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Afebrile Benign Convulsion Associated With Mild Gastroenteritis: A Cohort Study in a Tertiary Children Hospital

Nahid Khosroshahi, MD[1], Aliakbar Rahbarimanesh, MD[2], Farhad Asadi Boroujeni, MD[1], Zahra Eskandarizadeh, MD[1], and Mojdeh Habibi Zoham, MD[3]

Abstract

Background: Benign convulsion with mild gastroenteritis is a new clinical entity that occurs in children who are otherwise healthy. **Method:** This cohort study held among patients with afebrile convulsion and accompanying gastroenteritis in a tertiary children hospital during a 2-year period. Demographic and clinical data were analyzed. Neurodevelopmental milestones were observed during a follow-up period of 12 to 24 months. **Results:** Twenty-five patients aged 3 to 48 months with female predominance were enrolled. Ninety-three percent of cases experienced generalized tonic-clonic seizures. One-third of seizures occurred in clusters. Primary laboratory findings and electroencephalography were normal except for 3 with few epileptic waves. During the follow-up period, no seizure recurrence happened. Long-term antiepileptic treatment was unnecessary. **Conclusion:** Afebrile convulsion accompanying mild gastroenteritis is a convulsive disorder with reassuring prognosis. Due to its benign course, comprehensive neurodiagnostic evaluation and long-term antiepileptic drugs are usually avoidable.

Keywords

benign, convulsive seizures, gastroenteritis, infant

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Benign convulsion with mild gastroenteritis, a clinical entity primarily identified in East Asian countries, is now recognized in many countries worldwide.[1–3] It mostly manifests as generalized convulsions[4] in previously healthy children aged 1 month to 6 years, during the course of a mild gastroenteritis.[4,5] Patients are afebrile and show no evidence of electrolyte imbalance, serum glucose disturbance, and central nervous system pathologies such as meningitis, encephalitis, or encephalopathy.[6] Gastroenteritis is usually mild with no signs of moderate to severe dehydration in patients.[7] Seizures in these patients usually tend to occur in clusters, repetitively during the first several days of onset of diarrhea. Seizures can be tonic, clonic, generalized tonic-clonic seizure, and even partial attacks.[3,4,7,8] The interictal electroencephalogram findings usually do not reveal any prominent abnormality. Long-term antiepileptic drugs are usually not required. The prognosis of the seizures is usually warranted with no significant sequelae on psychomotor milestones.[7]

The authors conducted this study with the goal of contributing the Iranian experience to the growing body of literature with respect to benign convulsion with mild gastroenteritis.

Materials and Methods

In this cohort study, all patients aged 3 months to 5 years old who were admitted in the emergency department of Bahrami Children hospital, a tertiary children hospital with afebrile seizure and concurrent gastroenteritis from March 2012 to March 2014, were enrolled. Patients' demographic information including age, sex, season of admission, medical history of febrile, or afebrile seizure or any other medical condition, family history of febrile or any convulsive disorder, and

[1] Department of Pediatric Neurology, Bahrami Children Hospital, Tehran University of Medical Sciences, Tehran, Iran
[2] Department of Pediatric Infectious Disease, Bahrami Children Hospital, Tehran University of Medical Sciences, Tehran, Iran
[3] Department of Pediatric Intensive Care Unit, Bahrami Children Hospital, Tehran University of Medical Sciences, Tehran, Iran

Corresponding Author:
Mojdeh Habibi Zoham, MD, Department of Pediatric Intensive Care Unit, Bahrami Children Hospital, Tehran University of Medical Sciences, Imam Hossein Square, Damavand Avenue, Tehran, Iran.
Email: mjh_7409@yahoo.com

seizure characters (type of seizure, the number of seizures, the interval between the gastrointestinal symptoms and seizure, and number of cluster seizures) were collected from patients' medical reports that are generally filled by pediatric residents. Duration of seizures was not recorded and will not be analyzed. Information about the type of seizures was determined by direct observation of health-care providers (doctor/nurse), description of parents or both.

