

Evaluation of Demographic, Clinical, Laboratory Findings and Treatments of Our Febrile Seizures Cases

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Abstracts

The most common type of convulsion seen in children is Febrile Convulsions (FC). According to the American Academy of Pediatrics, FC is defined as a convulsion occurring between 6 and 60 months of age, caused by a fever due to an infection affecting the Central Nervous System (CNS) or without another identified cause (such as electrolyte imbalance, intoxication, metabolic disorder, or trauma), in children who didn't have afebrile convulsion before. The frequency of febrile convulsions can vary in different studies, ranging between 4-5%. It is estimated to be 5-10% in some regions of the world. The variation in the frequency of FC among different countries and regions is thought to be multifactorial, including local environmental factors and genetic reasons. Boys are more affected than girls. The male to female ratio is approximately 1.4:1. It has been found that children with a family history of FC have a fourfold increased risk compared to the general population. FCs are most commonly seen between 18-22 months of age. They are triggered when the axillary body temperature reaches 38.5°C and usually develop within 1-2 hours after the onset of fever. Upper Respiratory Tract Viral Infections (URTI) are seen to cause FC more frequently than other infections. In this study, we aimed to determine the sociodemographic, clinical, and laboratory characteristics of patients diagnosed with FC who presented to our clinic, for evaluating their responses to applied treatment options, and to identify risk factors for epilepsy development and FC recurrence, taking into account the importance of close monitoring and careful assessment of these patients.

Keywords: Prevalence; Traditional medicine practices; Mothers; Under-five children; Owerri

Introduction

Our study was conducted at the Pediatric Neurology Department of Trakya University Medical Faculty, Child Health and Diseases Outpatient Clinic, with patients diagnosed with FC who were followed up between January 2014 and April 2018. FC was defined as convulsions occurring between the ages of 6

months to 5 years, associated with fever of at least 38°C without CNS infection, metabolic imbalance, or a history of afebrile seizures. The convulsions lasting less than 15 minutes, not recurring within 24 hours, and without focal characteristics were classified as Simple Febrile Convulsions (SFC). Convulsions lasting longer than 15 minutes, recurring within 24 hours, or showing focal characteristics were classified as Complex Febrile Convulsions (CFC). Recurrence was defined as the reappearance of a convulsion at a different time period not associated with the same illness course. Epilepsy was diagnosed in patients who had at least two unprovoked seizures 24 hours apart. Patients' files were retrospectively reviewed, including data from the hospital's information system, laboratory tests, and radiological imaging results. The included cases were analyzed for gender, age at onset of FC, birth history, parental consanguinity, family history of FC and epilepsy, type of seizure, and clinical and laboratory findings [1-5].

Materials and Methods

The data regarding the form, duration, fever focus, body temperature during the seizure, frequency of FK seizures, and the effectiveness of the antiepileptics used by the patients, laboratory results, lumbar puncture, EEG and MR results were evaluated. Laboratory results including C-reactive protein and LP puncture results were evaluated alongside reference values from Trakya University Faculty of Medicine's laboratory, hemogram results were evaluated together with pediatric age group normal reference values. Patients' data were transferred to the "Patient Follow-up Form."

Statistical analysis

For the evaluation of the research data, "Statistical Package for the Social Sciences" version 19.0 was used. Categorical variables in the study were shown as number (n) and percentage (%), while numerical data were presented as mean and standard deviation. The prevalence of patients' diagnoses was calculated. In the comparison of categorical data, the Pearson *Chi-square* test was used, and in cases where the variables did not show normal distribution, the Mann-Whitney U test was used for

comparisons between variables. Statistical significance was considered at $p < 0.05$ [6,7].

Results

Of our patients, 110 were male, 90 were female (1.22/1). The patients' ages ranged from 6 months to 60 months, with a mean age of 21.82 ± 12.69 months. Most commonly, patients were

under 2 years old; 138 patients (69%) were observed in this age group. The average age for each gender was around 18 months.

At birth, 156 patients (78%) were full-term, 120 patients (60%) were born with normal delivery (NSVD), and 38 (19%) had a history of difficult delivery. Family history of FC was present in 50 patients (25%), and a history of epilepsy in 20 patients (10%). Table 1 shows the distribution of the patients' demographic characteristics [8,9].

