THE MEDICAL BULLETIN OF
SISLI ETFAL HOSPITAL

DOI: 10.14744/SEMB.2019.30633
Med Bull Sisli Etfal Hosp 2019;53(3):276–283

Original Research

Clinical Features and Evaluation in Terms of Prophylaxis of Patients With Febrile Seizures

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Abstract

Objectives: Febrile seizures are the most common seizure type of childhood, and prognosis is usually good. Many factors that increase the risk of recurrence and develop epilepsy have been identified. This study aims to determine the clinical characteristics of patients who were admitted with the febrile seizure, and determine the outcomes of the treatment, and the risk factors.

Methods: Between January 2017 and January 2019, 147 (42.6%) female and 198 (57.4%) male patients who were admitted with febrile seizure, and aged between 3-60 months were included in the study.

Results: The mean age at the time of admission was 30.4±15.4 months, and the mean age of the first seizure was 21.2±12.8 months. Simple febrile seizure was seen in 247 (71.6%) patients, and complex febrile seizure was seen in 89 (25.8%) patients while febrile status epilepticus was present in 9 (2.6%) patients. Amongst the patients, 59.1% of them had a history of repetitive febrile seizure. First-degree relatives of thirty (8.69%) patients had a history of epilepsy, while 176 (51%) patients had a family history of febrile seizure. Two hundred and seventy-five patients (79.7%) found to have an infection, most frequently upper respiratory tract infection (53.8%), during the examination, which might cause fever. One hundred and ninety-five patients were followed without treatment, while 48.6% of the patients were treated with rectal diazepam, 23.3% with sodium valproate, 23.3% with levetiracetam and 4.6% with phenobarbital. At the end of the one-year follow-up, only four patients (1.15%) with complex febrile seizure were diagnosed with epilepsy. The age of the onset of febrile seizures, family history of febrile seizures, short episodes of febrile seizure and the presence of epilepsy in the family history were found to be the significant risk factors for repetitive seizures.

Conclusion: Febrile seizures are generally benign and have a low risk of developing epilepsy. Determining the risk factors is essential for the treatment and follow-up plan.

Keywords: Febrile seizure; prophylaxis; risk factors.

Please cite this article as "Kılıç B. Clinical Features and Evaluation in Terms of Prophylaxis of Patients With Febrile Seizures. Med Bull Sisli Etfal Hosp 2019;53(3):276–283".

Febrile seizures (FSs) are the leading causes of pediatric emergency department admissions and affect approximately 2-5% of all young children.[1] The National Institute of Health (NIH) consensus statement defines FS as a fever-related seizure, usually seen between three months and five years of age, with no identified cause for intracranial infection or seizure.[2]

According to the League for the Fight Against Epilepsy (ILAE), FS has been defined as seizures associated with a febrile disease in previously afebrile children aged six months to five years without central nervous system (CNS) infection or a specific cause (such as acute electrolyte imbalance, metabolic disorder, trauma, intoxication).[3]

FSs are divided into two subgroups as follows: (i) simple

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Submitted Date: December 13, 2018 **Accepted Date:** March 25, 2019 **Available Online Date:** August 27, 2019

FS and (ii) complex FS. Simple FS is characterized with generalized seizures that lasts less than 15 minutes, do not recur within 24 hours, or during the same disease, and have no postictal neurological abnormalities. In complex FN, seizures may be focal, lasts longer than 15 minutes, recur within 24 hours, or during the same disease, and postictal neurological findings (such as Todd's paralysis) may be seen.[4, 5] When the seizure lasts longer than thirty minutes, or recurs within 30 minutes without an interval period of open conscious, it is called febrile status epilepticus (FSE), and accounts for 25% of all cases of status epilepticus.[4]

FSs peaks at most between six months and three years, and at most 18 months.[6] The reason for the increased incidence in this age is recurrent infections, and hypersensitivity of the developing brain to the body temperature.[7] Upper viral respiratory tract infections are the most frequently seen triggering factor for FSs.[8]

Although the pathogenesis of FS is not fully known, the most important etiologic factors are age, concomitant infection, fever, and genetic factors.[9] Gender, developmental retardation, duration of breastfeeding, sudden elevated body temperature, maternal alcohol and smoking history, family history, bacterial and viral infections, vaccines, iron and zinc deficiency have been implicated in the etiology. Recurrence rates of FS vary in different regions of the world.[9, 10]