The patients were observed in follow-up visits in outpatient pediatric neurology clinic from 12 to 24 months. Psychomotor milestones were monitored according to Denver Developmental Screening Test II. Individual neurological examinations of patients were assessed and registered in separate medical record files. Seizure relapse, need for antiepileptic drugs, and electroencephalography (EEG) findings were analyzed during the follow-up period. Eectroencephalography were obtained using 10 to 20 international system of electrode placement.[9]

Twenty-five patients who experienced afebrlie seizure and accompanying symptoms of mild acute gastroenteritis were evaluated. The patients were only mildly dehydrated (3%-5% of dehydration) and had normal laboratory parameters (including electrolytes and blood glucose in all patients and cerebrospinal fluid analysis in some patients) and were afebrile. All patients had normal core body temperature (less than 38.0°C) before and after seizures and had normal neurological examination and psychomotor development at study entry.

Those with fever (defined as core body temperature $\geq$38.0°C) either before or after the seizures, signs of moderate to severe dehydration, electrolyte imbalance, and previous positive history of any kind of seizure were excluded. Other exclusion criteria were any clinical and laboratory suspicion of meningitis, encephalitis, Reye syndrome, hepatic or renal failure, and acute disseminated encephalomyelitis.

This study was approved by the ethics committee of the Bahrami Children Hospital, and informed consent was waived as it was a descriptive study, and there was no need of any medical intervention. All patients' data remained anonymized before performing analysis.

Results

Demographic Features

Over a 2-year period, a total of 25 patients, 11 males and 14 females, aged 3 to 48 months (median age 14 months), were admitted to our hospital with presenting feature of new-onset afebrile seizures associated with mild diarrhea. Approximately half (46.7%) of the patients were between 12 and 24 months old.

On admission, they all were clinically stable and had normal body temperature. The patients' neurological examinations were completely intact. All patients had normal neurodevelopment milestones and none had the history of pervious febrile or afebrile seizures. The drug history of all patients was negative. All patients had negative family history of any kind of seizure, except one who had the history of febrile convulsion in his mother.

In 13 (52%) of children, seizures occurred during March to May, while the rest appeared in winter and autumn months (Table 1).

Table 1. Demographic Features of Patients Presenting With Afebrile Convulsion Associated With Mild Gastroenteritis.

Study Participants	Number of patients, N (%)
Age at presentation	
3-12 months	8 (33.3%)
12-24 months	2 (6.7%)
24-36 months	3 (13.3%)
36-48 months	NA
Gender	
Male	11 (46.7%)
Female	14 (53.3%)
Seasonal distribution	
Spring (March-May)	13 (52%)
Summer (June-August)	2 (8%)
Autumn (September-November)	4 (16%)
Winter (December-February)	6 (24%)

Abbreviation: NA, not applicable.

Clinical Features

Twenty-four (93.3%) patients experienced tonic-clonic seizure, while only 1 had presented with a focal clonic seizure. The authors did not recognize any variation happening in the type of the seizures in patients during their hospital admission.

The appearance of cluster and repetitive seizures happened in 8 (33.3%) patients. All patients experienced the first episode of convulsion and the repetitive ones in the third day of beginning of gastrointestinal symptoms.

The median days between the appearance of gastroenteritis symptoms and the seizure occurrence were 3.4 (range from 3 to 5 days) days. Meanwhile, 13 (52%) patients experienced the seizure 3 days after the beginning of diarrhea. None showed seizure after the fifth day of beginning of diarrhea. In our study, all patients demonstrated seizure after the development of gastrointestinal symptoms (Table 2).

Laboratory and Neurodiagnostic Findings

Biochemical blood examinations were completely normal in all patients. Blood sugar, blood urea nitrogen, creatinine, calcium, phosphate, urine analysis, and cultures were all normal. In 5 patients, lumbar puncture were performed with all measures of protein, glucose, and white and red cell counts being normal. Additionally, the gram stain and culture were negative. All stool cultures were negative for any bacterial pathogen. Enzyme immunoassay test for detection of probable viral pathogens was not performed.

Electroencephalogram was performed for all children. Twenty-two (88%) patients had normal EEG, while 2 patients showed few slow waves in the temporal region, and the other 1 had few generalized sharp wave discharge with predominance in frontal region in EEG.

