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Evaluation of clinical characteristics between febrile seizures and generalized epilepsy febrile seizure plus

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Abstract

In the present study, we aimed to compare the characteristics of febrile seizure (FS) and generalized epilepsy with febrile seizure plus (GEFS+) in terms of their clinical prognosis and treatment. Among the 95 patients between 5-18 years of age included in this single-center retrospective cross-sectional hospital-based study, 55 and 40 patients were diagnosed with FS and GEFS+, respectively. Clinical characteristics, family history, and treatment responses of both groups were statistically compared. The FS and GEFS+ groups were not significantly different in terms of the median and mean ages for the onset of FS. Prolonged FS was seen as significantly higher in the FS group than in the GEFS+ group (p=0.014). The mean age of afebrile seizure was 3.5 years in the GEFS+ group. The prevalence of febrile/afebrile seizures in the family was significantly higher in the GEFS+ group than in the FS group. Febrile seizure recurrence risk was significantly higher in GEFS + group. The rate of seizure recurrence was low in both groups, particularly in patients receiving anti-epileptic treatment. Levetiracetam was found to be effective in preventing seizures in both groups. It is important to investigate the risk factors for the development of GEFs in patients presenting with FS.

Keywords: A febrile seizure, GEFS plus, epilepsy, genetics

Introduction

Febrile seizures (FS) are seizures that occur due to fevers caused by infections arising outside the central nervous system in neurologically normal children [1]. The age of onset for FS is 6 months to 5 years and its peak incidence rate is seen in children aged 18 months; however, these seizures most commonly occur in children aged 12–30 months with an average prevalence of 4%–14% worldwide [2]. Generalized epilepsy with febrile seizures plus (GEFS+) was first identified in 1997; and in 2017, its diagnostic criteria were revised by Sheffer et al. [3,4]. GEFS+ was conceptualized as a familial epilepsy syndrome characterized by a distinctive pattern of phenotypic heterogeneity. The most common phenotype in GEFS+ families is FS, which is classified as a generalized tonic-clonic (GTC) seizure accompanied by fever in children of ages ranging from 3 months to 6 years [5]. The most common phenotypes are defined as those characterized by the continuation or addition of fever-accompanied seizures after the age of 6 years. If the disease progresses, this clinical spectrum goes as far as to lead to epilepsy with myoclonic-atonic seizures (MAE) and Dravet syndrome [6]. FS is considered to be the hallmark of the GEFS+ syndrome. Such questions as those including "is there a difference between simple FSs and the other is in GEFS+ families?" and "what are the similarities and differences between the clinical characteristics of these families?" have not been clarified fully. In the present study, we aimed to compare the clinical and socio-demographic characteristics of patients diagnosed with simple FS and those meeting the GEFS+ diagnostic criteria as updated by Sheffet et al. in 2017 [3].

Material and Methods

This single-center retrospective study was conducted following the principles of the Declaration of Helsinki. Informed parental consent was obtained for all patients. Ethical approval was

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Collection of Patient Data

To collect patient data for this study, the data of a total of 95 patients, 55 FS and 40 GEFS+, aged 5-18 years, who applied to our health center between 2020-2022, were scanned retrospectively in our hospital's automation system and the data were saved in an Excel file.

Selection of Patients With FS

Patients aged 5-18 years who meet febrile seizure criteria according to International League Against Epilepsy (ILAE) 2005 were included in the study.

Seizure in the presence of fever is defined as having a body temperature of ≥38°C or higher documented before or during the seizure, whereas a seizure accompanied by elevated fever is defined as an increase of 1°C in body temperature before and after the seizure, wherein the body temperature reaches ≥38°C.

Prolonged FS was described as patients who are admitted to the emergency room with an ongoing FS or whose seizures lasted more than 5 minutes following their hospital admission.

Selection of Patients With GEFS Plus

GEFS+ is diagnosed under the GEFS+ diagnostic criteria defined by Scheffer et al. in 1997 and 2017, as well as the 2017 epilepsy syndrome classification of ILAE included in the study [1,3-5]. Patients between the ages of 5–18 years who met these diagnostic criteria were included in the study.

Exclusion Criteria

The present study excluded those with Dravet syndrome, severe myoclonic epilepsy, and epileptic encephalopathies. Patients with a history of preterm birth or neonatal intensive care hospitalization were also excluded from the study. Patients with other syndromic or non-syndromic diseases that cause additional neurological or non-neurological mortality and morbidity were not included in the study.