Although FS generally leads a favorable course, the risk of developing epilepsy, and recurrence varies according to the case.[11] The decision to initiate prophylaxis, and prognosis of FS are important issues for clinicians. Family history, early-onset, low fever at the onset of FS, the short time interval between FS, and fever are risk factors for recurrent FS. However, the presence of epilepsy in the family, complex FS, and neurodevelopmental abnormalities are known as risk factors for the development of epilepsy. The role of recurrent FSs in the development of epilepsy is controversial.[4, 5]

The present study aimed to evaluate the efficacy of prophylactic treatment in consideration of demographic, etiologic, laboratory features, electroencephalography (EEG) and neuroimaging findings of our patients with FS.

Methods

The files of all patients with FS who were brought to our pediatric neurology outpatient clinic between January 2017 and January 2019 were retrospectively reviewed. All patients who were brought to our emergency department with FS were referred to the pediatric neurology. Outpatient clinic, and their evaluation and follow-up were performed by the same pediatric neurologist. Patients with FS aged between 3-60 months were included in this study. Exclusion criteria were afebrile seizures, CNS infection, structural or developmental anomalies of CNS, history of trauma, presence of intoxication, electrolyte disturbances, congenital metabolic disease and chronic disease. Seizures with focal features, lasting longer than 15 minutes, and recurrent seizures occurring within 24 hours were considered as complex FS, whereas seizures without these characteristics were considered as cases with simple FS.

Electroencephalography (EEG) was performed in patients with a family history of epilepsy, complex FS, and experienced more than three simple attacks of FS. Cerebral magnetic resonance imaging (MRI) was performed in patients with abnormal EEG findings, focal seizure characteristics or abnormal neurological examination findings.

Personal and family history and physical examinations of all cases were reviewed retrospectively. Patients were evaluated in terms of clinical findings and risk factors. Age, sex, family history, seizure type, blood hemoglobin and mean corpuscular volume (MCV) values, EEG and brain MRI results were recorded.

While initiating prophylactic treatment, together with risk factors sociocultural status of the families, the possibility of reaching the health institution during the seizure and their compliance to treatment were taken into consideration. Prophylactic treatment was initiated in all cases of complex FS, in patients with simple FS starting from the third seizure on. Intermittent treatment with rectal diazepam was recommended if the family had a good drug compliance. Families were given training on fever monitoring and seizure management.

During follow-up, patients received the diagnosis of epilepsy if they experienced at least two non-triggered seizures. After one year follow-up, demographic, etiologic, laboratory features, EEG and neuroimaging findings, and efficacy of prophylactic treatment were evaluated.

Statistical Analysis

SPSS 15.0 for Windows program was used for statistical analysis. In descriptive statistics, categorical variables were expressed as numbers and percentages and numerical, variables as median, minimum and maximum. Since numerical variables did not meet the normal distribution condition in the groups, independent comparisons of more than two groups were performed by Kruskal Wallis test. The ratio of categorical variables between the groups was tested by chi-square analysis. The level of statistical significance was accepted as $p<0.05$.

Results

A total of 345 patients, including 147 (42.6%) female and 198 (57.4%) male children, who were brought to the outpatient clinic of pediatric neurology due to FS, were included in this study. The mean age at admission was 30.4±15.4 months, and the mean age at first attack of seizure was 21.2±12.8 months. The first attack of seizure was experienced by indicated number of children aged <0.6 months (n=19:5.5%), 7-12 months (n=98:28.4%), 1-2 (n=134:38.8%), 2-3 (n=58:16%) 3-4 (n=24:6.9%), 4-5 (n=10:2.9%), and 5 years (n=2:0.57%). According to seizure characteristics, patients had simple FS (n=247:71.6%), complex FS (n=89:25.8%) and FSE (n=9:2.6%). There was no statistically significant difference about febrile seizure types between sex, mean age, first seizure age (respectively p=0.621, p=0.387, and p=0.115) (Table 1).

Two hundred four (59.1%) patients had recurrent febrile seizures, 114 (33%) had two, 52 (15%) had three, and 38 (11%) had more than three seizures. The mean duration of seizure was 6.2±6.8 minutes. The duration of seizure was 1-5 minutes in 254 (73.6%), 5-15 minutes in 72 (20.8%), 15-30 minutes in 10 (2.89%), and longer than 30 minutes in 9 (2.6%) patients

Three hundred and four patients (88.1%) patients had generalized seizures, and forty-one patients (11.9%) had focal seizures. Their personal medical history revealed the presence of prematurity in 38 (11%), perinatal asphyxia in seven (2%), intrauterine growth retardation in three (0.86%) and history of meningomyelocele surgery in one (0.28%) patient.