Brain imaging including brain computed tomography scan and magnetic resonance imaging was performed in 10 (40%) patients. All imaging results were normal (Table 2).

Clinical Outcomes

When followed up from 12 to 24 months, all 25 patients had normal psychomotor milestones according to Denver

Table 2. Clinical Features and Neurodiagnostic Findings in Patients With Afebrile Convulsion Associated With Mild Gastroenteritis.

Study Participants	Number of patients, N (%)
Type of seizures	
Generalized tonic clonic	24 (93.3%)
Focal clonic	1 (6.7%)
Varying type of seizure	0
Cluster seizure	8 (33%)
Interval between the GI and neurological symptoms	
3 days	13 (52%)
3-5 days	12 (48%)
More than 5 days	0
Family history	
Febrile seizure	1 (4%)
Afebrile seizure	0
EEG findings	
Normal EEG findings	22 (88%)
Abnormal EEG findings	
Slowing	2 (8%)
Generalized	1 (4%)
Focal	0
Brain imaging	
Normal	10 (100%)
Abnormal	0

Abbreviations: EEG, electroencephalography; GI, gastrointestinal.

Table 3. Clinical Outcomes of Patients With Afebrile Convulsion Associated With Mild Gastroenteritis.

Study Participants	Number of patients, N (%)
Developmental milestones in follow ups	
Normal	25 (100%)
Abnormal	0
Medication(s) usage at presentation	
Benzodiazepine and/or phenobarbital	22 (88%)
Phenytoin and phenobarbital	5 (20%)
Duration of antiepileptic treatment	
1 week	2 (8%)
1-11 weeks	22 (88%)
12 week	1 (4%)
Seizure recurrence	
Yes	0
No	25 (100%)

Developmental Screening Test II. Additionally, none of the patients experienced recurrence of seizure. In all patients having follow-up EEGs, no abnormalities were shown (Table 3).

Twenty-two (88%) patients were first treated with either a benzodiazepine (diazepam) or phenobarbital in the emergency department, while 5 (20%) patients with repetitive seizures received phenobarbital and phenytoin as antiepileptic drugs simultaneously. But all patients' antiepileptic drugs were discontinued during 1 week to 3 months following initiation of anticonvulsant therapy.

Discussion

Seizure disorders are among the most common medical problems in children worldwide. Febrile seizures are the most frequent type (2%-5%) of seizure happening in children between 6 and 60 months.[10] Meanwhile, epilepsy is a disorder of brain characterized by an enduring predisposition to generate seizure. For epidemiologic and routine clinical practice, epilepsy is described as 2 or more unprovoked seizure happening in the time frame of longer than 24 hours. The annual prevalence of epilepsy is 0.5%-1%.[11] Furthermore, afebrile epileptic seizures in children probably necessitate comprehensive neurodiagnostic evaluation and long-term antiepileptic treatment.[3] Exception to this rule is "afebrile convulsion associated with mild gastrointestinal," which is a unique entity that has an excellent long-term prognosis with undetermined pathophysiology that should be kept in mind in order to reassure parents and avoid unnecessary workups.

Benign convulsion with mild gastroenteritis has been described mostly in East Asian countries, while in recent years, several reports from western countries demonstrate the presence of this medical condition worldwide.[7] It seems that ethnical and geographic factors can play a role in the unknown pathogenesis of this disorder. Our study is the first study performed in Tehran, Iran.

In our study, findings with respect to age at presentation, female predominance, seasonal case clustering, seizure type at presentation, and tendency to cluster seizures were similar to previously published data in benign convulsion with mild gastroenteritis.[7,12–18]

Additionally, laboratory findings including biochemical and microbiologic findings turned out to be normal which was also in-line with the previous published literature.[7,19] Meanwhile, none of the 25 patients in our cohort study demonstrated seizures before initiation of gastrointestinal symptoms, although it has been previously reported in the literature.[2,13]

Recurrence of seizure or transformation of benign convulsion with mild gastroenteritis to epilepsy rarely appears while patients have reassuring prognosis.[20] In our series, no patient needed to receive anticonvulsants in long-term period regardless of seizure type. Additionally, there was not any recurrence of convulsion.

