Evaluation of the risk factors for recurrence and the development of epilepsy in patients with febrile seizure

Avaliação de fatores de risco para recorrência e desenvolvimento de epilepsia em pacientes com convulsões febris

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Abstract

Background Although febrile seizure (FS) is generally considered benign and self-limiting, there are differences regarding the risk factors, the prognosis, and the development of epilepsy.

Objective To examine the clinical and sociodemographic characteristics of patients diagnosed with FS, and to determine the risks of recurrence and the development of epilepsy.

Methods Between 2015 and 2019, we performed a retrospective evaluation of 300 patients with FS followed for at least 24 months.

Results The first episode of FS was simple in 72.7% of the patients and complex in 27.3%, and it recurred in 40%. Age under 12 months in the first FS, complex FS, and neurodevelopmental delay were found to statistically increase the risk of recurrence ($p < 0.05$). A total of 7% of the patients developed epilepsy, and this rate was found to be higher in patients with neurodevelopmental delay and long-term use of antiepileptic drugs ($p < 0.001$). The development of epilepsy was also observed in 77.8% of the patients with abnormal electroencephalogram (EEG). Epilepsy developed more frequently in those with abnormal EEG ($p<0.001$).

Conclusions Neurodevelopmental delay was an important risk factor for FS recurrence and the development of epilepsy. Abnormality in the EEG is an important risk factor for the development of epilepsy. We found that the long-term prophylactic treatment did not cause decreases in the recurrence of FS nor in the development of epilepsy.

Keywords
- Fever
- Epilepsy
- Seizures, Febrile
- Recurrence

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Resumo

Antecedentes Embora a convulsão febril (CF) seja geralmente considerada benigna e autolimitada, existem diferenças nos fatores de risco, prognóstico e desenvolvimento de epilepsia.

Objetivo O objetivo foi examinar as características clínicas e sociodemográficas de pacientes diagnosticados com CF e determinar os riscos de recorrência e desenvolvimento de epilepsia.

Métodos Trezentos pacientes com CF, acompanhados por pelo menos 24 meses, foram avaliados retrospectivamente entre 2015 e 2020.

Resultados A primeira CF foi simples em 72,7% dos pacientes e complexa em 27,3%. CS foi recorrente em 40% dos pacientes. Encontrou-se que a idade da primeira CF inferior a 12 meses, CF complexa e atraso no neurodesenvolvimento aumentaram estatisticamente o risco de recorrência ($p < 0,05$). Epilepsia se desenvolveu em 7% dos pacientes. A epilepsia foi maior em pacientes com atraso no desenvolvimento neurológico e uso prolongado de drogas antiepilépticas ($p < 0,001$). A epilepsia se desenvolveu em 77,8% dos pacientes com eletroencefalograma (EEG) anormal. Uma diferença estatisticamente significativa foi determinada em pacientes com EEG anormal em risco de epilepsia ($p < 0,001$).

Conclusões O atraso no neurodesenvolvimento foi um importante fator de risco para recorrência de CF e epilepsia. A anormalidade do EEG é um importante fator de risco para o desenvolvimento de epilepsia. O tratamento de profilaxia a longo prazo não diminuiu a recorrência de CS e o desenvolvimento de epilepsia.

Palavras-chave

- Febre
- Epilepsia
- Convulsões Febris
- Recorrência

INTRODUCTION

Febrile seizure (FS) is the most common type of seizure in children, and its incidence is higher in developing countries.[1] An important and common cause of admission in pediatric outpatient clinics and emergency services, FS causes severe anxiety in parents, and it has been defined as "a seizure accompanied by fever (temperature $\geq$ 100.4°F or $\geq$ 38.0°C by any method), without central nervous system infection, that occurs in infants and children 6 through 60 months of age".[2] The most common type is simple FS (SFS), which is defined as generalized seizures lasting less than 15 minutes and not recurring during a 24-hour period without a previous neurologic problem. Episodes of FS that are focal, prolonged, or multiple within the first 24 hours are defined as complex FS (CFS).[3] Although FS is generally considered benign and self-limiting, there are differences regarding the risk factors, the prognosis, and the development of epilepsy.

