Seizure: European Journal of Epilepsy 60 (2018) 110–114

Contents lists available at ScienceDirect

Seizure: European Journal of Epilepsy

journal homepage: www.elsevier.com/locate/seizure

Clinical outcome of recurrent afebrile seizures in children with benign convulsions associated with mild gastroenteritis

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ARTICLE INFO

Keywords:
Benign convulsions
Mild gastroenteritis
Prognosis
Seizure relapse
Epilepsy

ABSTRACT

Purpose: To assess the clinical outcome and evolution of recurrent afebrile seizures in children initially diagnosed with benign convulsions associated with mild gastroenteritis (CwG).
Methods: We reviewed and analyzed the medical records of 37 patients who were diagnosed as CwG at onset, followed by recurrent afebrile seizures and followed up for at least 24 months.
Results: The follow-up period ranged from 2 to 7 years (median, 40.1 months).Three patterns of recurrent afebrile seizures were recorded: afebrile seizures associated with gastrointestinal infection (AS-GI, n = 25), afebrile seizures associated with non-gastrointestinal infection (AS-nGI, n = 9), and unprovoked seizures (US, n = 3). Twenty eight patients (75.7%) had a second episode within 6 months after the first seizures. Five cases (13.5%) suffered three episodes of afebrile seizures. Seizure characteristics of the three patterns were similar, manifesting as clustered seizures in the majority. Focal epileptic activities in interictal EEG were found in 3 cases (9.4%) at onset, 10 cases (28.6%) at the second episode, respectively. Six patients were prescribed anti-epileptic drugs with apparently good responses. During at least 2 years' follow-up, all the cases showed normal psychomotor development. Only one patient was diagnosed with epilepsy.
Conclusions: All the recurrent afebrile seizures initially diagnosed as CwG, irrespective of the kinds and frequency of relapses, showed favorable prognoses. CwG maybe falls within the category of situation-related seizures, rather than epilepsy.

1. Introduction

Benign convulsions associated with mild gastroenteritis (CwG) were first described by Morooka et al. in 1982 in Japan [1]. Since then, a number of articles involving hundreds of patients have been published [2–8]. All the previous studies have agreed on a favorable prognosis for CwG. Based on afebrile seizures triggered by mild diarrhea and associated with good outcomes, some authors have proposed that CwG falls within the category of situation-related seizures [9,10] or is an epileptic syndrome [11] within benign infantile seizures. However, CwG has not been formally recognized as an epilepsy syndrome or situation-related seizures by the International League Against Epilepsy (ILAE) so far [12,13]. Furthermore, the pathogenesis of CwG is not well defined, and the conditions of relapse of afebrile seizures after the first CwG also impede full recognition of this entity.

Until now, the data on afebrile seizure recurrence in CwG have been limited and have varied considerably, especially regarding the recurrence of unprovoked seizures. It has been reported that CwG can recur during subsequent episodes of gastroenteritis in up to 20% of the cases [6]. By contrast, Verrotti found no recurrence of CwG at a minimum of 3 years long-term follow-up [14]. In the present study, we evaluated the recurrence of afebrile seizures and neurodevelopment in cases diagnosed as CwG with follow-up periods of at least 2 years. The aim of this study was to assess the neurological outcomes of children presenting with recurrent afebrile seizures after suffering a first CwG.

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https://doi.org/10.1016/j.seizure.2018.05.020
Received 1 February 2018; Received in revised form 22 May 2018; Accepted 28 May 2018
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2. Methods

2.1. Participants

In this study, hospitalized patients diagnosed with CwG were enrolled from October 2009 to December 2014. Previously reported cases [3,15] that occured during this period were included in this study. The inclusion criteria were identical to those described previously [7,16], and included (1) a diagnosis of CwG in previously healthy subjects 6 months to 3 years of age with afebrile convulsions; (2) seizure onset was associated with mild dehydration (< 5% of body weight); (3) seizures occurring in the course of gastroenteritis; (4) normal laboratory examinations (cerebrospinal fluid results, serum electrolytes, and blood glucose levels) were observed. Patients with mental or neurological deficits or those with a personal history of epilepsy were excluded from the study even though they had symptoms similar to CwG [8,16].

Each study participant had a detailed medical history and neurologic assessment on hospital admission that included seizure characteristics, infectious symptoms and family history of seizures. To exclude the potential etiologies for the seizures, blood glucose, electrolyte screening, lumbar puncture (to rule out intracranial infection), EEG, and computerized tomography/magnetic resonance imaging (CT/MRI) were performed. Three-hour video electroencephalography (EEG) studies according to the international 10–20 system were obtained within a week of the seizures and were evaluated by the attending pediatric neurologists. Seizure types were judged based upon parental interviews as well as observations of the pediatricians and were classified using ILAE terminology [17].

