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FEBRILE AND AFEBRILE SEIZURES ASSOCIATED WITH MILD ACUTE GASTROENTERITIS IN CHILDHOOD

FEBRILNI I AFEBRILNI NAPADI UDRUŽENI SA BLAGIM AKUTNIM GASTROENTERITISOM U DETINJSTVU

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Summary

Introduction. Seizures associated with mild acute gastroenteritis are very common in early childhood. The aim of this study is to provide basic information about seizures associated with acute gastroenteritis in order to distinguish these two entities and contribute to proper diagnosis and treatment. **Material and Methods.** Data were collected retrospectively from the medical records of consecutive children admitted to the Pediatric Clinic due to seizures associated with mild acute gastroenteritis in the period from October 2021 to April 2022. Patients were divided into two groups: febrile and afebrile. We compared the demographic and clinical characteristics of these two groups, as well as the microbiological, neurophysiological and neuroradiological characteristics. **Results.** Of the children with acute gastroenteritis and seizures, 11 were afebrile and 20 were febrile, with male predominance. The most frequently identified enteropathogen was rotavirus. Most patients presented with generalized seizures. The comparison of febrile and afebrile patients showed that cluster seizures were more common in the afebrile group ($p < 0.05$). Seven patients had a seizure that lasted longer than 5 minutes and all of them were from the febrile group ($p < 0.01$). All patients presented with normal neuroimaging findings. **Conclusion.** In clinical settings, making a distinction between febrile and afebrile gastroenteritis-related seizures as separate entities can be very difficult. It is still unclear what effect fever has on the onset of gastroenteritis-associated seizures, and whether febrile and afebrile seizures have a distinctly different pathophysiological mechanism, which is why further research is needed.

Key words: Seizures; Febrile; Seizures; Gastroenteritis; Child; Diagnosis; Rotavirus; Fever; Signs and Symptoms

Introduction

Acute gastroenteritis (AGE) is the leading cause of global morbidity in young children. The clinical manifestations of AGE include abdominal pain, vomiting, diarrhea and fever. Some patients with AGE may develop convulsions that may be febrile or afebrile. Specific enteric pathogens have been linked to convulsions in children, such as rotavirus,

Sažetak

Uvod. Konvulzije udružene sa akutnim gastroenteritisom su veoma česta pojava u ranom detinjstvu. Cilj ove studije je da pruži osnovne informacije o konvulzijama koje su udružene sa akutnim gastroenteritisom, od čega zavisi dalja dijagnostika i lečenje. **Materijal i metode.** Retrospektivno su prikupljeni podaci iz medicinskih kartona dece koja su bila hospitalizovana na Klinici za pedijatriju zbog konvulzija udruženih sa akutnim gastroenteritisom u periodu od oktobra 2021. do aprila 2022. Pacijenti su podeljeni u dve grupe: febrilni i afebrilni. Poredili smo demografske i kliničke karakteristike ove dve grupe, kao i mikrobiološke, neurofiziološke i neuroradiološke karakteristike. **Rezultati.** Od dece koja su imala akutni gastroenteritis i konvulzije, 11 dece je bilo afebrilno a njih 20 je bilo febrilno, sa predominacijom muškog pola. Najčešće izolovani enteropatogen je bio Rota virus. Najviše pacijenata je imalo generalizovani napad. Poređenjem febrilne i afebrilne grupe uočeno je da su ponavljane napade češće imala deca iz afebrilne grupe ($p < 0,05$). Sedam pacijenata je imalo napad koji je trajao duže od 5 minuta, od kojih su svi bili iz febrilne grupe ($p < 0,01$). Kod svih pacijenata su dobijeni uredni neuroradiološki nalazi. **Zaključak.** U kliničkim uslovima razlikovanje febrilnog i afebrilnog napada udruženog sa akutnim gastroenteritisom može biti veoma teško. Još uvek je nepoznato kakav uticaj ima temperatura na nastanak konvulzija udruženih sa gastroenteritisom, kao i da li febrilni i afebrilni napadi imaju drugačiji patofiziološki mehanizam, zbog čega su potrebna dalja istraživanja.

Ključne reči: febrilne konvulzije; napadi; gastroenteritis; dete; dijagnoza; rotavirus; visoka temperatura; znaci i simptomi

norovirus, adenovirus, Campylobacter and Shigella [1].

