CwG and hospitalized in the Hospital
Virgen del Camino between January 2001 and December 2008 were reviewed.

Inclusion criteria were the same as those described in previous reports [3,4,5]:
1. Seizures associated with symptoms of gastroenteritis without clinical signs of dehydration or hyderoelectrolytic disorder, and
2. Body temperature remained <38.0°C before and after the seizures.

Patients with bacterial or aseptic meningitis/encephalitis associated with a viral infection, or an apparent history of epilepsy were excluded. Patients with both febrile (body temperature ≥38.0°C) and afebrile seizures during a single episode of gastroenteritis were included in the study. Children with febrile seizures alone were excluded from the study, even if they had symptoms of gastroenteritis.

The epidemiological data obtained included sex, date, and age at the time of seizure, personal (pregnancy and delivery, neonatal period, psychomotor development, and febrile seizures) and familiar history (febrile seizures and epilepsy). The clinical data obtained included interval between episode of diarrhea and seizure, semiology (type, number, and duration) and treatment of seizures, as well as diagnostic procedures (rotavirus and adenovirus antigen in stool and stool culture, hemogram and serum biochemistry, lumbar puncture, EEG, neuroimaging studies, etc.). The evolution data obtained included anticonvulsant drugs prescription, clinical evolution (recurrence and/or epilepsy), and time of follow-up.

This research protocol has been approved by the Ethics Committee of the Hospital Virgen del Camino.

Results are shown as means and percentages with their confidence intervals (95% CI). Statistical analysis (frequency analysis) was made using the statistical program spss 17.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Epidemiological characteristics

There were 25 patients included in the study. Five of them (20%) presented with recurrence at the time of a new episode of gastroenteritis (one patient had two recurrences), accounting for 31 admissions (or episodes) and 67 seizures. The number of children admitted with acute gastroenteritis was 1225, and rotavirus antigen in stool was positive in 325 cases. This means, CwG counted for 2.5% of admissions in children with gastroenteritis (31 episodes) and 5.2% of gastroenteritis owing to rotavirus (17 episodes).

Table 1 displays some of the epidemiological data registered for the 25 patients included in the study. The totality of patients was born after full-term pregnancies and eutocic delivery, except for one case of instrumental delivery (forceps), birth weight between 3.080 and 3.750 g and had a normal neonatal period. Psychomotor development was normal in all of them prior to diagnosis. There was first-degree relative's history of CwG in two patients (brothers).

Female/male ratio was 2.6 (18 women and seven men). Age ranged between 12 and 24 months in 76% of patients (n = 19) was below 12 months in three of them (8, 9 and 10 months respectively), and above 24 months in three (31, 38, and 65 months, respectively). The incidence of CwG was high from November to March (25 episodes).

Clinical features

The average interval between the onset of gastroenteritis and seizures was 3.8 days (95% CI: 3.3–4.3 days), even though seizure preceded diarrhea in three cases. The average number of seizures per episode was 2.2 (95% CI: 1.8–2.6) and mode was 3.0. One single seizure was recorded in 11 episodes (35.5%). In 97%, the seizures were referred by the parents as generalized either presenting with tonic-clonic movements (n = 54) or with stiffness and/or hypotonia (n = 11), and two cases were hemi body clonic contractions. Nevertheless, generalized motor seizures were preceded by a lack of response to stimuli and/or eye deviation in six cases (8.9%). The mean duration of a seizure was 2.1 min. Duration was under 1 min in 52.2% of seizures, between 1 and 5 min in 38.8%, between 5 and 10 min in 4.4%, reached 20 min in two occasions (2.9%), and one patient had only one seizure whose duration was over

<table>
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<tr>
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<td><strong>Age at diagnosis (months)</strong></td>
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<td>18.1 (15.3–20.9)</td>
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<td><strong>Follow-up (years)</strong></td>
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CI, confidence interval.
30 min and required admission to the Intensive Care Unit (status epilepticus). In the case of multiple seizures, the average interval between the first seizure and the last one was 5.6 h (range: 3–16 h). None of the patients showed clinical signs of moderate–severe dehydration, and weight loss was always under 5%.

