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Original Article

The Prophylaxis of Febrile Convulsions in Childhood: Secular Trends in the Last Decade (2007-2008 versus 2017-2018)

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ABSTRACT

Aim: To analyze trends in the prophylaxis of febrile convulsions (FC) in childhood by comparing two cohorts from the previous two decades (2007-2008 versus 2017-2018).

Materials and Methods: The cohort consisted of 272 children with FC who were followed up during the 2007-2008 (n=105) and 2017-2018 (n=167) periods in Ege University Faculty of Medicine Children's Hospital. The following clinical parameters were analyzed: demographic data, FC types, prophylaxis types, selected anti-seizure medications (ASM), recurrence risk factors, and electroencephalography (EEG) characteristics.

Results: We defined two secular trends for the prophylaxis of FC in children in the last decade: (1) a reduced rate of FC prophylaxis (22.1%) in the period of 2017-2018 compared with a rate of 63.8% in 2007-2008, $p<0.01$, (2) no impact of recurrence risk factors for the initiation of prophylaxis for complex FC in the last decade ($p=0.028$). The mean number of previous seizures at the initiation of the ASM prophylaxis increased from 2.8±1.13 to 3.4±2.00 for simple FC and from 1.9±0.24 to 3.1±0.31 for complex FC ($p<0.01$) in the period of 2017-2018.

Conclusion: Prophylaxis rates were determined to be lower in the last decade in children with FC. There was no impact of recurrence risk factors for the initiation of prophylaxis in children with simple or complex FC.

Keywords: Febrile convulsion, ASM prophylaxis, febrile convulsion recurrence risk factors

Introduction

Febrile convulsions (FC) are common in childhood, with a risk of seizure recurrence of 33% (25-50) and also a low risk of developing epilepsy (1,2). FC recur in almost 1/3 of cases, and 10% of cases experience more than three seizures in a lifetime. The decision to initiate anti-seizure medication (ASM) prophylaxis and the prognosis is essential for the clinician in FC. In the past years, there have been certain recommendations on initiating prophylaxis of FC with ASM regarding the number of previous seizures and the risk factors of febrile seizure recurrence. In more recent years, the prophylaxis of simple FC (SFC) has not been recommended regardless of recurrence risk factors and the number of previous seizures due to the potential adverse effects of the drug (3-5). Children with complex FC are considered on a case by case basis for ASM prophylaxis.

The Japanese Society of Child Neurology (2015) suggested two types prophylaxis based on the certain criteria; (1)

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intermittent and (2) continuous prophylaxis to manage FC cases and they do not recommend prophylaxis for one or two SFC attacks without recurrence risk factors (5).

1) The initiation criteria for the use of intermittent prophylactic diazepam are as follows:

- History of prolonged FC lasting ≥15 min
- History of recurrent FC with a short interval in between (2 FC within 12 hours, >3 FC within 6 months)
- History of ≥2 FC with ≥2 of the risk factors stated below:
- Focal seizure, recurrent seizures within 24 hours
- Presence of developmental delay and neurological abnormality
- Family history of epilepsy on FC
- Age of patient <12 months
- Febrile seizure within 1 hour after the onset of fever
- FC with body temperature <38 °C.

2) Continuous use of phenobarbital, sodium valproate, and levetiracetam recommended after pediatric neurology consultation with the criteria given below:

• History of prolonged FC lasting ≥15 minutes without diazepam prophylaxis due to unawareness of fever before FC

• History of protracted FC lasting ≥15 minutes despite prophylactic diazepam treatment at the appropriate time and the right dose

• History of >2 repeated convulsions when body temperature <38 °C.

The drugs preferred for intermittent treatment can be rectal diazepam or oral clobazam. Oral sodium valproate, phenobarbital, or levetiracetam have been reported in continuous prophylactic treatment depending on the children's clinical features (6).

The aim of this study was to analyze the trends in the prophylaxis of FC in the new era (period: 2017-2018) and to include a comparison with the previous decade (period: 2007-2008).

Materials and Methods

Study Design

From the archive of the Child Neurology Department at Ege University Hospital, 272 children with FC were included in this study from two different follow-up periods (2007-2008 and 2017-2018). The inclusion criteria were children aged 6-60 months without any history of afebrile convulsion and with a history of convulsion during a febrile disease without significant CNS infection or acute metabolic dysfunction. The exclusion criteria were having a diagnosis of Dravet syndrome or generalized epilepsy with febrile seizure plus (GEFS+).

