

## Identification of clinical features and prognosis of children hospitalized with first afebrile seizure: A single-center study

İlk afebril konvülsiyon nedeniyle hastaneye yatırılan olguların klinik özelliklerinin ve prognozlarının araştırılması: Tek merkezli bir araştırma

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### Abstract

**Background:** It is aimed to evaluate the risk of recurrence of the first afebrile seizure according to the use of antiepileptics.

**Materials and Methods:** One year follow up of children hospitalized with first afebrile convulsion were investigated retrospectively. Age, gender, history, neurological findings, electroencephalogram, neuroradiological imaging were evaluated for seizure recurrence considering antiepileptic treatment use.

**Results:** Antiepileptic was started in 45.2% (33 out of 73) of patients. Seizure recurrence was 39.4% (13 out of 33) under treatment. No recurrence was observed in 92.5% (37 out of 40) of untreated patients (p=0.001).

**Conclusions:** After the first afebrile seizure, antiepileptic treatment could lower but could not remove recurrence risk totally. Seizure did not recur in most of children followed-up without treatment, therefore decision to start antiepileptic after the first unprovoked seizure should be carefully evaluated.

**Keywords:** Seizure; Anticonvulsant; Electroencephalogram; Neuroimaging

### ÖZ

**Amaç:** İlk afebril nöbetin tekrarlama riskinin, antiepileptik kullanımına göre değerlendirilmesi amaçlanmıştır.

**Gereç ve Yöntemler:** İlk afebril konvülsiyon nedeniyle hastaneye yatırılan çocukların bir yıllık takipleri retrospektif incelendi. Yaş, cinsiyet, özgeçmiş, nörolojik bulgular, elektroensefalogram, nöroradyolojik görüntüleme, nöbet tekrarı açısından antiepileptik tedavi kullanımı dikkate alınarak değerlendirildi.

**Bulgular:** Hastaların %45,2'sine (33/73) antiepileptik başlandı. Tedavi altında nöbet tekrarı %39,4 (13/33) idi. Tedavi almayan hastaların %92,5'inde (37/40) nöbet tekrarı görülmedi (p=0.001).

**Sonuç:** İlk afebril konvülsiyon sonrası, verilen tedavinin nöbet nüksünü azalttığı ama tamamen ortadan kaldırmadığı görülmüştür. İlk afebril konvülsiyon sonrası antiepileptik tedavi verilmeden izlenen olguların çoğunda nöbet tekrarlamamıştır, bu nedenle ilk afebril konvülsiyon sonrası antiepileptik başlanma kararı dikkatli değerlendirilmelidir.

**Anahtar Kelimeler:** Konvülsiyon; Antiepileptik; Elektroensefalogram; Nörogörüntüleme

### Highlights

- After the first seizure of a child, if the recurrence risk is high, antiepileptic treatment is started.
- If the recurrence risk is not high, seizure recurrence may not occur in the followed up without antiepileptic treatment.
- The decision to initiate treatment after the first seizure should be individualized according to risk of recurrence.

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## Introduction

In children, the prevalence of seizures is 4-10%, and seizures are 1% of pediatric emergency admissions (1). Brain infections, head injury, metabolic disorders may trigger seizures, but in the unprovoked seizure an immediate, clearly documented underlying cause could not be identified (1-4).

The most important and yet difficult point in the approach to the first unprovoked seizure, is to predict whether the seizure will recur (5-7). Epilepsy diagnosis is made according to the recurrence risk of the seizure, and this risk of recurrence is crucial for initiating antiepileptic therapy (AET) at the first seizure (1,4-6). The recurrence of first seizure is the most common in the following 1-2 years (14–65%) (5).

Focal type of seizure, head injury history, parental consanguinity, epilepsy diagnosis in family (genetic inheritance), specific findings on neurologic examination, epileptic electroencephalogram (EEG) and pathological cranial (CR) magnetic resonance imaging (MRI) evaluations are high risk factors for seizure recurrence (1-3,6-9). If EEG and CR images are normal, AET is debatable and usually AET is initiated after a second attack or at the first attack with the presence of high recurrence risk (3,10).

The guidelines underline that if a comprehensive evaluation of the recurrence risks of first seizure is desired, it should be taken into consideration that the most important determinant is treatment (6). There are few studies in the literature investigating whether starting AET at the first seizure affects recurrence (4,11).

We undertook a study with pediatric first afebrile seizure and aimed to assess the recurrence risk. While evaluating the risk factors of seizure recurrence, we wanted to research the effect of treatment on recurrence. We examined the patients with their determinants such as descriptive data, EEG and neuroimaging for seizure recurrence in 1 year follow-up by comparing whether they were under treatment or not. Our study is one of the few studies that conducted to determine whether recurrence is influenced by treatment.