Demographic Characteristics of The Patents

The patient data were recorded including age, sex, age at the onset of seizures, EEG findings, seizure characteristics, treatment, and family history.

EEG Recordings

Electrodes were placed according to the international 10–20 system of electrode placement. All patients underwent 20-minute sleep and wake EEG monitoring, including hyperventilation with sleep deprivation and photic stimulation.

Clinical Interview

All of the patients underwent face-to-face interviews with a pediatric neurologist using the semi-structured questionnaire designed specifically for this study. The questionnaire included sections regarding background and family history, information about seizure history and medication, as well as EEG records. The patient ages at the onset of FSs, at the onset of afebrile seizures, and the total number of seizures were obtained from the hospital records and using a face-to-face interview with the parents of the patients. All of the obtained data were recorded for statistical analysis.

Statistical Analysis:

NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum, and maximum) were used while evaluating the study data. To test the quantitative data for conformity to the normal distribution, the Shapiro–Wilk test and histograms were used. Mann–Whitney U test was used to compare the two groups in terms of their non-normally distributed quantitative variables. To compare the qualitative data, Pearson's chi-square test and the Fisher–Freeman–Halton Exact Test were used. Statistical significance was accepted as $p<0.05$.

Results

The research was conducted with a total of 95 patients who were admitted to the pediatric neurology and pediatric clinics of the tertiary central hospital between 2020 and 2022. The age range of the participants herein was from 5 to 18 years and the mean age of the study population here was 6.14±2.07. Furthermore, 57.9% of the cases (n=55) had FS, whereas 42.1% (n=40) had GEFS+. Demographic features of GEFS+ groups were shown in Table 1.

Table 1. Seizure-Related Findings of the GEFS+ Group

Age (month) at the time of first febrile seizure (n=33)	**Mean±SD**	16.76±12.31
	Median (Min-Max)	16(5–72)
Age (year) at the time of first afebrile seizure (n=20)	**Mean±SD**	3.65±3.05
	Median (Min-Max)	2(0.7–10)
Afebrile seizure (n=40)	**No**	7(17.5)
	Yes	33(82,5)
Afebrile seizure type (n=33)	**Focal**	11(33.3)
	GTC	6(18.2)
	Myoclonic	1(3.0)
	Absence	8(24.2)
	Unclassified	7(21.2)
Total number of febrile seizures (n=31)	**Mean ± SD**	3.77±2.50
	Median (Min-Max)	2(1-15)
Total number of afebrile seizures (n=29)	**Mean ± SD**	2.52±2.68
	Median (Min-Max)	1(1–12)
Age (year) at the time of last febrile seizure (n=32)	**Mean±SD**	4.20±3.36
	Median (Min-Max)	3(0.7–16)
Age (year) at the time of last afebrile seizure (n=29)	**Mean±SD**	5.94±4.58
	Median (Min-Max)	5(0.8–17)

Table 2. EEG characteristics of GEFS+

EEG finding	**Normal**	16(38.6)
	Left frontotemporal	2(2.0)
	Left Frontocentral	2(2.0)
	Generalized	13(12.9)
	Bil. Parieto-occipital	1(1.0)
	Right centroparietal	1(1.0)
	Right temporal	1(1.0)
	Right frontocentral	1(1.0)
	Bil. Central temporal	1(1.0)
	Bil frontal cental	1(1.0)
	Left parietooccipital	1(1.0)

Table 2 shows the distribution of EEG findings in the GEFS+ group.

Table 3. Evaluation of the Demographic Characteristics by Group

		GROUP		P
		FS	GEFS+	
Age	**Mean±SD**	5.36±0.72	6.86±3.08	*[a]0.083*
	Median (Min-Max)	5(5-8)	6(5-17)	
Fever status	**Seizure in the presence of fever**	41(74.5)	31(77.53)	*[b]0.740*
	Seizure in response to elevation of fever	14(25.5)	9(22.5)	
EEG	**No**	33(60.0)	0(0.0)	*[b]0.001***
	Yes	22(40.0)	40(100)	
EEG normality	**Normal**	20(90.9)	18(45.0)	*[b]0.001**
	Abnormal	2(9.1)	22(55.0)	

[a] Mann–Whitney U Test [b] Pearson Chi-Square Test *p<0.05 **p<0.01

A comparison of demographic characteristics according to GEFS+ and FS groups is shown in Table 3.