Mean rectal temperature at the moment of first seizure was 37.1°C (95% CI: 36.8–37.4). However, seven patients (22.6%) also presented with febrile convulsions during the time they remained hospitalized, with temperature fluctuating between 38.2 and 39.6°C. Mean hospital stay was 3.8 days (95% CI: 3.3–4.3) with a mode of 3.0.

**Complementary studies**

Rotavirus antigen was positive in stool in 17 episodes (54.8%) and negative in eight episodes. Adenovirus antigen detection was negative in all patients. There was no stool collection in four episodes. Stool culture was positive in two episodes (*Campylobacter jejuni* and *Yersinia enterocolitica*).

There were no abnormalities in the laboratory test, including complete blood counts, serum biochemistry, and serum electrolytes. Blood samples were collected to perform blood culture, obtaining negative results in all of them.

Lumbar puncture was accomplished in eight episodes (25.8%); cerebrospinal fluid (CSF) cell count, glucose, and proteins were normal. Likewise, CSF cultures, herpes virus, and adenovirus polymerase chain reaction (PCR) in CSF were negative.

Electroencephalogram studies were accomplished in all patients in every hospitalization. EEG recordings in immediate postictal situation were obtained in 18 episodes, (58%). There were EEG anomalies in four cases:

1. Slow background activity with interference of sharp and slow potentials and occasional generalized spike–wave activity: EEG recording was normal after 3 months.
2. Generalized slow activity with right posterior focal predominance. EEG was normal after 3 days.
4. Intermittent focal spike–wave activity on right rolandic area with frequent spreading to adjacent areas (right frontal and left parietal areas). There were no posterior controls.

After a mean time of follow-up of 3.5 years, none of these patients had suffered from relapse. In the rest of episodes (n = 13), recordings were obtained late after convulsion (mean time: 2.5 days), and there were no significant EEG findings.

Neuroimage studies were accomplished in 11 patients (44%): cranial computerized tomography (CT) in 10 patients and magnetic resonance imaging in one patient. All of them were normal.

**Treatment**

Anticonvulsant drugs were prescribed in 40.3% of seizures (n = 27). Seizures ended after rectal diazepam administration in 22 cases, although they reappeared in 11 cases. Intravenous phenytoin was added to treatment in four cases, and it was kept for 24 h in three cases. Sodium valproate was added to treatment in one case. Seizures did not reappear in any of these cases.

Treatment of gastroenteritis consisted basically in administration of oral rehydration solutions. Intravenous acyclovir was prescribed in four cases, and one patient was also prescribed cefotaxime until the results of analytic and microbiological results were known.

Four patients were prescribed anticonvulsant drugs to keep continuous treatment (three received sodium valproate and one received phenobarbital). Two of them were prescribed after relapse at the time of a new diarrhea episode, and another two were prescribed because of anxiety parental (there were EEG anomalies in one of them). Treatment was withdrawn in all cases, after a mean duration of 2.0 years. There were no relapses after withdrawn and mean time of follow-up of 3 years.

**Prognosis**

Mean age at present time is 5.7 years (95% CI: 4.6–5.8), and all of them have undergone normal development and schooling. From the total of 25 patients who were included in the study, five of them (20%) had a relapse at the time of a new episode of gastroenteritis 4, 8, 11, and 14 months after the first episode (one patient had two relapses at 2 and 4 months after the first episode). Another patient had a short episode of generalized hypotonia with ocular and head movements 9 months after hospitalization, coinciding with a febrile respiratory episode.

It is also remarkable to know the evolution of a male patient who had familiar history of epilepsy (mother) and had presented only one afebrile seizure in a context of mild gastroenteritis with normal post-ictal EEG. At the age of three, he began suffering from recurrent polymorphic seizures (right arm clonic movements, generalized tonic–clonic movements and episodes of staring with no response to stimuli and body falls). There were no evident parainfectious signs; the EEG...
recordings showed paroxysmal activity in both frontal areas, and the neuroimaging studies were normal. He was diagnosed with focal epilepsy and was prescribed sodium valproate, showing good response to treatment.