When seizures occur concomitantly with AGE, it is usually referred to as benign convulsions associated with mild gastroenteritis (CwG). The CwG are benign seizures that occur in infants and children aged from 6 months to 6 years and they were first described by Morooka et al. in 1982 [2, 3]. Komori et al. defined **benign convulsions with gas-**

Abbreviations

AGE – acute gastroenteritis

CwG – convulsions associated with mild gastroenteritis

troenteritis as afebrile tonic-clonic convulsions in healthy children, which occur between the first and fifth sick day of viral gastroenteritis and are typically associated with normal electrolyte and glucose levels with low risk of recurrence. They are short-lasting seizures (≤ 5 minutes) that can occur in clusters within 24 hours. Additionally, if the season is early winter or spring when rotavirus and norovirus are prevalent, CwG must be considered [4–6]. Although the mean interval between enteric symptom onset and seizure onset in CwG is roughly 2 days, some patients may experience seizures before enteric symptoms, meaning that clinicians should exercise caution during early winter and spring, when the prevalence of CwG is especially high [7]. In clinical settings, a fever accompanying an AGE episode is not a rare scenario. High-grade fever accompanying AGE may induce seizures, particularly among infants and young children, who are more susceptible to febrile stimuli due to immaturity of the brain [2].

Febrile seizures typically occur in children from 6 months to 5 years of age in association with fever over 38°C , who do not have evidence of an intracranial cause, another definable cause of seizure (e.g., electrolyte imbalance, hypoglycemia, drug use, or drug withdrawal), or a history of an afebrile seizure. In most cases, febrile seizures occur within the first day of the fever. The seizure usually lasts for a few seconds to at most 15 minutes (usually less than 5 minutes), followed by a brief postictal period of drowsiness, and does not recur within 24 hours [8, 9].

In clinical settings it is necessary to characterize the seizure to determine the nature of examination and treatment, although distinguishing febrile and afebrile gastroenteritis-related seizures as separate entities may be difficult. Convulsions are very common phenomena in children, but there is still insufficient data that compare the characteristics of febrile and afebrile seizures during a mild AGE episode [2, 10].

Material and Methods

Data were collected retrospectively from the medical records of consecutive children admitted to our hospital due to seizures associated with mild gastroenteritis from October 2021 to April 2022, in the period of the year when gastrointestinal infections are most common in young children. We defined “mild AGE” as a single AGE episode without moderate to severe complications, such as dehydration, electrolyte imbalance, or hypoglycemia.

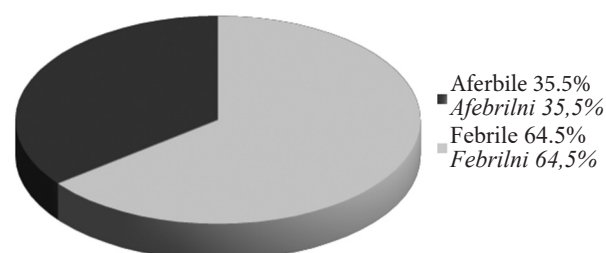
The inclusion criteria for patients in this study were as follows: being previously healthy, aged from 6 months to 6 years, with normal neurological development, and negative history of epilepsy. The exclusion criteria included having a history of men-

ingitis, encephalitis, encephalopathy, cerebral trauma, brain tumor, hypoxia, or any other underlying diseases of the central nervous system. Patients were categorized into two groups: febrile group included children who had a central body temperature higher than 38°C within 24 h of AGE-related seizures; and afebrile group of patients with an average temperature throughout the AGE course. Background, demographic data, clinical and microbiological characteristics, neurophysiological and neuroradiological presentations were compared in the two groups. The data were analyzed using the Statistical Package for Social Science for Windows. The chi-squared (χ^2) was used to compare categorical variables according to the analyzed sample size and the student t-test was used to compare continuous variables between the febrile and afebrile group. The $p < 0.05$ was considered statistically significant.