The demographic features of the patients were recorded; seizure parameters such as duration (≤15 min and >15 min), type (focal, generalized), number of seizures in the same disease period; risk factors for FC recurrence, age at first FC, family history of FC, body temperature when FC occurred (≥39 °C vs. <39 °C), time passed between the onset of fever and convulsion occurrence; EEG findings and the presence of prophylaxis of FC were registered according to the children's records.

Based on the previously defined departmental FC recurrence risk factors, we evaluated the following four predominant factors as follows: first convulsion before the age of one year, family history of FC, FC occurrence with body temperature <39 °C via rectal measurement, and FC onset within the first hours of fever onset (1).

The ratio of initiating prophylaxis for FC, the FC recurrence risk factors, and the demographic characteristics which could be determined at the initiation of the ASM prophylaxis were compared between the two groups.

Statistical Analysis

The study data was evaluated via the SPSS 22.0 Windows version of the SPSS statistical package (SPSS, Chicago, IL, USA). Variables displaying a parametric distribution were analyzed using the independent t-test, and the results are presented as mean and standard deviation. Variables indicating a non-parametric distribution were compared via the Mann-Whitney U test, and the results are presented as median (minimum-maximum). Categorical variables were analyzed using the chi-squared test and Fisher's exact test, depending on the sample size. The results are given as number and percentage. The level of statistical significance was set at $p<0.05$.

The Ege University Hospital Ethics Committee granted ethics committee approval (project no: 22-6.1T/34, date: 23.06.2020).

Results

Demographics

A total of 272 children were admitted into this study. The male/female ratio was 1.47/1. The mean age of the sample group was 19.9±12.5 (6-110) months. Within the study group, 68.4% had simple FC, and 31.6% had complex FC. Febrile status epilepticus (>30 minutes of seizure duration)

was determined in 16 patients (5.9%). The percentages of family history of FC and epilepsy were 52.6% and 14%, respectively. All children had electroencephalography (EEG). The EEG analyses were normal in 83.5% of the study group (Table I). When the cases were grouped regarding their follow-up periods as either 2007-2008 or 2017-2018, there was no statistical significance found between the two groups in terms of age, sex, seizure type, diagnosis of status epilepticus, family history of FC, or the total number of risk factors for FC recurrence (p>0.05) (Table II). However, there were statistically significant differences between the two group for prophylaxis rate, type and drug used (Table II). The rate of prophylaxis was significantly reduced in the second period (2017-2018).

Prophylaxis with ASM

ASM prophylaxis was initiated for 38.2% (104/272) of all study groups; intermittent and continuous prophylaxis in 28.8% and 71.2% of the children, respectively. The intermittent rectal diazepam prophylaxis rate significantly reduced in the second period (p=0.001) (Table II). Valproic acid was the most preferred drug for prophylaxis in both periods. However, levetiracetam became an alternative drug for prophylaxis (p=0.001).

The ratio of prophylaxis for FC cases was 63.8% (CFC: 38.9% and SFC: 61.1%) in the 2007-2008 period and 22.1% (CFC: 59.4% and SFC: 40.6%) in the 2017-2018 period (Table III). Our ratio of initiating prophylaxis for FC with ASM decreased significantly over the years, and ASM prophylaxis was preferred for CFC cases more than SFC (p<0.01).

Table IV presents the comparison of the two cohorts (2007-2008 versus 2017-2018) on FC prophylaxis regarding their follow-up periods. The mean number of total seizures increased from 2.8±1.13 to 3.4±2 for SFC (p=0.254) and from 1.9±0.24 to 3.1±0.31 for CFC (p<0.05) in the second period. Children with SFC on ASM prophylaxis had more normal EEGs in 2007-2008 when compared to the period of 2017-2018. However, there was no significant EEG difference between the two periods of those children with CFC on ASM.

Risk factors analysis for prophylaxis

The impact of FC recurrence risk factors for the initiation of prophylaxis was compared for the two periods. In the second period (2017-2018), the number of risk factors was significantly higher in those children who did not initiate ASM prophylaxis for complex FC (p=0.028) (Table V).