Discussion

The new ILAE classification of epileptic seizures and epileptic syndromes only recognizes two types of benign infantile seizures: familial and non-familial [23]. However, other types of benign infantile seizures have been described, such as the benign familial neonatal–infantile seizures [26], the familial infantile convulsions and choreoatetosis [27], and the benign infantile focal epilepsy with midline spikes and waves during sleep [28]. The syndromic classification of the CwG could match, according to different authors, either as a new type of benign infantile seizures [1,25] or as a special syndrome and/or condition with epileptic seizures that do not require a diagnosis of epilepsy [3,5].

Initially, it was suggested that CwG were a location-restricted pathology limited to Asian countries [2–5,9]. The incidence of afebrile seizures with mild gastroenteritis in general and caused by rotavirus would range between 2–3.5% and 4.1–6.4% [2,5,7], respectively. The published series of patients in occidental countries are short [10–14,22], but an incidence of afebrile CwG caused by rotavirus of 5.1% [15] has been estimated. This number, together with the data registered in this work (incidence of afebrile CwG in general of 2.5% and caused by rotavirus of 5.2%) allows us to consider that the lower frequency of cases registered in occidental literature is attributed to the lack of knowledge of this nosologic entity rather than to genetic, racial of bacterial typification peculiarities.

One of the most remarkable epidemiological aspects of this series is the fact that 96% of patients were between 8 and 38 months old, with a maximum incidence between 12 and 14 months of age, which matches the published data [1,3–5,11,16]. There was one patient who exceeded these limits (5.4 years old). In addition, there was a predominance of female sex. Neonatal history and psychomotor development in these patients were normal. However, the percentage of patients who referred familiar history of epilepsy was higher than the registered data in other series [3,5,29]. Besides, the fact that two patients were brothers could suggest, as is has been pointed out [3,8], a certain genetic susceptibility.

The episode of gastroenteritis is usually mild; this means, there are neither external signs of dehydration nor biochemical and/or hydroelectrolitic imbalance that could explain seizures. Viruses are the most frequent causal agents related to these seizures, especially rotavirus [2–4,7,9,14,16,22]. Routine analyses in our laboratory only detect rotavirus and adenovirus in stool. Therefore, a negative result does not exclude the presence of other viruses (calcivirus, astravirus, norovirus, enterovirus, etc.) related to acute gastroenteritis [4,6]. Thus, in this series, gastroenteritis etiology is assumed to be of viral etiology, with evident predominance of rotavirus, except for two cases of bacterial etiology and four cases in which sample was not collected. This eventuality would explain that the majority of registered patients were admitted between the months of October and February, because viral gastroenteritis usually affects to infant population showing epidemic and seasonal distribution during the coldest months [1–3,5,11].

The sequence of events that allows suspicion and/or recognition of this syndrome is fairly uniform; there is little variability in the published series. Typical presentation consists of generalized seizures happening short time after the beginning of an episode of mild gastroenteritis. Seizures are short, afebrile, and tend to recur in the following hours. However, it is remarkable that seizures may present before diarrhea, thus explaining the request of complementary studies and even prescription of antiviral drugs. The majority of authors refer generalized tonic–clonic seizures and, to a lower extent, tonic and/or atonic seizures. Nevertheless, apart from the EEG findings that will be discussed further on, focal signs are described in these patients, such as alteration in consciousness and/or eye deviation that make us suspect they could constitute focal seizures with secondary generalization [1,16]. One of the most characteristic manifestations is the high frequency they present as a cluster. In other words, they tend to recur in the following 24–28 h, although our series shows that time interval between the first and the last seizure in a same process ranges between 3 and 16 h. Seizures are usually short (<5 min) and self-limited, as it occurred in 91% of seizures registered in this series. However, it should be emphasized that seizures are longer in some cases, and even manifest as status epilepticus that could make us think of a neurologic severe involvement, as it occurred in one case of this series.