In the present retrospective study, we aimed to examine the clinical and sociodemographic characteristics of patients who diagnosed with FS and to determine the risks of recurrence and the development of epilepsy.

METHODS

In total, 300 patients with FS who had been followed-up for at least 24 months were evaluated retrospectively between 2015 and 2019 in the pediatric clinic of a tertiary hospital. In the present study, the patients who had two or more unprovoked seizures after an episode of FS and those with a single unprovoked seizure with epileptic discharges on the electroencephalogram (EEG) were evaluated for epilepsy.[4] An EEG was requested for patients with more than two episodes of FS, with CFS, or one FS but with neurodevelopmental delay.

The parents were interviewed by a research assistant for updates and to collect missing information. We collected data regarding: age, sex, type of delivery, week of birth and birth weight, prenatal and perinatal history, consanguinity between the parents, history of FS and epilepsy among first- and second-degree relatives, neuromotor development, age at the first FS, cause of fever, the interval between fever onset and seizure, type of seizure, duration of seizure and body temperature, FS recurrence, development of epilepsy, and EEG and neuroimaging findings. Patients whose fine motor and gross motor skills lagged behind those of their peers were considered to have neurodevelopmental delay. Patients with speech retardation alone were not considered to have neurodevelopmental delay.

For the statistical analysis, we used the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, IBM Corp., Armonk, NY, US) software, version 21.0, and values of $p < 0.05$ were considered statistically significant. The compatibility of the variables regarding the normal distribution was examined using the Shapiro-Wilk test. The categorical variables were expressed as numbers and percentages. The Mann-Whitney U test was used in the comparisons between two groups according to the results of the normality test. The Pearson Chi-squared, the Fisher exact Chi-squared and the Fisher-Freeman-Halton tests were used for the intergroup

comparisons of the categorical variables. Logistic regression analysis was performed to determine the risk factors affecting the presence of epilepsy during the follow-up of patients with recurrent FS.

RESULTS

A total of 300 patients were included in the present study. Of these, 55,7% were male, while 44.3% were female (male/female ratio 1,26:1). The mean age at the first FS was of 21.59 months (21.39 ± 12.12 months). The first episode of FS occurred between the ages of 6 and 11 months in 56 patients (18.7%), and between 12 and 17 months in 78 patients (28%). Prematurity was reported in 51 patients (17%) and consanguinity of the parents, in 59 (19.7%). Family history of FS and epilepsy were noted in 180 (60%) and 68 (22.7%) patients respectively. The most common cause of fever in the first episode of FS was upper respiratory tract infection (URTI; 263; 87.7%). Fever $\geq$ 39°C was observed in 155 (51.7%) patients. In 166 (55.3%) patients, FS was observed 1 hour after the onset of fever. The sociodemographic and clinical characteristics of the patients are presented in ►**Table 1**. The first FS was simple in 72.7% of the patients (218) and complex in 27.3% (82). There was no statistically significant relationship regarding the type of FS and sex, week of birth, birth weight, delivery type, and consanguinity between the parents ($p > 0.05$).

An EEG was performed in 204 (68%) patients, and 18 (8.8%) were abnormal, in 5 (3.6%) of the patients who had SFS, and in 13 (20%) of those with CFS. The rate of abnormal EEGs was higher among CFS patients ($p < 0.001$). While the EEGs of all the patients who had a single seizure were normal, an abnormality was found in 12.1% of the patients who had more than one seizure. This difference was statistically significant ($p = 0.004$). The EEG could not be performed in 3 of 15 patients with neurodevelopmental delay, and it was was abnormal in 6 (50%) out of the remaining 12 patients in this group. There was a statistically significant difference in the risk of anormal EEG between neurodevelopmental delay ($p < 0.001$). Neuroimaging was performed in 56 patients (18.7%). Abnormal findings (leukomalacia, cortical atrophy, image signal changes, arachnoid cysts, pineal gland cysts) were detected in 13 (23.2%) patients. Neuroimaging could not be performed in 8 of the 15 patients with neurodevelopmental delay, and the findings were abnormal in the 7 (87.5%) patients in whom it could be perfomed. Abnormal neuroimaging was statistically significant in patients with neurodevelopmental delay ($p < 0.001$).