## Materials and Methods

### Characteristics of Patients

This was a study of children aged 1 month to 16 years who were hospitalized for a first afebrile seizure between January 2009 to December 2009 at the pediatric emergency department of University of Health Sciences Turkey Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital. Syncope, chorea, tic, tremor, migraine and febrile seizures were excluded. Status epilepticus was included.

### Data collection

This study was designed as a retrospective study. The data were collected from patient files. Characteristics like age, gender, previous history (febrile convulsion, mental motor retardation), family histories (consanguineous marriage, febrile convulsion, epilepsy), neurologic examination findings at emergency department were noted. Results of EEG taken during hospitalization at emergency department (early EEG) were obtained. The decision to start or not to start AET at discharge from hospital was stated. Children were separated in two different categories according to the decision whether to start AET or not. They were followed for 1 year at pediatric neurology outpatient clinic for seizure recurrence. Late EEG and CR MRI results taken during follow-up in the pediatric neurology outpatient clinic after discharge were obtained. The relationships between patients' descriptive data, AET decision at discharge from hospital, and seizure recurrence at 1 year follow-up were investigated.

### Ethics committee approval

This article is derived from thesis published in 2011 and ethics committee approval was obtained from Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital Ethics Committee (Number: B-10-4-ISM-4-35-65-72 Date:28.04.2011). This study complied with the principles stated in the Declaration of Helsinki that developed by the World Medical Association. Since this study was retrospective, informed patient consent statement was not collected.

### Statistical Analysis

Data were statistically evaluated. Descriptive findings were presented as numbers, percentages for categorical variables. Chi-square test and Fisher's exact test were used for assessing associations between variables of categorical data. A p-value less than 0.05 ( $\leq 0.05$ ) was considered statistically significant.

## Results

Our study conducted with 73 patients. At discharge from hospital AET was initiated in 45.2% (33 out of 73) of patients. At 1-year follow-up seizure recurrence was observed in 39.4% (13 out of 33) of the treated group and no recurrence was observed in 92.5% (37 out of 40) of the untreated group. The relationship between the decision to start AET at discharge and seizure recurrence was found to be statistically significant ( $p=0.001$ ) (Table 1).

There were 32 (43.8%) girls and 41 (56.2%) boys. The median age was 34.7 months. History of mental motor retardation was found in 2 (2.7%) patients. Six (8.2%) patients had complex febrile convulsion history. Seven (9.6%) consanguineous marriages, 10 (13.7%) febrile seizures, 11 (15.1%) epilepsy were detected in family history (Table 2). Nineteen (26%) patients had neurological deficits (Table 3).

Early EEG was performed during hospitalization in 49 (67.1%) patients and 40.8% (20 out of 49) were pathological. Antiepileptic was initiated in 60% (12 out of 20) of patients with pathological EEG. In patients with pathological early EEG, seizure recurrence was 33.3% (4 out of 12) under treatment and 12.5% (1 out of 8) without treatment (Table 4). Late EEG was obtained in 64 (87.7%) patients after discharge at neurology outpatient clinic and 40.6% (26 out of 64) were pathological. Antiepileptic was initiated in 57.7% (15 out of 26) of patients with pathological EEG. In patients with pathological late EEG, seizure recurrence was 46.7% (7 out of 15) under treatment and no recurrence was observed without treatment (Table 4).

CR MRI was performed in 57 (78.1%) patients after discharge and 19.3% (11 out of 57) were pathological. Antiepileptic was initiated in 45.5% (5 out of 11) of patients with pathological CR MRI. In patients with pathological CR MRI, seizure recurrence was 60% (3 out of 5) under treatment and 16.7% (1 out of 6) without treatment (Table 4).

**Table 1. Decision to start antiepileptic therapy at discharge from hospital and seizure recurrence**

Anti-epileptic treatment	Total patients	Seizure recurrence		P
		Yes	No	
Started, n (%)	33(45.2)	13(39.4)	20(60.6)	0.001
Not started, n (%)	40(54.8)	3(7.5)	37(92.5)	

**Table 2. Patient characteristics, antiepileptic treatment initiation at discharge and seizure recurrence**

Category	Total	Anti-epileptic initiation	Total	Seizure recurrence	
				Yes	No
<b>Gender</b>	32(43.8)	Yes	16(50)	6(37.5)	10(62.5)
Girl, n (%)		No	16(50)	1(6.3)	15(93.7)
Boy, n (%)	41(56.2)	Yes	17(41.5)	7(41.2)	10(58.8)
		No	24(58.5)	2(8.3)	22(91.7)
Mean age (months)	34.7	Yes		36.1	33.8
		No		33.3	34.9
<b>History</b>	2(2.7)	Yes	2(100)	1(50)	1(50)
Mental motor retardation, n (%)		No	00(0)	00(0)	00(0)
Febrile convulsion, n (%)	6(8.2)	Yes	5(83.3)	2(40)	3(60)
		No	1(16.7)	00(0)	1(100)
<b>Family History</b>	7(9.6)	Yes	4(57.1)	2(50)	2(50)
Consanguineous marriages, n (%)		No	3(42.9)	0(0)	3(100)
Febrile convulsion, n (%)	10(13.7)	Yes	8(80)	4(50)	4(50)
		No	2(20)	0(0)	2(100)
Epilepsy, n (%)	11(15.1)	Yes	6(54.5)	4(66.7)	2(33.3)
		No	5(45.5)	0(0)	5(100)