Table 1: Distribution of patients according to demographic characteristics.

		n (number of people)	% (percentage)
Gender	Male	110	55,0
	Female	90	45,0
Birth week	Borderline preterm (37-38 week)	24	12,0
	Term (38-42 week)	156	78,0
	Postterm (>42 week)	20	10,0
Type of birth	Cesarean section (C/S)	80	39,9
	Spontaneous vaginal delivery (NSVD)	120	60,1
Difficult birth history	No	162	81,0
	Yes	38	19,0
Parental consanguinity	No	196	98,00
	Yes	4	2,00
Family history of epilepsy	No	180	90,00
	Yes	20	10,00
Family history of FC	No	150	75,00
	Male	50	25,00
Note: n: number of people, (%): percentage			

When the foci were examined, the most frequently observed focus was URTI in 166 (83.0%) patients. No focus was detected in 2 (1.0%) patients. Lumbar Puncture (LP) was performed on these two patients, but no evidence of a Central Nervous System (CNS) infection was found. The distribution of the patients' fever foci is shown in Figure 1.

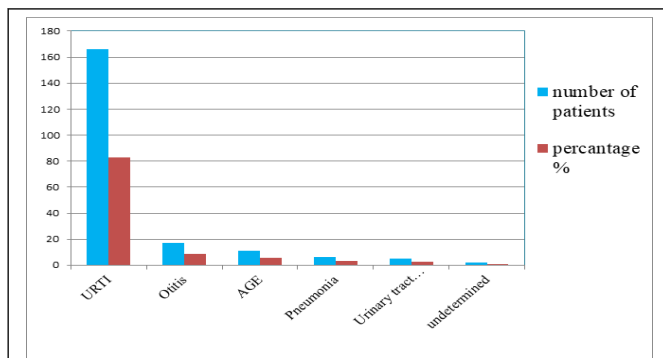


Figure 1: Fever focus distribution of patients.

When the follow-up process of patients was examined, it was found that 45 (22.5%) patients experienced recurring seizures, and 26 (13.0%) patients received a diagnosis of epilepsy. Patients who were on continuous antiepileptic treatment had a higher rate of seizure recurrence, while those with tonic-clonic and focal seizure clinics had lower rates compared to other clinics. It was observed that patients with abnormal EEG results had a higher rate of seizure recurrence compared to other clinics (Table 2).

Table 2: Comparison of patients' seizure recurrence with other variables.

		Seizure recurrence		p*
		No n (%)	Yes n (%)	
Gender	Male	84 (76,4)	26 (23,6)	0,670
	Female	71 (78,9)	19 (21,1)	
Age	Below 1 year old	39 (70,9)	16 (29,1)	0,136
	1-2 years old	70 (84,3)	13 (15,7)	
	Above 2 years old	46 (74,2)	16 (25,8)	
Type of birth	Cesarean section (C/S)	62 (77,5)	18 (22,5)	0,105
	Spontaneous vaginal delivery (NSVD)	107 (89,2)	13 (10,8)	
Birth week	Borderline preterm (37-38 week)	14 (58,4)	10 (41,6)	0,134
	Term (38-42 week)	144 (92,3)	12 (7,7)	
	Post-term (>42 week)	18 (90,0)	2 (10,0)	
Difficult birth history	No	143 (89,4)	19 (10,6)	0,574
	Yes	35 (92,2)	3 (7,8)	
Family history of epilepsy	No	138 (76,7)	42 (23,3)	0,572
	Yes	17 (85)	3 (15)	
Parental consanguinity	No	152 (77,6)	44 (22,4)	0,904
	Yes	3 (75)	1 (25)	
Family history of FC	No	114 (76)	36 (24)	0,379
	Yes	41 (82)	9 (18)	
Body temperature at which the seizure occurred	Below 38,3 degrees	90 (75,0)	30 (25,0)	0,300
	Above 38,3 degrees	65 (81,3)	15 (18,8)	

Number of seizures	1	57 (65,0)	3 (5,0)	<0,001
	>1	98 (70,0)	42 (60,0)	
EEG	Normal	97 (75,2)	5 (9,1)	0,033
	Abnormal	8 (50,0)	32 (24,8)	
Radiological imaging	Normal	50 (80,3)	18 (26,5)	0,513
	Abnormal	3 (60,0)	2 (40,0)	
Treatment	No, antipyretic if necessary	65 (86,7)	10 (13,3)	0,035
	Intermittent rectal diazepam	12 (80,0)	3 (20,0)	
	Continuous antiepileptic	84 (71,2)	34 (28,8)	
Febril seizure type	Simple	67 (81,7)	15 (18,3)	0,689
	Complex	88 (74,6)	30 (25,4)	
Seizure clinic	Tonic	7 (100)	0 (0)	0,010
	Klonic	3 (100)	0 (0)	
	Atonic	7 (46,7)	8 (53,3)	
	Tonic klonic	128 (78)	36 (22)	
	Focal	84 (76,4)	26 (23,6)	

Note: n: number of patients, (%): percentage, *Ki Square Test.