2.2. Ethics

This study was approved by the Ethics Committee of the Children's Hospital of Chongqing Medical University, and informed consent was obtained from the legal guardians of each patient.

2.3. Follow-up

During the study period, 514 hospitalized cases with first seizures were diagnosed as CwG. All of them were followed up for a minimum of 2 years except 33 cases that were lost to follow-up. Among the 481 remaining patients, 37(7.7%) cases suffered more than one afebrile seizure and formed the cohort for the present study.

Starting from the second afebrile seizure, all the patients in this cohort were followed-up closely for at least 24 months by telephone or face-to-face interview every 3–6 months. Psychomotor development was evaluated, including fine and gross motor, language, and adaptive personal/social skills. If an abnormality in any of the above categories was suspected, the patients were asked to have a thorough neurological examination and neurodevelopment assessment at the outpatient department.

Based on the accompanying symptoms, the recurrent seizures were categorized into the following three patterns: afebrile seizures with mild gastroenteritis (AS-GI), afebrile seizures with non-gastrointestinal infection (AS-nGI) and unprovoked seizures (US). Afebrile seizures are defined as seizures in which fever was not present on the same day [18]. Afebrile seizures with minor infections are an afebrile seizure that occurs in association with an acute infection (occurring during the week prior to or 3 days after the seizure occurrence) that usually do not affect the brain. There may have been fever at some time during the illness, but the child was afebrile on the day of the seizure[18]. An unprovoked seizure is a seizure that occurres in the absence of any fever or infectious illness or acute (usually within a week) systemic or central nervous system insult [19].

Table 1
Demographic characteristics of 37 patients by group.

	AS-GI (n = 25)	AS-nGI (n = 9)	US (n = 3)
Male (%)	7 (28%)	1 (11.1%)	2 (66.7%)
Family history of seizures	4 (16%)	2 (22.2%)	1 (33.3%)
Median age at onset (months)	15	14.5	13
Interval between the onset and recurrence			
0-3 months	11 (44%)	4 (44.4%)	1 (33.3%)
-6 months	7 (28%)	3 (33.3%)	2 (66.7%)
-12 months	3 (12%)	1 (11.1%)	0
-18 months	4 (16%)	1 (11.1%)	0

3. Results

3.1. Demographic characteristics

In this cohort, the age at seizure onset was 14.0 ± 7.3 months. The female:male ratio was 2.7.

Out of 37 patients, seven patients had a positive family history of seizures. All patients showed normal psychomotor development prior to the diagnosis of CwG.

According to the classification criteria, 25 cases, 9 cases and 3 cases were categorized into the AS-GI, AS-nGI and US groups, respectively. Nine cases classified as AS-nGI were associated with acute upper respiratory tract infection or acute bronchitis concomitantly without fever on the day of seizure occurrence. The demographic features by group were shown in Table 1. The median ages at seizure onset for the AS-GI, AS-nGI and US groups were 15 months, 14.5 months and 13 months, respectively. One patient in the AS-GI group had two first degree relatives with febrile and afebrile seizures, respectively.

3.2. Clinical and EEG features

As shown in Table 1, 44% (11/25), 44.4% (4/9) and 33.3% (1/3) of patients from the AS-GI, AS-nGI and US groups, respectively, presented with a second episode within 3 months of the first; the median interval duration from seizure onset to recurrence was 4 months, 4.7 months and 6 months, respectively.

Four parameters (Table 2) were recorded and evaluated – seizure type, seizure frequency, seizure duration and the interval between gastroenteritis onset and seizure. The most common seizure type in the AS-GI group for both onset and recurrent seizures was tonic seizures, with a prevalence of 48% and 64%, respectively. Regarding seizure frequency, over half of the patients had clustered seizures for both onset and recurrent episodes (56% vs. 72%, respectively). Duration of seizures of 1–5 min accounted for the largest proportion of both the onset (48%) and recurrent (72%) episodes. Finally, we assessed the interval between gastroenteritis onset and seizure occurrence, and found that nearly 90% of patients in both groups had a time interval of 3 or fewer days. The rates of the above four items were similar among all the three groups

In the cohort, there were five cases that experienced a third episode of seizures. The seizure type and frequency of this group were similar to the others. The clinical features of cases with two or more seizure episodes and medication details are summarized in Table 3.

3.3. Interictal EEG and neuroimaging

The findings of interictal EEG recordings are presented in Table 4. Overall, during the first episode, there were only 3 cases (9.4%) with focal discharges, which were located in the occipital and parietal regions. For the recurrent episode, the total percentage of focal discharges was higher at 27.8% (10/36), with discharge area in the frontal region

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