Table I. Demographic data of the study cohort

Follow-up period, n (%)	2007-2008	105 (38.6)
	2017-2018	167 (61.4)
Age at first seizure, month (mean ± SD)		19.9±12.5
Gender, n (%)	Female	110 (40.4)
	Male	162 (59.6)
Febrile convulsions type, n (%)	Simple	186 (68.3)
	Complex	86 (31.4)
Presence of febrile status epilepticus, n (%)		16 (5.9)
Recurrence risk factors	First convulsion before the age of one year	83 (30.5)
	Family history of febrile convulsion	143 (52.6)
	Febrile convulsion occurrence with body temperature <39 ºC	28 (10.3)
	Febrile convulsion onset within the first hours of fever onset	37 (9.9)
Electroencephalography	Normal	227 (83.5)
	Focal intermittent slow waves	4 (1.5)
	Paroxysmal epileptiform discharges	35 (12.8)
	Generalized epileptiform discharges	6 (2.2)
Prophylaxis rate, n (%)		104 (38.2)
Prophylaxis type, n (%)	Intermittent (rectal diazepam)	30 (28.8)
	Continuous	74 (71.2)
Seizure after prophylaxis, n (%)		20 (19.2)

Table II. Demographic data comparison of the two study groups with febrile convulsions (n=272)				
		Follow-up period		
		I: 2007-2008 (n=105)	**II: 2017-2018 (n=167)**	**p-value**
Age at first seizure, month (mean ± SD)		20.76±11.6	19.5±13.04	0.561*
Gender, n (%)	Female	41 (39)	69 (41.3)	0.826$^{\Delta}$
	Male	64 (61)	98 (58.6)	
Febrile convulsions type, n (%)	Simple	73 (69.5)	113 (67.6)	0.685$^{\Delta}$
	Complex	32 (30.5)	54 (32.4)	
Presence of febrile status epilepticus, n (%)		6 (5.7)	10 (6)	0.901$^{\Delta}$
Family history of febrile seizure, n (%)		50 (47.1)	93 (55.6)	0.154$^{\Delta}$
Recurrence risk factors	None	16 (15.2)	16 (9.6)	0.086$^{\Delta}$
	1-2 risk	79 (75.3)	124 (74.2)	
	3 risks	10 (9.5)	27 (16.2)	
Prophylaxis rate; n (%)		67 (63.8)	37 (22.1)	**0.001**$^{\Delta}$
Prophylaxis type, n (%)	Intermittent (rectal diazepam)	26 (38.8)	4 (10.8)	**0.001**$^{+}$
	Continuous	41 (61.1)	33 (89.1)	
Drug used for continuous prophylaxis, n (%)	Phenobarbital	5 (12.2)	5 (15.2)	**0.001**$^{\Delta}$
	Valproic acid	36 (87.8)	19 (57.6)	
	Levetiracetam	0	9 (27.2)	

*Independent t-test, $^{\Delta}$Chi-squared test, +Fisher's exact test

Table III. Prophylaxis of febrile convulsions				
Follow-up period	**Febrile convulsion type**	**Prophylaxis (+) n, (%)**	**Prophylaxis (-) n, (%)**	**p-value**
I: 2007-2008 (n=105)	Simple Complex Total	41 (61.1) 26 (38.9) 67 (63.8)	31 (81.5) 7 (18.5) 38 (36.1)	**0.003**$^{\Delta}$
II: 2017-2018 (n=167)	Simple Complex Total	15 (40.6) 22 (59.4) 37 (22.1)	99 (76.2) 31 (23.8) 130 (77.9)	**0.004**$^{\Delta}$

$^{\Delta}$Chi-squared test

Discussion

In recent years, prophylaxis of FC in children is not preferred because of the adverse effects of the drugs and the benign nature of the seizures (2). The most rational use of prophylactic treatment in children with FC is to prevent prolonged seizures. In this study, we defined two secular trends regarding the prophylaxis of FC in children: (1) a significantly reduced rate of FC prophylaxis (22.1%) and (2) no significant impact of recurrence risk factors on the initiation of prophylaxis in complex FC in the recent period.

Before 2008, the recommendation for the initiation of prophylaxis for FS was as follows:

• If there was no risk factor for FC recurrence, the presence of three seizures for boys and the presence of two seizures for girls,

• If there was only one risk factor, the presence of two seizures for either sex was an indication for prophylaxis.

• If there were two or more risk factors, immediate prophylaxis was recommended.