Seizures recurred in 180 (60%) of the patients. Of these, 82 (27.3%) had 2 seizures, 43 (14.3%) had 3 seizures, and 55 (18.3%) had 4 or more episodes of FS. The recurrence rate was low in patients whose first seizure was an SFS ($p < 0.001$). We found that the incidence of three or more attacks was higher in CFS patients ($p < 0.001$). No statistically significant correlation was found regarding sex, week of birth, birth weight and mode of delivery, consanguinity between the parents, family history of FS, and FS recurrence. We were able to determine that history of epilepsy in first- and second-degree relatives statistically increased the odds of FS recurrence ($p = 0.028$). ►**Table 2** shows the risk factors for recurrence and epilepsy. According to the logistic regression analysis, patients with FS within the first hour after the onset of fever had a 6.7-fold greater risk of recurrence, and those with seizures lasting $\geq$ 15 minutes had a 2.5-fold greater risk of recurrence.

In total, 21 (7%) patients developed epilepsy. The median age at the development of epilepsy was of 42 months (42.57 ± 23.45 months). There was no significant relationship regarding sex, birth weight, week of birth, delivery type, consanguinity between the parents, family history of FS or epilepsy, and epilepsy ($p > 0.05$). A total of 18 (12.4%) out of 145 patients with a fever of $<$ 39°C during the seizure developed epilepsy, as well as 3 (1.9%) out of 155 patients with a fever of $\geq$ 39°C. The rate of epilepsy was higher in the group with fever of $<$ 39°C than in the group with fever of $\geq$ 39°C ($p < 0.001$). Epilepsy developed in 19 (14.2%) out of 134 patients who had seizures within the first hour after of the onset of fever, and in 2 (1.2%) of 166 patients who had seizures after 1 hour of the onset of fever. The rate of epilepsy was found to be statistically higher in patients who had FS within the first hour after the onset of fever ($p < 0.001$). The development of epilepsy was observed in 9 (16.1%) out of 56 patients whose age at the first FS was $<$ 12 months, and in 12 (4.9%) out of 244 patients whose age at the first FS was $\geq$ 12 months. The risk of developing epilepsy was found to be higher among those who aged $<$ 12 months at the first FS ($p = 0.007$). We observed the development of epilepsy in 5 (2.3%) out of 218 patients who had SFS, and in 16 (19.5%) out of 82 patients who had CFS. The risk of developing epilepsy in the follow-up was found to be higher in patients with CFS ($p < 0.001$). There was no significant relationship between focal or generalized seizure and the development of epilepsy. Among 21 patients who developed epilepsy, the type of seizure was tonic-clonic (7 cases), clonic (6 cases), tonic (4 cases), and atonic (4 cases). In those who had clonic seizures, the rate of epilepsy in the follow-up was higher than in those with other types of seizure ($p < 0.001$).

Epilepsy was observed in 11 (4.2%) out of 263 patients with a seizure duration of $<$ 15 minutes, and in 10 (27%) out of 37 patients whose seizure lasted longer than 15 minutes. Patients with a seizure duration of $\geq$ 15 minutes had a higher rate of epilepsy ($p < 0.001$). The development of epilepsy was observed in 9 (60%) out of 15 patients with neurodevelopmental delay. The rate of epilepsy was found to be higher in patients with neurodevelopmental delay ($p < 0.001$). In total, 66 (22%) of the patients were using long-term antiepileptic drugs (AEDs). Overall, 20 of these patients (30.3%) developed epilepsy during the follow-up. When patients who used long-term prophylaxis were compared with those who did not use AEDs, the rate of development of epilepsy was found to be higher in the group using long-term AEDs ($p < 0.001$). A total of 4 patients (1.33%) were undergoing intermittent prophylaxis treatment, but no significant relationship was found regarding this fact and epilepsy. In 14 (77.8%) out of 18 patients with abnormal EEG, the development of epilepsy was observed. Patients with abnormal EEG had a statistically