Patients suffering from febrile and afebrile seizures within the same diarrhea episode have been included as Uemura et al. [3] did. It is surprising that most authors (that, on the other hand, quote repeatedly this author) do not refer this eventuality as it is well known that fever, diarrhea, and vomiting are characteristic signs of gastroenteritis caused by rotavirus; as we previously said, rotavirus is the most frequent biological agent in diarrhea episodes of these patients. Seven patients presented afebrile as well as febrile seizures during the same hospitalization period in this series, but none of them suffered from febrile seizures exclusively; this
would be more predictable when associating seizures and acute gastroenteritis and, of course, it would be questionable that coincidence of fever and any seizure in these patients were to constitute a reason for excluding this diagnosis.

Diagnosis in these patients is essentially clinical, and EEG initially could be considered unnecessary [5,11,13,16] because, as it happens in febrile seizures, interictal EEG recording is repeatedly normal [3,4,11,12,30]. Nevertheless, ictal EEG recordings have shown mainly focal paroxysmal discharges of variable localization: frontal, centro temporal, parietal, or occipital [29,31]. This fact supports the idea that seizures associated with mild gastroenteritis are focal seizures with secondary generalization. Amongst all EEG recordings achieved in immediate postictal situation, some of them revealed slow background activity as well as focal or generalized epileptic activity, with variable persistence, but without clinical manifestations [2,32]. However, diffuse slow background activity seemed compatible with postictal tracing, especially taking clinical context into account. Intravenous acyclovir was prescribed in these cases until the results of complementary studies were known, including negative PCR results for herpes virus and enterovirus in CSF.

The pathophysiologic mechanism that could explain the relation between seizures and gastroenteritis is unknown. However, after discarding fever and biochemical and/or hydroelectrolitic alterations as triggering factors, it could be said that it is a neurologic manifestation secondary to an encephalopathy [2], possibly of viral etiology, that would exceptionally manifest as meningoencephalitis [33,34]. Detection of rotavirus antigens and genome in CSF in these patients suggests direct invasion [6], although it is thought that it could be a contaminant agent [33].

The shortness of seizures would explain, to a great extent, that only a small percentage of patients have received treatment. Regarding drug administration, even when rectal diazepam is effective to control seizures, it does not seem to be effective enough to avoid the phenomenon of seizure clustering in these patients [2–5,9,14]. This has motivated clinical trials with carbamazepine, lidocaine, phenobarbital [4,5,9,35], etc. However, despite the anxiety this eventuality might generate in the family environment, it would be convenient to keep a restrictive prescription of anticonvulsant drugs because it constitutes a self-limited condition. That is, rectal and/or intravenous diazepam should be used for seizure’s recurrence and, whenever seizures were prolonged and/or repetitive, fenitoin and/or sodium valproate should be administered, rather than phenobarbital, midazolam, etc. whose hypnotic effects can interfere negatively in the evolution control of the patients [3,22]. All authors coincide in good prognosis of this entity and, consequently, propose therapeutic abstention, as well as they do in febrile seizures (except for multiple recurrence and/or parental anxiety), thus avoiding continuous prophylactic treatment.

Mean time of follow-up has been relatively long. Consequently, this implies an additional value in definite diagnosis and syndromic classification of these patients. This continuous follow-up has allowed to notice, in contrast to bibliographic references [1–3,11,14,22], that a relatively important percentage of patients relapse when suffering a new diarrhea episode. In addition, we should point out that one of the patients included in this series was later diagnosed with focal epilepsy. Even when the relation with the previous presentation of infantile CwG is a matter of opinion, we should take this eventuality into account to keep evolution control in these patients.

As a conclusion, infantile CwG would constitute a well-differentiated convulsive syndrome that we should consider when diagnosing patients with repeated afebrile seizures, in the absence of personal or familial history of epilepsy and/or neurologic pathology; it would be mandatory to find out whether there is domestic environment of diarrhea or changes in stool characteristics which could suggest a diarrhea episode.

References
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