Since 2008, the American Academy of Pediatrics has not recommended prophylaxis for SFC, regardless of risk factors and the number of FC recurrences (4). The Japanese Society of Pediatric Neurology (2015) recommended

Table IV. Demographic data comparison of the two groups on febrile convulsion prophylaxis (n=104/272, 38.3%)

		Simple febrile convulsion		p-value	Complex febrile convulsion		p-value
Follow-up years		**I: 2007-2008**	**II: 2017-2018**		**I: 2007-2008**	**II: 2017-2018**	
Gender n, (%)	Male Female	27 (65.8) 14 (34.2)	10 (66.6) 5 (33.4)	0.609$^{\Delta}$	19 (60.2) 7 (39.8)	11 (50) 11 (50)	0.100$^{\Delta}$
Number of seizures		2.8±1.13	3.4±2	0.254*	1.9±0.24	3.1±0.31	**0.04***
Age at first febrile seizure (month)		16±3.42	14 ±9.48	0.867*	21±2.7	14.6±1.8	**0.047***
Electroencephalography n, (%)	Normal Abnormal	31 (75.7) 10 (24.3)	7 (46.6) 8 (53.4)	**0.040**$^{\Delta}$	14 (42.3) 11 (53.8)	14 (27.3) 8 (72.7)	0.595$^{\Delta}$

*Independent t-test, $^{\Delta}$Chi-squared test

Table V. The impact of recurrence risk factors on the initiation of febrile convulsion prophylaxis

			Follow-up periods		p-value
			I: 2007-2008	**II: 2017-2018**	
Simple febrile convulsion n, (%)	**Prophylaxis (+)**	No-risk 1-2 risks 3 risks	4 (9.8) 25 (60.9) 12 (29.3)	1 (6.7) 10 (66.7) 4 (26.7)	0.91
	Prophylaxis (-)	No-risk 1-2 risks 3 risks	3 (9.7) 22 (71) 6 (19.4)	17 (17.1) 75 (75.8) 7 (7.1)	0.10
Complex febrile convulsion n, (%)	**Prophylaxis (+)**	No-risk 1-2 risks 3 risks	2 (7.7) 19 (73.1) 5 (14.2)	0 20 (90.9) 2 (9.1)	0.48
	Prophylaxis (-)	No-risk 1-2 risks 3 risks	3 (42.9) 4 (57.1) 0	2 (6.5) 28 (90.3) 1 (3.2)	**0.028**

$^{\Delta}$Chi-squared test

restricted guidelines for the prophylaxis of FC in children (5). Today, there is no clear consensus on the initiation of FC prophylaxis.

In this study, we determined a significantly reduced rate (22.1%) of prophylaxis in children with FC in the last decade (2017-2018). In a study conducted at the same time as our study (2017-2018), it was reported that 43.3% of all children used intermittent or continuous prophylaxis for FC, with 24.7% for SFC and 89.1% for CFC. Another study conducted between 2002 and 2006 revealed the prophylaxis rate to be 64.8%, similar to the rate (63.8%) of the 2007-2008 period in our study (7-11).

Risk factors for FC recurrence have been reported in previous studies (1,2,7). However, there has been no clinical study evaluating the impact of risk recurrence factors for initiating ASM prophylaxis in children with simple or complex FC. Following a single simple FC, the probability of recurrence generally ranges between 30 and 40%. In the presence of one or two risk variables, the recurrence frequency rises to 25–50% from 10% in those children without risk factors. If there are three or more risk factors, it may rise even further to 50-100% (8). In a prospective study, a two-year risk of recurrence in children with a single febrile seizure was reported at 14%, 24%, 32%, 63%, and 75% in the presence of 0, 1, 2, 3, or 4 risk factors, respectively. No difference was reported in the risk of recurrence based on whether the initial febrile seizure was simple or complex (9). The prognosis of a child with FC who was neurologically normal prior to their first FC is unaffected by its recurrence (10). Therefore, the need for any prophylaxis for FC should be carefully considered on a case-by-case basis. In the present study, we found no significant impact of recurrence risk factors on the initiation of prophylaxis in both types of FC. We also determined that the mean number of seizure recurrences without prophylaxis increased in simple and complex FC sample groups, and that prophylaxis decisions were made independently of the risk factors for FC recurrence.