Table 1 The sociodemographic and clinical characteristics of the study sample

Characteristics		n	(%)
Sex	**Female**	**133**	**44.3**
	Male	**167**	**55.7**
Birth week	< week 37	51	17
	Weeks 37–42	244	81.3
	> week 42	5	1.7
Birth weight	< 2,500 g	34	11.3
	≥ 2,500 g	266	88.7
Mode of delivery	Cesarean section	143	47.7
	Vaginal delivery	157	52.3
Consanguinity between the parents	Yes	59	19.7
	No	241	80.3
Febrile seizure in first- and second-degree relatives	Yes	180	60
	No	120	40
Epilepsy in first- and second-degree relatives	Yes	68	22.7
	No	232	77.3
Age at first febrile seizure	6–11 months	56	18.7
	12–17 months	78	28
	18–23 months	55	18.3
	≥ 24 months	111	37
Cause of fever	URTI	263	87.7
	Viral rash diseases	16	5.3
	AGE	9	3
	LRTI	6	2
	AOM	5	10.70
	UTI	1	0.3
Body temperature before the febrile seizure	< 39°C	145	48.3
	≥ 39°C	155	51.7
Duration of the fever before the febrile seizure	< 1 hour	134	44.7
	≥ 1 hour	166	55.3
Type of febrile seizure	SFS	218	72.7
	CFS	82	27.3
Number of episodes of febrile seizure	1	120	40
	2	82	27,3
	3	43	14.3
	≥4	55	18.3
Characteristic of the seizure	Focal	8	2.7
	Generalized	292	97.3
Type of seizure	Tonic	137	45.7
	Tonic-clonic	110	36.7
	Atonic	46	15.3
	Clonic	7	2.3
Duration of the seizure	< 15 minutes	263	87.7
	≥ 15 minutes	37	12.3
Electroencephalogram findings ($n = 204$)	Normal	186	91.2
	Abnormal	18	8.8
Neuroimaging findings ($n = 56$)	Normal	43	76.8
	Abnormal	13	23.2

Abbreviations: AGE, acute gastroenteritis; AOM, acute otitis media; CFS, complex febrile seizure; LRTI, lower respiratory tract infection; SFS, simple febrile seizure; URTI, upper respiratory tract infection; UTI, urinary tract infection.

higher risk of developing epilepsy than those with normal EEG ($p < 0.001$). There was no statistically significant difference regarding the risk of developing epilepsy between patients with normal and those with abnormal neuroimaging ($p > 0.05$). The rate of epilepsy in the follow-up was found to be higher among patients who had ≥ 3 episodes of FS than among those who had 1 or 2 seizures ($p < 0.001$ and $p < 0.001$, respectively). The risk factors for epilepsy are shown in ►**Table 2**. According to the logistic regression analysis, the risk of developing epilepsy was 17,2 times higher in subjects whose age at the first FS was < 12 months, and the risk was determined to be 73,9 times higher in subjects with pathological EEG after FS and 9.4 times higher in those with seizure duration of ≥ 15 minutes.

DISCUSSION

Febrile seizure has been defined as a convulsion that occurs during a febrile disease in children aged between 6 and 60 months without the presence of electrolyte imbalance, metabolic disorder, intoxication, trauma, history of a previous afebrile seizure, or an infection involving the central nervous system.[2,5] Occurrences before 6 months and after 6 years of age are rare, and the peak of occurrence of FS is at the age of 18 months.[1,4] It is more common in boys than in girls;[6] the exact cause is not known, and it has been stated[7] that it can be explained by the fact that males are more susceptible to infection. In the present study, the mean age at the first FS was of 21.39 ± 12.12 months and the male/female ratio was of 1.26. It is known that history of FS in first-degree relatives plays an important role in the development of the first FS. In the study conducted by Offringa and Moyer,[8] family history of FS was found in 24% of the patients. Canpolat et al.[9] reported that the most important risk factors for first FS were family history of FS (57.1%) and epilepsy (5.9%), neurodevelopmental delay (5.3%), and attending kindergarten (3.9%). Prematurity was also reported[10] among the risk factors. Studies[11] have reported that the prevalence of epilepsy in families ranges from 1.6% to 9%. In the present study, 17% of the patients had a history of

Table 2 Risk factors for recurrence and the development of epilepsy in febrile seizure