Table 1. Demographic and clinical characteristics of the cases in different types of febrile seizures

	Types of Febrile Seizures						
	Simple		Complex		Febrile Status		
	n	%	n	%	n	%	p
Gender							
Female	109	44.1	34	38.2	4	44.4	0.621
Male	138	55.9	55	61.8	5	55.6	
Age							
Mean±SD (median)	30.9±15.3 (29)		28.8±15.4 (25)		27.4±16.4 (20)		0.387
Age at first episode of seizure							
Mean±SD (median)	21.8±13.0 (18)		19.0±11.7 (15)		20.8±12.3 (13)		0.115
Number of seizures (n)							
1	101	40.9	36	40.4	4	44.4	0.424
2	88	35.6	24	27.0	2	22.2	
3	35	14.2	16	18.0	1	11.1	
>3	23	9.3	13	14.6	2	22.2	
Body temperature							
Mean±SD (median)	38.7±2.2 (39)		38.9±0.7 (39)		38.7±0.8 (39)		0.637
Time interval between febrile episode, and onset of seizure							
<1 hour	17	6.9	17	19.1	7	77.8	<0.001
1-12 hrs	119	48.2	54	60.7	2	22.2	
12-24 hrs	104	42.1	18	20.2	0	0.0	
>24 hrs	7	2.8	0	0.0	0	0.0	
Obstetric history							
Unremarkable	217	87.9	71	79.8	8	88.9	0.167
Present	30	12.1	18	20.2	1	11.1	
Preterm	24	9.7	13	14.6	1	11.1	
Perinatal asphyxia	5	2.0	1	1.1	1	11.1	
İntrauterine growth retardation	0	0.0	3	3.4	0	0.0	
Operated meningocele	1	0.4	0	0.0	0	0.0	
Kinship	22	8.9	7	7.9	1	11.1	0.922
Family history of febrile seizure	120	48.6	49	55.1	6	66.7	0.369
Family history of epilepsy	16	6.5	12	13.5	0	0.0	0.079
Maternal history of smoking	14	5.8	8	9.3	1	11.1	0.484
Duration of breastfeeding							
Mean±SD (median)	15.3±8.0 (15)		13.6±8.1 (12)		15.8±8.9 (13)		0.287

Thirty (8.69%) patients had the first-degree kinship among their parents, 28 (8.1%) patients had first-degree relatives with epilepsy, and 176 (51%) had a family history of FS. No statistically significant difference was found between FS types in terms of the history of epilepsy in the first degree relatives (p=0.369). The mothers of 23 (6.6%) patients with FS had a history of smoking during pregnancy. There was no significant difference between FS types in terms of smoking and the mean duration of breastfeeding during pregnancy (p=0.48, p=0.28) (Table 1).

The mean axillary body temperature was measured as 38.8±0.6°C (min: 38°C, and max. 42°C) during the seizure. The most frequently measured body temperatures ranged between 39-39.5°C in 188 (54.3%) patients. Duration of fever before seizure was between 0-12 hours in 216 (62.6%) patients, lasted more than 12 hours in 129 (37.3%) patients.

Time intervals between onset of febrile episodes and attacks of seizure were statistically significantly different between FS types (p<0.001). In simple FS, it was determined that the time between the onset of febrile episode and seizure was between 12-24 hours, and in complex FS it was between 1-12 hours (Table 1). Two hundred and seventy-five (79.7%) patients had an infection that could cause fever during the examination. Upper respiratory tract infection (53.8%) followed by acute otitis media (17%), lower respiratory tract infection (12.7%), acute gastroenteritis (6.1%), urinary tract infection (4.3%), hand-foot-mouth disease (2.9%), sixth disease (2.1%) and sepsis (0.72%) were detected.

When FS types were compared regarding causes of fever, lower respiratory tract infection was statistically significantly higher in complex FS patients (p=0.002). Lumbar puncture (LP) was performed in five of 42 febrile infants under one year old. None of the patients had significant signs of CNS infection.