In patients receiving continuous antiepileptic therapy, a higher rate of epilepsy development was observed. Patients with abnormal EEG results were found to have a higher rate of receiving an epilepsy diagnosis. When comparing the body temperature during seizures, it was found that patients who experienced seizures below 38.3 degrees Celsius had a higher

rate of receiving an epilepsy diagnosis. Patients who had multiple seizures also had a higher rate of receiving an epilepsy diagnosis (Table 3).

Table 3: Comparison of patients' epilepsy development with other variables.

		Development of epilepsy		p*
		No n (%)	Yes n (%)	
Gender	Erkek	98 (89,1)	12 (10,9)	0,331
	Kız	76 (84,4)	14 (15,6)	
Age	Below 1 year old	39 (70,9)	16 (29,1)	0,678
	1-2 years old	70 (84,3)	13 (15,7)	
	Above 2 years old	46 (74,2)	16 (25,8)	

Type of birth	Cesarean section (C/S)	64 (80,0)	16 (20,0)	0,072
	Spontaneous vaginal delivery (NSVD)	108 (90,0)	12 (10,0)	
Birth week	Borderline preterm (37-38 week)	16 (66,7)	8 (33,3)	0,184
	Term (38-42 week)	145 (92,9)	11 (7,1)	
	Post-term (>42 week)	19 (95,0)	1 (5,0)	
Difficult birth history	No	143 (89,4)	19 (11,7)	0,524
	Yes	35 (87,5)	3 (7,8)	
Family history of epilepsy	No	156 (86,7)	24 (13,3)	0,674
	Yes	18 (90)	2 (10)	
Parental consanguinity	No	170 (86,7)	26 (13,3)	0,435
	Yes	4 (100)	0 (0)	
Family history of FC	No	127 (84,7)	23 (15,3)	0,089
	Yes	47 (94)	3 (6)	
Body temperature at which the seizure occurred	Below 38,3 degrees	98 (81,7)	22 (18,3)	0,004
	above 38,3 degrees	76 (95,0)	4 (5,0)	
Number of seizures	1	57 (95,0)	3 (5,0)	0,028
	>1	117 (83,6)	23 (16,4)	
EEG	Normal	117 (90,7)	12 (9,3)	<0,001
	Abnormal	3 (18,8)	13 (81,3)	
Radiological imaging	Normal	55 (80,9)	13 (19,1)	0,265
	Abnormal	3 (60,0)	2 (40,0)	
Treatment	No, antipyretic if necessary	73 (97,3)	2 (2,7)	0,001
	Intermittent rectal diazepam	14 (93,3)	1 (6,7)	
	Continuous antiepileptic	94 (79,7)	24 (20,3)	
Febril seizure type	Simple	71 (86,6)	11 (13,4)	0,786
	Complex	103 (87,3)	15 (12,7)	
Seizure clinic	Tonic	6 (85,7)	1 (14,3)	0,689
	Klonic	3 (100)	0 (0)	
	Atonic	13 (86,7)	2 (13,3)	

	Tonic klonic	141 (86)	23 (14)	
	Focal	11 (100)	0 (0)	

Note: n: number of patients, (%): percentage, *Ki Square Test.

It was observed that EEGs were conducted for 145 out of 200 patients (72.5%). Among them, 129 (64.5%) showed normal EEG results, while 16 (8%) showed abnormal EEG results. Among the 49 patients (24.5%) with simple febrile convulsions (SFC), abnormal EEG results were found in 5 (2.5%), and among the 96 patients (48%) with complex febrile convulsions (CFC), abnormal

EEG results were found in 11 (5.5%). There was no significant relationship found between the type of febrile convulsion and EEG findings ($p=0.605$) (Table 4).

Table 4: Evaluation of EEG findings according to the type of febrile convulsion.

	Normal EEG n (%)	Anormal EEG n (%)	Total n (%)	P*
Simple FC	44 (22)	5 (2,5)	49 (24,5)	0,605
Complex FC	85 (42,5)	11 (5,5)	96 (48)	
Total	129 (64,5)	16 (8)	145 (72,5)	

Note: n: number of patients, (%): percentage, *Ki Square Test.

Patients with recurrent seizures were found to have higher laboratory values and the development of epilepsy (Tables 5 and 6). CRP (C-Reactive Protein) and platelet levels compared to patients with epilepsy. No relationship was found between other

Table 5: Comparison of laboratory variables with patients' seizure recurrence.