		Recurrence of febrile seizure			Development of epilepsy		
		Yes n (%)	No n (%)	*p*value	Yes n (%)	No n (%)	*p*value
Sex	Male	68 (40.7)	99 (59.3)	0.776	13 (7.8)	154 (92.2)	0.551
	Female	52 (39.1)	81 (60.9)		8 (6)	125 (94)	
Birth week	< week 37	22 (43.1)	29 (56.9)	0.542	6 (11.8)	45 (88.2)	0.097
	Weeks 37–42	95 (38.9)	149 (61.1)		14 (5.7)	230 (94.3)	
	> week 42	3 (60)	2 (40)		1 (20)	4 (80)	
Birth weight	< 2,500 g	14 (41.2)	20 (58.8)	0.882	3 (8.8)	31 (91.2)	0.718
	≥ 2,500 g	106 (39.8)	160 (60.2)		18 (6.8)	248 (93.2)	
Mode of delivery	Cesarean	58 (40.6)	85 (59.4)	0.850	11 (7.7)	132 (92.3)	0.654
	Normal vaginal delivery	62 (39.5)	95 (60.5)		10 (6.4)	147 (93.6)	
Consanguinity between the parents	Yes	23 (39)	36 (61)	0.859	6 (10.2)	53 (89.8)	0.267
	No	97 (40.2)	144 (59.8)		15 (6.2)	226 (93.8)	
Family history of febrile seizure	Yes	80 (44.4)	100 (55.6)	0.054	14 (7.8)	166 (92.2)	0.518
	No	40 (33.3)	80 (66.7)		7 (5.8)	114 (94.2)	
Family history of epilepsy	Yes; no	35 (51.5); 85 (36.6)	33 (48.5); 147 (63.4)	0.028	4 (5.9); 17 (7.3)	64 (94.1); 215 (92.7)	0.793
Body temperature before the febrile seizure	< 39°C	67 (46.2)	78 (53.8)	0.034	18 (12.4)	127 (87.6)	< 0.001
	≥ 39°C	53 (34.2)	102 (65.8)		3 (1.9)	152 (98.1)	
Interval between fever onset and seizure	< 1 hour	88 (65.7)	46 (34.3)	< 0.001	19 (14.2)	115 (85.8)	< 0.001
	≥ 1 hour	32 (19.3)	134 (80.7)		2 (1.2)	164 (98.8)	
Age at first febrile seizure	< 12 months	35 (62.5)	21 (37.5)	< 0.001	9 (16.1)	47 (83.9)	0.007
	≥ 12 months	85 (34.8)	159 (65.2)		12 (4.9)	232 (95.1)	
Type of febrile seizure	Simple	69 (31.7)	149 (68,3)	< 0.001	5 (2.3)	213 (97.7)	< 0.001
	Complex	51 (62.2)	31 (37.8)		16 (19.5)	66 (80.5)	
Characteristic of seizure	Focal	4 (50)	4 (50)	0.718	2 (25)	6 (75)	0.101
	Generalized	116 (39.7)	176 (60.3)		19 (6.5)	273 (93.5)	
type of seizure	Tonic	51 (37.2)	86 (62.8)	0.048	4 (2.9)	133 (97.1)	< 0.001
	Clonic	6 (85.7)	1 (14.3)		6 (85.7)	1 (14.3)	
	Tonic-clonic	41 (37.3)	69 (62.7)		7 (6.4)	103 (93.6)	
	Atonic	22 (47.8)	24 (52.2)		4 (8.7)	42 (91.3)	
Duration of the seizure	< 15 minutes	95 (36.1)	168 (63.9)	< 0.001	11 (4.2)	252 (95.8)	< 0.001
	≥ 15 minutes	25 (67.6)	12 (32.4)		10 (27)	27 (73)	
Neurodevelopmental delay	Yes	14 (93.3)	1 (6.7)	< 0.001	9 (60)	6 (40)	< 0.001
	No	106 (37.2)	179 (62.8)		12 (4.2)	273 (95.8)	
Prophylactic treatment with long-term antiepileptic drugs	Yes	52 (78.8)	14 (21.2)	< 0.001	20 (30.3)	46 (69.7)	< 0.001
	No	68 (29.1)	166 (70.9)		1 (0.4)	233 (99.6)	
Electroencepahlogram findings	Normal	83 (44.6)	103 (55.4)	< 0.001	6 (3.2)	180 (96.8)	< 0.001
	Abnormal	16 (88.9)	2 (11.1)		14 (77.8)	4 (22.2)	

preterm birth, 19.8% had consanguinity between parents, 5% had neurodevelopmental delay, 60% had a history of FS, and 22.7%, a history of epilepsy.