Laboratory findings of the patients were consistent with iron deficiency anemia in 201 (58.2%) patients. EEG was performed in 268 (77.6%) patients, and 14 of them (5.2%) demonstrated epileptic activity. Fifty (14.4%) patients had cranial imaging, one patient had hippocampal hyperintensity in T2W and FLAIR MRI, 2 patients had an arachnoid cyst, two patients had periventricular hyperintensity in T2W and FLAIR MRI (Table 2). The patient with hippocampal hyperintensity had a history of FSE. There was no statistically significant difference between FS types regarding EEG and cranial imaging results (p=0.306, p=0.086) (Table 2).

Table 2. Evaluation of EEG, cranial imaging, and prophylaxis in febrile seizure types

	Febrile Seizure Type						
	Simple		Complex		Febrile Status		
	n	%	n	%	n	%	p
EEG							
Present	71	28.7	7	7.9	1	11.1	<0.001
Absent	176	71.3	82	92.1	8	88.9	
Normal	169	96.0	77	93.9	7	87.5	0.306
Focal	6	3.4	5	6.1	1	12.5	
Generalized	1	0.6	0	0.0	0	0.0	
Cranial imaging							
Absent	219	89.8	66	75.0	6	66.7	0.001
Present	25	10.2	22	25.0	3	33.3	
Results of cranial imaging							
Normal	24	96.0	19	86.4	2	66.7	0.143
Abnormal	2	8.0	2	9.0	1	33.3	
Arachnoid cyst	1	4.0	1	4.0	0	0.0	
Hyppocampal hyperintensity	0	0.0	0	0.0	1	33.3	
Periventricular hyperintensity	1	4.0	1	4.5	0	0.0	
Prophylactic treatment							
None	186	75.3	9	10.1	0	0.0	<0.001
Rectal diazepam	33	13.4	40	44.9	0	0.0	
Sodium valproate	14	5.7	18	20.2	3	33.3	
Phenobarbital	4	1.6	3	3.4	0	0.0	
Levetiracetam	10	4.0	19	21.3	6	66.7	
Recurrent seizures after prophylactic treatment							
Present	6	9.2	7	8.8	1	11.1	0.972
Absent	59	90.8	73	91.3	8	88.9	

One hundred and ninety-five patients (56.5%) were followed up without treatment. One hundred and fifty patients received prophylaxis with intermittent rectal diazepam (n=73:48.6%), sodium valproate (n=35:23.3%), levetiracetam (n=35:23.3%) and phenobarbital (n=7:4.6%). For complex FS patients, rectal diazepam, and in cases with FSE sodium valproate, and levetiracetam were most frequently preferred drugs. During one-year follow-up recurrent seizures were observed in 12 patients (8%) despite treatment. Of these patients, seven patients were receiving intermittent rectal diazepam, three patients were treated with sodium valproate, and in two patients, phenobarbital was prescribed. There was no recurrence of seizures during the one-year follow-up in patients receiving levetiracetam. There was no statistically significant difference between FS types regarding treatment response (p=0.972) (Table 2).

There was not a significant difference between the drugs used for FS prophylaxis in terms of seizure duration (p=0.132). No side effects were observed in any patient receiving treatment.

After one-year follow-up, afebrile seizures were seen in four (1.15%) patients and epileptic activity was found in their EEGs. All of these patients had a history of the complex, and recurrent FS, and during follow-up, generalized FS recurred, in two, and focal seizures in another two patients. Three of these patients had a history of epilepsy in their first -degree relatives.

In this study, in terms of recurrence of FS, smaller age at admission (p<0.001), being less than 12 months at the onset of the first FS episode (p=0.014), family history of FS (p=0.008), shorter febrile period before the seizure (p<0.001) family history of epilepsy (p=0.009) were found to be statistically significant triggering factors for the recurrence of FS (Table 3).