		Seizure recurrence		
		Yok n (%)	Var n (%)	p*
C-reaktif protein	Normal	98 (77,2)	29 (22,8)	0,881
	High	57 (78,1)	16 (21,9)	
White blood cells	Low	16 (72,7)	6 (27,3)	0,772
	Normal	125 (77,6)	36 (22,4)	
	High	14 (82,4)	3 (17,6)	
Neutrophil count	Low	7 (77,8)	2 (22,2)	0,286
	Normal	118 (76,1)	37 (23,9)	
	High	30 (83,3)	6 (16,7)	
Hemoglobin	Low	57 (76)	18 (24)	0,694
	Normal	98 (78,4)	27 (21,6)	
MCV	Normal	63 (77,8)	18 (22,2)	0,177
	High	92 (78)	26 (22)	
Platelet count	High	2 (28,5)	5 (71,5)	0,009

	low/normal	122 (78,2)	34 (21,8)	
Note: n: number of patients, (%): percentage, *Ki Square Test				

Table 6: Comparison of laboratory variables with patients' development of epilepsy.

		Development of epilepsy		
		No n (%)	Yes n (%)	p*
C-reaktif protein	Normal	106 (83,5)	21 (16,5)	0,049
	High	68 (93,2)	5 (6,8)	
White blood cells	Low	18 (81,8)	4 (18,2)	0,526
	Normal	140 (87)	21 (13)	
	High	16 (94,1)	1 (5,9)	
Neutrophil count	Low	9 (100)	0 (0)	0,881
	Normal	132 (85,2)	23 (14,8)	
	High	33 (91,7)	3 (8,3)	
Hemoglobin	Low	65 (86,7)	10 (13,3)	0,914
	Normal	109 (87,2)	16 (12,8)	
MCV	Normal	75 (92,6)	6 (7,4)	0,647
	High	98 (83,1)	20 (16,9)	
Platelet count	High	7 (100)	0 (0)	0,355
	low/normal	134 (85,9)	22 (14,1)	
Note: n: number of patients, (%): percentage, *Ki Square Test.				

A statistically significant relationship was found between the development of epilepsy during follow-up and the body temperature at which seizures occurred and the number of seizures ($p=0,048$, $p<0,001$). It has been determined that in patients who develop epilepsy, the body temperature value at

which seizures occur is lower and also the number of seizures is 3 or more. No statistically significant relationship was found between the development of epilepsy during follow-up and the duration of seizures, the age of the patient, and the age at which the first seizure occurred (Table 7).

Table 7: Comparison of patients' development of epilepsy with other factors.

	Development of epilepsy (no)		Development of epilepsy (yes)		p*
	Mean $\pm$ standard deviation	Median	Mean $\pm$ standard deviation	Median	
Body temperature	38,4 $\pm$ 0,6	38	38,2 $\pm$ 0,5	38	0,048

Number of seizures	2,1 ± 1,2	2	3,3 ± 1,9	3	<0,001
Duration of seizure	8 ± 8,5	5	4,9 ± 6,9	3	0,091
Age (months)	45 ± 25,6	44	54 ± 27,1	57	0,081
Seizure age (months)	22,1 ± 13	18	20,2 ± 10,8	18	0,575

Note: *Mann Whitney U test.

Discussion

Febrile Convulsions (FC) are the most common neurological problem in childhood and the most frequently encountered type of convulsion. Although they generally have a favorable prognosis, they can recur and evolve into afebrile seizures. Therefore, understanding predisposing factors is of great importance.

FC is more commonly observed in boys compared to girls. In studies conducted abroad and in our country, the male-to-female ratio has been reported as 1.3/1 and 1.36/1 respectively [8, 9]. In our study with 200 patients, a similar male-to-female ratio of 1.22/1 was found.

Genetic factors are known to play a significant role in FC. However, the complete genetic transmission remains unclear. In studies conducted abroad and in our country, a history of FC among first-degree relatives has been found to be 26.6% and 20.8% respectively [10,11]. In our study, the frequency of FC among first-degree relatives was found to be 25%, similar to the literature.

The accepted fever threshold in FC has been reported as axillary 38°C in one group of studies, and 38.5°C and above in another group. In our study, the body temperature ranged from 37.5°C to 40°C, with an average of 38.3°C. It was found that 120 patients (60%) had seizures at temperatures below 38.3°C, and in this group, the risk of developing epilepsy was significantly higher [12,13].