The most common cause of fever in FS is URTI,[12] which was also the most common cause of infection (87.7%) in the present study . Unlike the literature, acute gastroenteritis (AGE) was the second most common fever etiology in the present study. Other causes of infection were lower respiratory tract infection (3%), viral rash disease (2%), acute otitis media (1.7%), and urinary tract infection (0.3%). The

frequency of FS is low in cases of AGE. Some studies[13] have reported that gastroenteritis is protective against FS. The most important risk factors in FS are the age of the patient and fever. Seizures are usually observed within one to two hours after the fever increases.[14,15] Okumura et al.[15] found that 21% of their sample had FS within the first hour, 57%, between 1–24 hours after the onset of fever, and 22%, within 24 hours after the onset of fever. In the present study, seizure was observed while the fever was $< 39°C$ and 1 hour after the onset of fever in about half of the patients.

Most of the FSs are short-term, generalized seizures, and partial seizures are rarely observed. Approximately 80% of the seizures are of the generalized tonic-clonic type.[16] In the present study, 97.3% of the seizures were generalized, and the most common type was tonic (45.7%), rates similar to those of the study by Canpolat et al.[9] Approximately three-quarters had SFS. There was no statistically significant relationship between the type of FS, sex, consanguinity between the parents, family history of FS or epilepsy, and the birth characteristics (gestational week, delivery type, birth weight) ($p > 0.05$). The presentation of FS as a single seizure occurs at a rate of $\sim$ 60% to 70%. Only 10% of the patients have three or more seizures.[16] In different studies,[13,17] the rate of FS recurrence was reported to range from 27% to 55.3%. Recurrence of FS is most frequently observed in the first two years of life, including the first six months after the first seizure.[18] Younger age at the first seizure, fever of short duration before the onset of the first FS, lower temperature at onset, family history of FS, and CFS are risk factors for FS recurrence.[19] Some studies have reported that the occurrence of the first seizure before 12 months, and, other studies, before 18 months, is a risk factor for FS recurrence.[9] The risk of recurrence increases as the duration between fever and seizure shortens. The risk of recurrence has been reported to be of 46% in patients with seizures within 1 hour of the onset of fever, of 25% in patients with seizures between 1 and 24 hours, and of 15% in those with seizure more than 24 hours after the onset of fever.[13] Recurrence has been reported[20] in 39.2% of patients whose first FS occurred before the age of 12 months, and in 48.4% in those who had their first FS before the age of 18 months. In the present study, the mean follow-up of the patients after the first FS was of 29.74 ± 3.52 months. Recurrence was observed in 40% of the sample, and in 62.5% of the patients whose age at the first seizure was < 12 months. We found that the first seizure before the age of 12 months and the time between the onset of fever and FS shorter than 1 hour increased the risk of recurrence ($p < 0.001$ and $p < 0.001$ respectively). Fever of $< 39°C$ during FS increased the risk of recurrence ($p = 0.034$). Studies[7,20] have found that FS recurred in approximately half of the patients with a history of FS in first-degree relatives. The results regarding the family history of epilepsy and the risk of FS recurrence are conflicting.[21] In the present study, we found that consanguinity between the parents and history of FS in first- and second-degree relatives were not related to FS recurrence. History of epilepsy, CFS, seizures occurring within the first hour after the elevation of the fever, seizures lasting for ≥ 15 minutes, neurodevelopmental delay, and anormal EEG were found to increase the risk of FS recurrence ($p = 0.028$, $p < 0.001$, $p < 0.001$ and $p < 0.001$ respectively). According to the multivariate logistic regression model, having seizures within the first hour after the onset of fever increased the risk of seizure recurrence by 6.65, and a seizure lasting ≥ 15 minutes increased the risk of recurrence by 2.47. In addition, abnormalities on the EEG and neuroimaging were found to be higher in patients with neurodevelopmental delay ($p < 0.001$, $p < 0.001$ respectively)