Two meta-analyses revealed that intermittent oral or rectal diazepam, phenobarbital, phenytoin sodium, sodium valproate, ibuprofen, diclofenac sodium, or paracetamol do not prevent recurrent FC (12,13). In subsequent meta-analyses, a significant reduction of recurrent febrile seizures with intermittent diazepam and phenobarbital versus placebo or no treatment was reported (6,14). However, in the meta-analysis presented in 2017 and 2021, Cochrane drew attention to the drugs' adverse effects, even if prophylaxis prevents seizure recurrence. At the end of their meta-analysis, they made the following suggestions: Children with febrile seizures are not recommended to receive continuous or intermittent anti-seizure or antipyretic treatment. Parents and families should be provided with contact information for medical services, as well as information about recurrence, first aid, and the phenomena's benign nature (6,15). If prophylactic treatment is to be initiated, intermittent rectal diazepam treatment has been highlighted as the first step in the Japanese Society of Child Neurology recommendations, and recent reviews (5,16). Conversely, our study's rate of intermittent prophylaxis decreased in the second period of the study cohort. In addition, in the 2021 Cochrane meta-analysis, it was stated that intermittent oral levetiracetam and clobazam treatment reduced the frequency of FC compared to a placebo (15).

There is no proof that EEG findings obtained at the presentation of a straightforward FC or during the next month may be used to predict the likelihood of either a future FC recurrence or the onset of epilepsy within the next two years. Furthermore, there is no proof that any interventions based on the EEG results will change the child's prognosis of developing epilepsy in later life (10). For this reason, EEG is not recommended for children with normal neuromotor development or simple FC. However, if EEG is planned, it should be carried out 7-14 days after FC to eliminate the possibility of false evaluation which may be caused by infection or fever (17,18). On the other hand, after a CFS, a routine EEG should be considered. An EEG recorded on the day of or soon after the seizure may help to clarify whether there is any doubt that the event was a seizure. Otherwise, there is conflicting information about how well the detection time and characteristics of EEG abnormalities may predict future febrile or afebrile seizures. However, it has been suggested that getting an EEG within seven days may enhance the chances of identifying abnormalities. Furthermore, there has been no conclusive proof that specific EEG abnormalities might indicate the likelihood of developing epilepsy; instead, the persistence of EEG abnormalities is regarded to have a more substantial predictive power (19). In a retrospective analysis of 113 cases with their first FC, EEG findings were grouped as pseudo-petit mal discharge, epileptiform discharge, and normal. It was reported that FC recurrence risk doubles with an abnormal EEG (20). In another study from Turkey, EEGs were performed on 22.5% of FC cases (10.7% of SFC and 75% of CFC). Thirty-five percent of the first EEG results obtained were normal, while 98.1% of the last EEG results were normal. They concluded that EEG could not be used as a guide for the follow-up or treatment of FC (2). Although we did not consider EEG abnormalities while initiating prophylaxis for FC, our retrospectively analyzed data showed that, in the 2017-2018 period, children with a history of SFC tended to have a higher ratio of abnormal EEG findings. Nevertheless, EEG abnormalities in simple FC had little influence on our decision to initiate FC prophylaxis with ASM.

In our study, the male/female ratio was 1.47, similar to other studies carried out in our clinic and country (1,7). In a study including 1,385 FC cases, 1,245 (89.8 %) were reported as SFC and 140 (10.2%) as CFC. In this study, both children who were followed by the pediatric neurology clinic and those who applied to the emergency care unit were evaluated (21). In another study with a student population, the total percentile of CFC was reported as 18.4% (2). In another study in which only children followed in the pediatric neurology clinic were included, the SFC rate was 71.6%, and the CFC rate was 28.4%, similar to our cohort, as the percentages of simple and complex FC in our study were 68% and 32%, respectively (11).

Study Limitations

The small sample size and absence of a standard departmental protocol to initiate prophylaxis for FC were the main limitations of our study. Additionally, this paper could not evaluate the odds ratio of risk factors which we believed to affect the decision on the initiation of prophylaxis. Also, our study was designed as a retrospective comparative study for two different follow-up periods. We therefore could not perform a comparison of the prophylaxis sub-group in terms of their long-term recurrence ratios and their epilepsy risk ratios.

Conclusion

Prophylaxis for FC has significantly decreased during the previous decade, with a current rate of 21%. Despite the guidelines' recommendations, the rate of prophylaxis with ASM is still high in children with FC. Validated scoring models, including predominant risk factors, are needed to determine those children with FC who require prophylaxis.