Table 3. Risk factors for recurrent febrile seizures

	Recurrence of Seizures				
	Yes		No		
	n	%	n	%	p
Gender					
Female	58	40.8	89	43.8	0.580
Male	84	59.2	114	56.2	
Age					
Mean±SD (Min-Max)	25.6±14.6 (21)		33.6±15.0 (31)		<0.001
Type of febrile seizure					
Simple	102	71.8	145	71.4	0.970
Complex	36	25.4	53	26.1	
Febrile Status	4	2.8	5	2.5	
Age at first episode of seizure					
<12 months	18	12.7	47	23.2	0.014
≥12 months	124	87.3	156	76.8	
Family history of febrile seizure	60	42.3	115	56.7	0.008
Family history of epilepsy febrile	5	3.5	23	11.4	0.009
Time interval between the episode and onset of the seizure					
<1 hr	5	3.5	36	17.7	<0.001
1-12 hrs	44	31.0	131	64.5	
12-24 hrs	86	60.6	36	17.7	
>24 hrs	7	4.9	0	0.0	
Body temperature					
≥39	81	57.0	124	61.1	0.452
<39	61	43.0	79	38.9	
Hb					
Mean±SD (Min-Max)	11.3±1.0 (11.5)		11.3±1.0 (11.5)		0.730
MCV					
Mean±SD (Min-Max)	76.9±5.8 (77)		76.7±7.8 (78)		0.716
Smoking	10	7.2	13	6.6	0.841
Duration of breastfeeding					
Mean±SD (Min-Max)	14.7±7.6 (12.5)		15.0±8.4 (14)		0.648
Kinship	9	6.3	21	10.4	0.189
EEG					
Abnormal	3	3.8	10	5.3	0.761

Discussion

FS is the most common seizure type in childhood, but its etiology is not completely known. Although a complex genetic transmission in FS is accepted, some studies have shown an autosomal dominant type of transmission.[12] In cohort studies in patients with FS, the risk was found to be 10-45% in twins.[13]

Children experiencing FS have a higher rate of epilepsy in their families than the normal population. In one study, the findings showed that 9.2% of patients with FS had a history of epilepsy in first-degree relatives.[14]

Although any significant difference in the frequency of FS by gender has not been mentioned in the literature, Pavlovic et al.[15] reported a relatively higher incidence of FS in boys and Sillanpää et al.[16] reported in girls.

FSs usually occur due to an infection progressing with fever, and manifest within the first days of the disease. Most frequently, seizures triggered by viral infections. In the literature, upper respiratory tract infection has been reported as a cause of fever in 53%-78.6% of the FS patients.[17, 18]

Although the frequency of complex FS constitutes 20-30% of all seizures, there is little information regarding sensitivity and etiology in different populations.[19, 20] The American Academy of Pediatrics reported that the risk of recurrence was 50% in patients with simple FS who had their first seizure before 12 months of age. Its incidence decreases to 30% after 12 months. When there is a second seizure, the probability of experiencing another episode of FS is 30-50%.[5] Generally, the first seizure is seen between 16-22 months of age.[14, 21]

FSE constitutes 5-9% of the first FS episodes in children.[22] In FEBSTAT (Consequences of Prolonged Febrile Seizures in Childhood) study, children with FSE were shown to be at risk for mesial temporal sclerosis and temporal lobe epilepsy. In this study, abnormalities in the hippocampus were reported in 9.7% of all FSE patients.[23]

Although computed tomography is often preferred method of cranial imaging in patients with focal neurological findings, and to rule out herniation risk before lumbar puncture (LP), most of the studies report that the contribution of neuroimaging to diagnosis is limited.[24] In prolonged FSs, high resolution cranial MRI can be used to show mesial temporal sclerosis.[22, 23] In this study, one patient with FSE showed hippocampal hyperintensity on T2W and FLAIR images on cranial MRI.

CNS infection is vital importance in the differential diagnosis in a pediatric patient who was brought to the emergency department with FS. Presence of meningeal irritation, complex FS, prolonged postictal period, impaired general health status, the tendency to sleep, and the presence of behavioral changes should be warning signs. The American Academy of Pediatrics recommends LP in the presence of the first complex FS in children under 12 months due to the high risk of bacterial meningitis, and the lack of adequate immunization.

In children aged 12-18 months who are inadequately immunized, and children with a history of antibiotic use before FS, and in cases with complex FS, LP can be considered.[25] In a retrospective study investigating 157 patients with simple FS, the findings showed that LP is unnecessary if there is no neurological symptom in children under 18 months of age.[26]

In the etiology of FS, low levels of serum iron and zinc are thought to be triggering factors. Iron and zinc are involved in the metabolism of many neurotransmitters in the CNS, and participate in the structure of various enzymes.[27] In the literature, it has been shown that patients with FS have lower serum zinc levels than patients with febrile patients without seizures.[28]

In another study, serum iron levels were found to be significantly lower in the group with recurrent FS compared to the control group, and it was emphasized that cases with FS should be examined for iron deficiency anemia.[29] In this study, it was observed that, findings consistent with iron deficiency (58.2%) were common in patients with FS.