It has been reported[22] that $\sim$ 10% to 15% of epileptic children have previously had FS. The rate development of epilepsy after FS varies between 2% and 7%. The risk is considered to be low in children with a single SFS.[9,23] Epilepsy development after FS has been reported at rates of 1% to 4% after SFS and of 4% to 15% after CFS.[5,22] The most important risk factors for epilepsy are the duration of high fever before FS, neurodevelopmental delay, and CFS.[24–26] History of premature birth, early age at the first seizure (< 1 year), fever at the time of the seizure of $< 39°C$, prolonged seizures, and recurrence during the same period as the febrile illness increase the risk of FS developing to epilepsy.[24–28] In a study[25] conducted with 244 FS patients, the onset of FS after the age of 3, family history of epilepsy, abnormal findings on the EEG, and a temperature of $< 39°C$ at the time of the seizure were reported to be risk factors for epilepsy.

In a large-scale study,[26] the authors reported that 5.4% of FS patients developed epilepsy, and a short duration of fever, four or more seizures, and focal seizures increased the risk of developing epilepsy. In the present study, 68% of the patients were submitted to an EEG, and 8.8% had abnormal findings. While the rate of abnormal EEGs was of 3.6% in patients with SFS, it was of 20% in CFS patients. In accordance with the literature, the rate of abnormal EEGs was higher in the patients with CFS and among those who had more than 1 seizure ($p < 0.001$ and $p = 0.004$ respectively). No statistically significant correlation was found regarding the EEG findings and consanguinity between the parents, FS, family history of epilepsy, and birth characteristics (gestational age, birth weight, mode of delivery) ($p > 0.05$). In the present study, we found that 7% of the patients developed epilepsy. Sex, type of delivery, week of birth, birth weight, consanguinity between the parents, family history of FS, and recurrence of FS within 24 hours did not increase the risk of developing epilepsy. Fever of $< 39°C$ during the seizure, seizure duration of ≥ 15 minutes, seizure within the first hour after the onset of fever, age at first FS of < 12 months, neurodevelopmental delay, multiple FS, and first seizure being a CFS were found to increase the risk of epilepsy ($p < 0.001$). We also found that age < 12 months at the first FS increased the risk of developing epilepsy by 17.15, and a seizure duration of ≥ 15 minutes increased the risk by 9.37. Another finding was that clonic seizure increased the risk of developing epilepsy. Despite the fact that it was thought that the EEG had no relevance for the prognosis of FS, Hwang et al.[25] reported that abnormal findings on the EEG increased the risk of developing epilepsy by 5.95. In the present study, we found that an abnormal EEG increased the risk of developing epilepsy by 73.88. This suggests that the EEG may be relevant for the prognosis of FS. In the present study, we found that the rate of development of epilepsy was higher among patients using long-term

ADES ($p < 0.001$); 22% of our sample were using long-term AEDs, and about a third of these patients developed epilepsy. These results show that long-term prophylactic treatment does not reduce the rate of development of epilepsy. Therefore, it would be appropriate not to prefer long-term AEDs in FS prophylaxis.[29]

The limitations of the present study are its retrospective design, the fact that the missing information was completed by calling the families, and that the EEG and neuroimaging could not be performed in every patient, especially those with neurodevelopmental delay.

In conclusion, although FS has a good prognosis, recurrence and the development of epilepsy may be observed. Seizure in the first hour after the onset of fever was determined to be the most important risk factor for FS recurrence, and abnormal EEG findings were found to be the most important risk factor for the development of epilepsy. This suggests that the EEG is important in the follow-up and prognosis of FS. We also found that long-term prophylactic treatment did not decrease the recurrence of FS and the rate of development of epilepsy.

Authors' Contributions

ABC, AE: participated in protocol development and primary data analysis, interpretation and writing of the first version of the manuscript, and finalized the manuscript; CH, NK, MB: collected the samples and performed the clinical part of the study. All authors have read and approved the final version of the article.

Conflict of Interest

The authors have no conflict of interests to declare.

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