Results

During the study period from October 2021 to April 2022, 31 children with febrile and afebrile seizures and mild gastroenteritis were admitted to the Pediatric Clinic in Novi Sad. The patients were divided in two groups – 20 febrile patients and 11 afebrile patients (**Graph 1**). The seizures were more frequent in male (58%) than in female (42%) patients. The mean age in febrile patients was 21.5 months, and 16.8 months in afebrile. The youngest patient was 6 months old, and the oldest 68 months old. Diarrhea was the most common symptom: 14 patients (45%) presented only with diarrhea, 11 patients (35.5%) had both diarrhea and vomiting, and 6 patients (29.5%) experienced only vomiting. Sixteen patients were examined for causative enteropathogens. The most commonly identified enteropathogen was rotavirus (43.75%), followed by adenovirus (18.75%) and coxsackievirus B (6.25%). Three patients (18.75%) presented only with severe acute respiratory syndrome coronavirus 2. One patient had bacterial gastroenteritis, with *Salmonella enteritidis* isolated from the stool, and one patient had concomitant infection with rotavirus and *Campylobacter jejuni*.

The comparison of medical history data showed that 4 patients in the febrile group and 3 patients in



Graph 1. Patients with febrile and afebrile seizures associated with mild gastroenteritis

Grafikon 1. Pacijenti sa febrilnim i afebrilnim napadima udruženi sa akutni gastroenteritisom

Table 1. Clinical-demographic characteristics of patients with febrile and afebrile seizures associated with mild acute gastroenteritis**Tabela 1.** Kliničko-demografske karakteristika pacijenata sa febrilnim ili afebrilnim napadima udruženi sa blagim akutnim gastroenteritisom

	Febrile/Febrilni (n/br.=20)	Afebrile/Afebrilni (n/br.=11)	p value/p vrednost
Age in months (mean, standard deviation and range)/Uzrast u mesecima (srednja vrednost standardna devijacija, raspon)	21.5 +/- 12.3 (11 – 68)	16.8 +/- 9.4 (6 – 36)	p > 0.05
Male gender/Muški pol	11	7	p > 0.05
Past history of febrile seizures Pozitivna anamneza o ranijim febrilnim napadima	4 (20%)	3 (27%)	p > 0.05
Family history of febrile seizures or epilepsy/Pozitivna porodična anamneza o febrilnim napadima ili epilepsiji	8 (40%)	4 (36.4%)	p > 0.05
Seizure semiology/Semiologija napada			
Generalized tonic-clonic seizure Generalizovani tonično-klonični napad	20 (100%)	7 (63.6%)	p < 0.05
Generalized atonic seizure Generalizovani atonični napad	/	2 (18.2%)	
Partial seizure/Parcijalni napad	/	2 (18.2%)	
Patients with cluster seizures Pacijenti sa klaster napadima	4 (20%)	6 (54.5%)	p < 0.05
Seizure frequency/Učestalost napada	1.3 +/- 0.6 (range 1-3)	3.63 +/- 3.04 (range 1 - 10)	p < 0.05
Seizure duration > 5 minutes Trajanje napada > 5 minuta	7 (35%)	/	p < 0.01
Interval from the onset of gastrointestinal symptoms/Interval od početka gastrointestinalnih tegoba	1.5 +/- 0.82 (1-4 days)	1.72 +/- 0.9 (1-3 days)	p > 0.05

the afebrile group had a history of previous febrile seizures (**Table 1**). Family history of febrile seizures or epilepsy was positive in 4 patients in the afebrile group and in 8 patients in the febrile group. One patient from the febrile group that presented with convulsions had a positive past history of febrile seizures and a positive family history. As of the seizure semiology, generalized tonic-clonic seizure was the most prevalent in both groups. Two patients presented with partial seizure and two patients had generalized atonic seizure, all of them from the afebrile group. Ten patients had clustered seizures. There were 6 patients in the afebrile group who had two or more seizures, that is from one to ten episodes. Furthermore, there were 4 patients in the febrile group who had multiple seizures ranging from one to three episodes. Seven patients had a seizure that lasted longer than 5 minutes and all of them were from the febrile group. We observed intervals between the onset of acute gastroenteritis symptoms and the first seizure, and most of the patients from both groups presented with a seizure in the first day of sickness (54.8%). Normal neuroimaging findings were reported in all patients. Five patients had abnormal electroencephalographic findings, with temporary abnormalities like slow background activity and sharp wave discharge. Emergency anticonvulsant treat-

ment was administered to children who had prolonged or repeated seizures. Diazepam or midazolam were used as first line treatment. Twelve patients responded well to the initial treatment; however, 5 patients were unresponsive to the repeated doses of benzodiazepines and received phenobarbital. None of the patients was discharged with continuous anticonvulsant therapy.