Table 4. Evaluation of Seizure-Related Findings by Group

		GROUP		P
		FS	GEFS+	
Prolonged febrile seizure	**No**	44(80.0)	38(95.0)	*[b]0.036**
	Yes	11(20.0)	2(5.0)	
Age in the month at the time of first febrile seizure	**Mean±SD**	18.74±10.00	16.76±12.31	*[a]0.165*
	Median (Min-Max)	18(4-52.8)	16(5-72)	
Total number of febrile seizures	**Mean±SD**	2.75±2.91	3.77±2.50	*[a]0.005***
	Median (Min-Max)	2(1-15)	3(1-10)	
Presence of FS in the family	**No**	23(41.8)	9(22.5)	*[b]0.049**
	Yes	32(58.2)	31(77.5)	
Presence of afebrile seizures in the family	**No**	46(63.9)	12(30)	*[b]0.001***
	Yes	9(16.4)	28(70.0)	
Kinship	**No**	45(81.8)	36(86.8)	*[b]0.517*
	Yes	10(18.2)	4(13.2)	
Age in the year at the time of last febrile seizure	**Mean ± SD**	2.49±1.29	4.20±3.36	*[a]0.007***
	Median (Min-Max)	2(0.6-6)	3(0.7-16)	
Treatment	**No**	36(65.5)	4(10.0)	*[b]0.001***
	Yes	19(34.5)	36(90.0)	
Post-medication seizures	**No**	25(96.2)	32(84.2)	*[c]0.225*
	Yes	1(5.2)	6(15.8)	

[a] Mann-Whitney U Test [b] Pearson Chi-Square Test [c] Fisher's Exact Test *p<0.05 **p<0.01

The incidence of febrile status in the FS group cases was found to be statistically significantly higher than those in the GEFS group (p=0.033; p<0.05).

There was no statistically significant difference between the first febrile seizure months of the cases according the groups (p>0.05).

The total number of febrile seizures in the GEFS group cases was found to be statistically significantly higher than those in the FS group (p=0.005; p<0.1).

Familial incidence of FS in the GEFS group cases was found to be statistically significantly higher than those in the FS group (p=0.049; p<0.05).

The incidence of familial afebrile seizures in the GEFS group cases was found to be statistically significantly higher than those in the FS group (p=0.001; p<0.01) (Table 4).

Table 5. Evaluation of Treatments by Group

		GROUP		P
		FS	GEFS+	
Treatment	**Levetiracetam**	7(36.8)	14(38.9)	*[d]0.980*
	Valproic acid	9(47.4)	14(38.9)	
	Carbamazepine	1(5.3)	2(5.6)	
	Mysoline	0(0)	1(2.8)	
	Phenobarbital	2(10.5)	2(5.6)	
	Carbamazepine>Valproic acid	0(0)	1(2.8)	
	Phenobarbital>Levetiracetam	0(0)	1(2.8)	
	Levetiracetam>Valproic acid	0(0)	1(2.8)	

d Fisher–Freeman–Halton Test

Notably, 64.2% of the cases (n=61) were administered treatment. According to the available study data, the patients started receiving treatment between their 1st and 15th seizures, and the mean number of seizures until the start of the treatment was 3.03±2.49. There was no statistically significant difference between the treatments applied to the cases according to the groups (p>0.05). The rate of seizure recurrence was low in both groups, particularly in patients receiving anti-epileptic treatment. Levetiracetam was found to be effective in preventing seizures in both groups. (table 4-5).

Discussion

To the best of our knowledge, although studies have reported the risks of unprovoked seizures after FSs, only a handful of studies have compared GEFS+ and FSs. The onset of FSs coincided with 6 months to 5 years of age, while the peak age was reported to be 12–18 months of age [7]. In our study, the age of the first FS in the FC group was 18.54±9.80 months, which was consistent with the literature. In the GEFS+ group, the age of the first FS was 16.76±12.31 months. In the literature, the age of the first FS for GEFS+ is reported to be 14 months and is consistent with our data herein [3]. The age of first FS in Dravet and Dravet-like syndromes were reported to be <12 months [8-9]. In our study, patients clinically diagnosed with Dravet syndrome were excluded from the study. There was no significant difference between the FS and GEFS+ groups in terms of the age of the first FS. However, in the GEFS+ group, the age of the last FS was significantly higher than that of the FS group.