Ethics

Ethics Committee Approval: The Ege University Hospital Ethics Committee granted ethics committee approval (project no: 22-6.1T/34, date: 23.06.2020).

Informed Consent: Our study was designed as a retrospective comparative study for two different follow-up periods.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Design: Data Collection or Processing: Analysis or Interpretation: Literature Search: Writing: All authors have contributed equally.

Conflict of Interest: The authors declared that there were no conflicts of interest.

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References

1. Tosun A, Koturoglu G, Serdaroglu G, et al. Ratios of Nine Risk Factors in Children With Recurrent Febrile Seizures. Pediatr Neurol 2010; 43:177-82.
2. Canpolat M, Per H, Gumus H, Elmali F, Kumandas S. Investigating the prevalence of febrile convulsion in Kayseri, Turkey: An assessment of the risk factors for recurrence of febrile convulsion and for development of epilepsy. Seizure 2018; 55:36-47.
3. Committee on Quality Improvement S on FS. Practice Parameter: Long-term Treatment of the Child With Simple Febrile Seizures. Pediatrics 1999; 10:1307-9.
4. Steering Committee on Quality Improvement and Management, Subcommittee on Febrile Seizures American Academy of Pediatrics. Febrile seizures: clinical practice guideline for the long-term management of the child with simple febrile seizures. Pediatrics 2008; 121:1281-6.
5. Natsume J, Hamano Shin-ichiro, Iyoda K, et al. New guidelines for management of febrile seizures in Japan. Brain Dev 2017; 39:2-9.
6. Offringa M, Newton R, Cozijnsen MA, Nevitt SJ. Prophylactic drug management for febrile seizures in children. Cochrane Database Syst Rev 2017; 2:CD003031.
7. Renda R, Yüksel D, Gürer YKY. Evaluation of Patients With Febrile Seizure: Risk Factors, Reccurence, Treatment and Prognosis. Pediatr Emerg Care 2020; 36:173-7.
8. Ursin Knudsen F. Recurrence risk after first febrile seizure and effect of short term diazepam prophylaxis. Arch Dis Child 1985; 60:1045-9.
9. Berg AT, Shinnar S, Darefsky AS, et al. Predictors of recurrent febrile seizures. A prospective cohort study. Arch Pediatr Adolesc Med 1997; 151:371-8.
10. Wanigasinghe J. Management of simple febrile seizures. Sri Lanka J. Child Health 2017; 46:165-71.
11. Kilic B. Clinical Features and Evaluation in Terms of Prophylaxis of Patients With Febrile Seizures. Sisli Etfal Hastan Tip Bul 2019; 53:276-283.
12. Offringa M, Newton R. Prophylactic drug management for febrile seizures in children. Cochrane Database Syst Rev 2012; 4:CD003031.
13. Masuko AH, Castro AA, Santos GR, et al. Intermittent diazepam and continuous phenobarbital to treat recurrence of febrile seizures: a systematic review with meta-analysis. Arq Neuropsiquiatr 2003; 61:897-901.
14. Chen X, Wang J, Su X, et al. Prophylactic treatment of the recurrence of febrile convulsion by different drugs: A meta-analysis. Int J Clin Exp Med 2017; 10:6453-60.
15. Offringa M, Newton R, Nevitt SJ, Vraka K. Prophylactic drug management for febrile seizures in children. Cochrane Database Syst Rev 2021; 6:CD003031.
16. Gupta A. Febrile Seizures. Continuum (Minneapolis, Minn). 2016; 22:51-9.
17. Leung AKC, Hon KL, Leung TNH. Febrile seizures: An overview. Drugs Context 2018; 7:1-12.
18. Canpolat M, Kumandaş S. Febril konvülziyon. Kumandaş S, Canpolat M. Çocukluk Çağı Epilepsileri. Ankara. 1. Baskı Türkiye Klinikleri; 2020. pp. 72-90.
19. Whelan H, Harmelink M, Chou E, et al. Complex febrile seizures-A systematic review. Dis Mon 2017; 63:5-23.
20. Cappellari AM, Brizio C, Mazzoni MB, et al. Predictive value of EEG for febrile seizure recurrence. Brain Dev 2018; 40:311-5.
21. Özaydin E, Yaşar MZ, Güven A, Değerliyurt A, Vidinlisan S, Köse G. The clinical characteristics and risk factors of 1385 cases wıth febrile convulsion. Turkish J Pediatr Dis 2011; 5:11-8.