The source of fever in febrile convulsions is often viral infections such as Upper Respiratory Tract Infections (URTI), pharyngitis, Urinary Tract Infections (UTI), Acute Otitis Media (AOM), pneumonia, roseola infantum, and non-infectious diseases. In the study by Abuekteish et al. involving 203 patients, URTI was reported as the fever focus in 53% of cases, while in the study by Öztürk et al., this rate was 75.8%. Similarly, in our study, URTI was most frequently detected at a rate of 83%, consistent with the literature.

In the study by Verrotti et al.s, Complex Febrile Convulsions (CFC) were found in 27.2% of cases, and in the study by Kolfen, they were found in 22.5% of cases. Ling reported that 90% of seizures in his study and Knugsen reported 96% of seizures lasted less than 15 minutes. In our study, the number of cases with CFC was found to be 105 (52.5%). This result may be due to our institution being a tertiary care center, where complicated and recurring cases are referred or transferred from lower-level

healthcare facilities. Among the CFC cases in our study, 85 (80.9%) had recurrence within 24 hours, 22 (20.9%) lasted longer than 15 minutes, 9 (8.6%) had focal seizures, and 2 (1.9%) were diagnosed as complex due to both focal seizures and lasting longer than 15 minutes [14-16].

In previous studies, imaging tools such as EEG, MRI, and BBT have been found to be largely normal in children with Febrile Convulsions (FC), and they were concluded to not be associated with recurrence or development of epilepsy. In our study, imaging was performed on 73 patients, of whom 15 patients received a diagnosis of epilepsy. Pathology was detected in the imaging of 2 patients who also developed epilepsy during follow-up. Patients with abnormal EEG results were found to have a higher rate of receiving an epilepsy diagnosis [17,18].

Previous studies have suggested a relationship between convulsions triggered by different mechanisms of the immune system and elevated acute-phase reactants such as CRP, which are indicators of inflammation, with epilepsy. Another study found that thrombocytosis, seen as an acute-phase reactant, was also associated with febrile seizures, and IL-6 levels and platelet levels were found to be higher in febrile seizure patients compared to the control group [19]. In our study, patients with recurrent seizures were found to have higher levels of CRP and platelets compared to patients with epilepsy.

Both simple and complex febrile convulsions have shown a higher recurrence rate in patients receiving treatment compared to those who did not receive treatment. One treatment option is continuous use of antiepileptic drugs [20. reported in their study that phenobarbital, diazepam, phenytoin, and antipyretics did not show significant superiority in preventing FC recurrence attacks over each other. In our study, a recurrence rate of 28.8% was observed in patients using long-term antiepileptic drugs. There was no statistically significant relationship found between seizure recurrence and development of epilepsy based on the type of treatment received.

Our study had some limitations. A majority of our patients had complex febrile convulsions, which differs from the data in the literature. Based on the data we analyzed, we believe that some patients' seizures were terminated in the emergency department after admission, hence their duration was recorded as <5 minutes. However, according to the literature, seizure recurrence and epilepsy are directly proportional to seizure duration. We attribute this to providing information to families for seizure management and termination of seizures in the emergency department for some cases, resulting in shorter

durations. Additionally, no relationship was found between family history of FC recurrence and epilepsy in our region. We believe this may be due to healthcare providers and families in our region providing more appropriate follow-up and treatment during febrile illness periods, potentially raising the threshold for experiencing FC.

In the literature, the role of sodium channels in the pathogenesis of epilepsy and FC is mostly mentioned, and in addition, some studies have pointed out the relationship between FEB gene loci and related syndromes. On the other hand, the condition known as Dravet Syndrome may be mistakenly perceived as FC. Dravet Syndrome should be considered if afebrile focal seizures and myoclonies are added to febrile seizures and negatively affect the child's mental functions over time.

SCN1A gene analysis should be used, especially in the presence of prolonged and lateralized febrile seizures. If a mutation is detected, the diagnoses of GEFS+, typical or borderline Dravet Syndrome should be reviewed, taking into account the patient's clinic. We believe that with the data obtained as a result of comprehensive epidemiological and genetic studies, the data currently available in the literature will solidify and illuminate the role of genetic predisposition in the etiopathogenesis of FC in the future.

Conclusion

Febrile convulsions are the most common type of convulsion in childhood. Although they generally have a benign course, they can recur and transform into afebrile seizures. Therefore, understanding predisposing factors is crucial. Despite being considered a benign condition, the high frequency of recurrence and increased risk of epilepsy compared to the general population necessitates careful monitoring. Since follow-up is mostly conducted in primary and secondary healthcare settings, careful examination for epilepsy risk factors is essential.

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