According to previous investigations, inter ictal EEG findings were normal in almost all patients with benign convulsion with mild gastroenteritis except for some minor abnormalities such as epileptic discharge, slow waves, or focal spikes that will generally disappear in follow-up period.[13,17,21] All EEGs accomplished in follow-up visits in this study turned out to be normal. So it seems that EEG has little diagnostic value in the setting of benign convulsion with mild gastroenteritis and its usage should be limited in selected individuals. It is also suggested that utilizing neuroimaging is also unnecessary in patients with benign convulsion with mild gastroenteritis as it is almost always normal.[16]

Most of the patients with benign convulsion with mild gastroenteritis rarely need long-term antiepileptic drugs after the

acute phase of illness. Several investigations have shown probable efficacy of low-dose carbamazepine, lidocaine, and fosphenytoin in treatment of acute phase of benign convulsion with mild gastroenteritis.[22–24] These findings emphases the possible hypothesis of sodium channelopathy in pathogenesis of benign convulsion with mild gastroenteritis.[23] Other investigations also showed a lack of efficacy of benzodiazepines and phenobarbital in treatment of benign convulsion with mild gastroenteritis.[6,22] In some other studies, phenobarbital played an important role in controlling of benign convulsion with mild gastroenteritis seizures specifically the repetitive ones as it was the same in our study.[2,12] Consequently, the dilemma about the drug of choice in treatment of benign convulsion with mild gastroenteritis is still present. So large prospective studies are needed in order to identify the benign convulsion with mild gastroenteritis's drug of choice.

Although the exact role of genetic susceptibility in mechanism of benign convulsion with mild gastroenteritis is not well understood, 4% of our patients had positive family history of febrile seizure. Only a few investigations like Verrotti et al's study had demonstrated the positive family history in benign convulsion with mild gastroenteritis.[2] It seems that further studied are needed to determine the role of genetic susceptibility in this issue.

The finding of seasonal clustering of benign convulsion with mild gastroenteritis cases strongly suggests the role of infectious pathogens specifically rotavirus as the possible etiology in benign convulsion with mild gastroenteritis. Several investigations have been performed in order to detect the exact virus-dependent mechanism in febrile seizures associated with gastroenteritis and benign convulsion with mild gastroenteritis, but this pathogenesis still remains unclear.[12,13,25–27] Additionally recent data have shown controversial results in decreasing benign convulsion with mild gastroenteritis incidence after rotavirus vaccination introduction.[28,29] Therefore, larger prospective studies required in order to consider the exact pathophysiology of benign convulsion with mild gastroenteritis.

Conclusion

Benign convulsion with mild gastroenteritis is a distinct clinical entity that has not been categorized by the International League against Epilepsy. It is known as a situation-related seizure. It mostly happens in infants and has a favorable prognosis and neurologic evaluations usually turned out to be unnecessary. The exact pathophysiology remains undetermined. Further prospective investigations needed to be performed in this entity. Increased awareness of pediatricians and pediatric neurologists of this newly recognized clinical disorder can lead to enhance case detection and avoid expensive and unnecessary neurodignostic investigations.

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Author contribution

NK contributed to conception and design, acquisition, analysis, and interpretation; critically revised manuscript; gave final approval; and agrees to be accountable for all aspects of work ensuring integrity and accuracy. AR contributed to design and interpretation; gave final approval; and agrees to be accountable for all aspects of work ensuring integrity and accuracy. FAB contributed to conception and analysis; drafted manuscript and agrees to be accountable for all aspects of work ensuring integrity and accuracy. ZE contributed to conception, design, acquisition and analysis; gave final approval; and agrees to be accountable for all aspects of work ensuring integrity and accuracy. MHZ contributed to conception and design, acquisition, analysis, and interpretation; critically revised manuscript; gave final approval; and agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

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Ethical Approval

This manuscript was reviewed and approved by the ethics committee of the Bahrami children Hospital, Tehran, Iran.

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