Discussion

It is well known that seizures are one of the complications of acute gastroenteritis in pediatric patients. Although seizures may be explained by hypoglycemia, electrolyte imbalance and dehydration, patients included in this study had normal laboratory findings. Benign convulsions associated with gastroenteritis are a relatively newly recognized entity described by Mooroka et al. in 1982. Since then, several studies have described it, as well as the similarities between CwG and febrile seizures [1, 2, 4–6, 11, 12]. In our study, clinical and demographic characteristics of febrile and afebrile seizures associated with acute gastroenteritis were analyzed. We found that the afebrile and febrile patients with AGE-related seizures shared similar clinical and laboratory features; however, there were still some distinct characteristics between the two groups.

When it comes to the age at which seizures occur, our data are similar to previously published papers about CwG [2–4, 12, 13]. Studies have shown that their incidence is similar in both sexes, with few reports of female dominance, with a male to female ratio of 1: 1.5 - 1.8 [5, 10]. Our study showed male predominance with 58% of male patients. As described in many studies, the most commonly identified enteropathogen was rotavirus [2, 3, 5, 11]. The finding of seasonal clustering of CwG cases strongly suggests the role of infectious pathogens, specifically rotavirus as the possible cause of benign convulsions. Several researches have been performed to detect the exact virus-dependent mechanism in febrile CwG, but this pathogenesis still remains unclear [10, 12–14]. Most of the patients presented with diarrhea and seizures on the first day of sickness. Reports of other studies show that afebrile patients have longer intervals between the onset of enteric symptom and seizures than febrile patients [2, 4, 5, 7]. Some patients may even experience seizures before enteric symptoms [5, 7, 11]. When it comes to the interval between the onset of gastrointestinal symptoms and seizure onset, our study showed no statistical significance between the two groups, as reported in a study conducted by Kawano et al. [15]. The previously conducted studies showed that there were significant differences between the two groups when it comes to past history of febrile seizures and positive family history of febrile seizures or epilepsy [2, 13, 15]. Our study showed no statistically significant difference. However, comparison of seizure characteristics in the febrile and afebrile group revealed some significant differences. The majority of seizure types associated with CwG are known to be generalized seizures, focal features such as lateral eye deviation or complex partial seizures [4, 6, 9]. Most of our patients from both groups experienced a generalized tonic-clonic seizure, with 4 patients from afebrile group experiencing partial

or generalized atonic seizures, with a significantly higher prevalence. The CwG is characterized by clusters of attacks, and children with CwG are at a higher risk of experiencing another seizure within 24 hours of the first seizure [3, 4, 6].

The duration of each seizure mostly ranged from 30 seconds to less than 5 minutes. Seven patients from febrile group presented with convulsions and two of them experienced seizures lasting around 30 minutes. The convulsions were treated with first line therapy - diazepam and midazolam, with good therapeutic response [16]. We registered statistically significant differences between the two groups, since data obtained from other studies differed, showing no significant difference between the two groups [2, 13]. Although many studies in the past showed good prognosis of CwG, in recent years, with the increase in follow-up studies being conducted, it was found that children with CwG have some risk of seizure recurrence. Furthermore, if the age of seizure onset is ≤ 18 months and if there is a positive family history of epilepsy or febrile seizures, these children should be closely followed up within 6 - 12 months from the first episode [17].

Conclusion

Distinguishing febrile and afebrile gastroenteritis-related seizures as separate entities may be difficult, since fever accompanying acute gastroenteritis in children is not a rare finding. It is still unclear what effect fever has on the onset of gastroenteritis-associated seizures, and whether febrile and afebrile seizures have distinctly different pathophysiology. Further follow up studies are needed to better understand characteristics and prognosis of benign convulsions associated with mild gastroenteritis. Comprehensive knowledge of pediatricians should help to avoid unnecessary diagnostic tests and usage of anticonvulsants.

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