The total number of febrile seizures in the GEFS group cases was found to be statistically significantly higher than those in the FS group (p=0.005; p<0.1). Therefore, frequent FS has been revealed as a risk factor for GEFS. However, according to Ogino et al 2020, the number of febrile seizures in FK plus patients was not different from the FS group [10]. The risks of converting to afebrile seizures from FSs were investigated and reported to include the presence of growth retardation, familial history of epilepsy, and ongoing FSs at later ages [11]. Prolonged FSs and the onset of FSs before the age of 12 months are more characteristic of Dravet syndrome and Dravet-like syndromes [12]. When patients with Dravet syndrome were removed from the GEFS+ group, the FS group was found to have a significantly higher rate of prolonged FSs than the GEFS+ group. This situation shows that the presence of prolonged FSs

in patients who do not have the Dravet phenotype does not pose a risk factor for GEFS+ to develop. Are simple FSs a reaction to the elevation in fever rather than the fever itself? As reported in the studies, having seizures at lower levels of fever is a risk factor for subsequently developing unprovoked seizures [13]. Slightly differently, we compared the two states, i.e., elevation in fever and presence of fever in the FS and GEFS+ groups. Having seizures upon elevation in fever was higher in the FS group than in the GEFS+ group, but there was no statistical intergroup difference in this regard.

In our study, there was a statistically significant intergroup difference in terms of familial history of FSs. And also the GEFS+ group had a higher rate of patients with familial history of afebrile seizures. As already shown by other studies, having a familial history of afebrile seizures is a risk factor for the development of unprovoked seizures, as well as a risk factor for GEFS+ [14,15]. In our study, although 37% of patients underwent EEG in the FS group, all of the patients in the GEFS+ group underwent EEG. Furthermore, 8% of the patients in the FS group had an abnormality on EEG; however, the rate of patients found to have EEG abnormality was 60% in the GEFS+ group and was significantly higher than in the FS group. EEG is not recommended in cases of simple FSs [16,17]. In our study, we support this finding as well, with only one particular regarding the patients with familial history of afebrile/febrile seizures. We recommend close follow-up for these patients against any risk of GEFS+ development.

In the GEFS+ group, the age of first afebrile seizures was 3.65±3.05 years. This rate was reported to be 5 years by Scheffer et al. in 2017 and 3.2±3.1 years by Kim et al. in 2019 [3,8]. In our study, the most common type of afebrile seizure in the GEFS+ group was focal/focal secondarily generic seizure. In 2017, Sheffer et al. reported this seizure type as the second most common type of seizure after GTC [3,5,8]. Further studies are still needed to recognize GEFS spectrum phenotypes.

In addition, 34% of the patients in the FS group received preventive anti-epileptic treatment, whereas 90% of the GEFS+ patients received the treatment. Therefore, there is a significant difference between the two groups in this regard, with the rate being significantly higher in the latter group. Preventive anti-epileptic treatment is not recommended for FS in the existing publications [18]. However, to evaluate both groups for their rates of seizure recurrence after the treatment was started, they were found to have no significant difference in terms of seizure recurrence although 6% of the patients in the FS group and 3% of the patients in the GEFS+ group used anti-epileptics. The most common preventive anti-epileptic treatments were levetiracetam and valproic acid. In a study conducted by Kılıç et al. in 2019, intermittent use of rectal diazepam, valproic acid, and levetiracetam was the most commonly used prophylactic anti-epileptic drug in a group of 150 patients followed up for FS, and there was no significant difference between the group of patients using levetiracetam and the groups of patients using other drugs in terms of recurrence [19,20]. Likewise, levetiracetam has been to be effective in preventing the recurrence of focal epilepsy seizures [21]. In our study, levetiracetam was as successful in seizure prevention as other anti-epileptics in both the FS group and the GEFS+ group.

The present study has some limitations. These limitations include the study design being a single-centered study and the short follow-up period for the patients.

Conclusion

The FS and GEFS+ groups did not have any significant difference in terms of the median and mean ages for the onset of FSs. The number of FSs was found slightly higher in GEFS+. The number of prolonged FSs was significantly higher in the FS group compared to the GEFS+ group. The age when the last FS occurred was significantly higher in the GEFS+ group than in the FS group. The mean age of afebrile seizure incidence was reported to be 3.5 years in the GEFS+ group. The familial history of febrile/afebrile seizures was significantly higher in the GEFS+ group. There was no significant difference between the two groups in terms of seizure recurrence risk, and the rate of seizure recurrence was low in both of the groups in the group of patients receiving anti-epileptic treatment. Levetiracetam was found to be effective in preventing seizures in both groups.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical approval
Ethical approval was obtained from the Ethics Committee of Kartal Dr. Lutfi Kirdar City Hospital with the approval number 2021/514/212/5.

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