Transient findings are seen in 33-42% of EEGs obtained within 7-10 days following seizures.[16] Even if abnormal EEG findings were detected after the first seizure episode, they do not give information about the risk of developing recurrence and epilepsy, also it does not affect the treatment decision. If indicated, EEG is performed 10-15 days after the seizure. While EEG examination is not recommended for a single simple FS, EEG is predictive of prognosis in the presence of complex FS.[24, 30] In our study, interictal epileptiform activity was found in the EEG of four patients diagnosed with epilepsy during the 1-year follow-up.

Prophylactic antiepileptic treatment after a simple FS episode is not recommended. However, recurrent or prolonged FS-related complications may be seen. Therefore, the administration of intermittent prophylaxis or continuous antiepileptic treatment is still controversial. Side effects of antiepileptic drugs should be considered. In intermittent prophylaxis, oral or rectal use of benzodiazepine has been shown to reduce the incidence of FS.[5, 31] In addition, it has been shown that with intermittent clobazam treatment, incidence of FS was significantly reduced compared to placebo.[32] Phenobarbital, primidone and sodium valproate have been preferred for continuous prophylaxis, but the side effects associated with these drugs may be more

than their benefits.[33] In particular, it has been shown that phenobarbital can cause agitation, hyperactivity and retardation in cognitive development.[34]

Carbamazepine, oxcarbazepine and phenytoin were not found to be effective in preventing FS recurrence.[33] Therefore, these drugs should not be used in the prophylaxis of complex FS. Although new antiepileptic drugs may be safer due to their lesser side effects, studies on their use are quite insufficient.[5] Intermittent use of levetiracetam at doses of 15-30 mg/kg twice a day for one week during febrile periods, tapering of its dose, and finally discontinuation of the drug in the subsequent second week was recommended, and a significant reduction in the frequency of FS was found during 48-week follow-up period.[35] In this study, intermittent rectal diazepam prophylaxis was used in 48.6%, sodium valproate in 23.3%, levetiracetam in 23.3%, and phenobarbital prophylaxis in 4.6% of the patients.

At the end of one-year follow-up, seizure recurrence was observed in 12 patients (8%) using rectal diazepam, sodium valproate and phenobarbital. There was no recurrence of seizures in any patient under levetiracetam prophylaxis.

Parents should be warned that FS may recur. In a cohort study, 32% of children with FS for the first time had a recurrence, and 75% had recurrence within one year.[36] Risk factors for recurrence after the first FS episode are as follows: onset of the first episode of seizure before the age 18 months, time interval of less than one hour between the febrile episode, and the FS attack, seizure in the presence of a low-grade fever, and family history of seizure in the first-degree relatives.[36] It has been indicated that as the number of these factors increases, the frequency of recurrences also increases.

Accordingly, the risk of FS recurrence within two years; in 14% children who have no risk factors, however, its risks are 20%, 50%, and 70% in children with one, two, three, and four risk factors, respectively.[37]

In this study, a statistically significant correlation was found between FS recurrence, smaller age at first episode of FS (<12 months), family history of FS, and epilepsy, and shorter pre-seizure febrile period.

Some cohort studies have shown that children with a history of FS – though at a lower incidence-have an increased rate of epilepsy.[38] The risk of epilepsy after the first simple episode of FS has been reported to be approximately 2%.[6, 39] This risk increases in children with complex FS.[6] Risk factors for the development of epilepsy in the future have been shown to be complex FS, family history of epilepsy, seizures less than one hour after a febrile episode, and neurodevelopmental retardation.[4] In this study, four (1.15%) patients were diagnosed as epilepsy at the end of one-year follow-up. The rate of development of epilepsy lower compared to other studies, which is thought to be due to the short follow-up period.

Conclusion

In conclusion, FS is the most frequent seizure in childhood. In general, most FSs are of the simple type and have a good prognosis. The risk of developing epilepsy is low. It is important to identify risk factors to determine a follow-up and treatment plan and to reduce family anxiety. Levetiracetam may be an effective treatment option in continuous prophylaxis. Family compliance and patient age are the determinants of prophylactic drug selection. The limitation of this retrospective study is that there is no randomization in drug selection. Further studies with longer follow-up periods, and have a higher number of patients are needed.

Disclosures

Ethics Committee Approval: The study was approved by the Institutional Review Board of University of Health Sciences Non-invasive Clinical Research Studies Ethics Committee (25.01.2019/02).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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