**Table 3. Decision to start antiepileptic therapy at discharge from hospital and seizure recurrence in patients with neurologic deficit**

Antiepileptic therapy	Patients with neurologic deficit	Seizure recurrence	
		Yes	No
Started, n (%)	13(68.4)	5(28.5)	8(61.5)
Not started, n (%)	6(31.6)	0(0)	6(100)

**Table 4. Results of EEG taken both during hospitalization (Early EEG) and after discharge (Late EEG), CR MRI taken after discharge, decision to start antiepileptic therapy at discharge from hospital and seizure recurrence**

Investigation	Results	Patients	Anti-epileptic treatment	Patients	Seizure recurrence	
					Yes	No
Early EEG	Normal, n (%)	29(59.2)	Yes	8(27.6)	4(50)	4(50)
			No	21 (72.4)	1(4.8)	20(95.2)
	Pathologic, n (%)	20(40.8)	Yes	12(60)	4(33.3)	8(66.7)
			No	8(40)	1(12.5)	7(87.5)
Late EEG	Normal, n (%)	38(59.4)	Yes	16(42.1)	5(31.2)	11(68.8)
			No	22(57.9)	1(4.5)	21(95.5)
	Pathologic, n (%)	26(40.6)	Yes	15(57.7)	7(46.7)	8(53.3)
			No	11(42.3)	0(0)	11(100)
CR MRI	Normal, n (%)	46(80.7)	Yes	28(60.9)	10(35.7)	18(64.3)
			No	18(39.1)	2(11.1)	16(88.9)
	Pathologic, n (%)	11(19.3)	Yes	5(45.5)	3(60)	2(40)
			No	6(54.5)	1(16.7)	5(83.3)

CR: Cranial, EEG: Electroencephalogram, MRI: Magnetic resonance imaging

## Discussion

### Treatment

Our study is one of the few studies in the pediatric setting that conducted with the first unprovoked seizure and aimed to provide data on the risk of recurrence under the determinant of antiepileptic treatment use status.

Seizure recurrence rates in 2 years were 36% in prospective, 47% in retrospective research of a meta-analytic review which examined 16 articles (12). In a study that observed 208 children, seizure recurrence rates were found to be 14% in 1 year, 29% in 3 years, and 34% in 5 years (13).

In 397 patients with first unprovoked seizure aged 2 to 70 years, recurrence rate in 24 months follow-up was 25% in patients that randomized to immediate treatment group who started treatment within 7 days and 51% in patients that randomized to delayed treatment group who treated after recurrence (14). This trial confirmed that immediate treatment of to the first unprovoked seizure decreases recurrence (14).

In another trial that assess the treatment that initiated for the first seizure, the recurrence rate was 24% in immediate treatment group and 42% in delayed treatment group (15). One year seizure free interval was estimated 87% versus 83%, and 2 years seizure free interval was estimated 68% versus 60%, in treated and untreated patients respectively (15). In untreated group, 50% of the patients, the seizure never recurred (15). This study concluded that antiepileptic treatment reduces recurrence risk after first unprovoked seizure, however was not effective at long-term follow-up (15).

In a randomized controlled trial, recurrence rate was 32%, 42% and 46% in immediate treatment group and 39%, 51%, and 52% in deferred treatment group, in 2, 5 and 8 years follow-up respectively (11). Two years remissions were 69%, 92%, 95% in immediately treated patients and 61%, 92%, 96% in patients whose

treatment were delayed, at 2, 5, 8 years follow-up, respectively (11). Within 2 years, immediate treatment group achieved 2-years remission at a higher rate than the delayed group, so immediate treatment extended seizure-free period in short-term, but by 5 and 8 years follow-up, treatment did not affect 2 years remission (11).

In updated Cochrane review which included 6 studies, immediate treatment group is compared with control group that included deferred treatment, placebo and no treatment (16). Immediate treatment lowers recurrence rate in following 12 months but this decline decreases at 2 and 5 years (16). At long term follow-up, treatment had no effect on time to 2 or 5 years remission (16). As a result, considering the short and long-term prognosis, the treatment decision should be individualized by taking into account the clinical characteristics of the patient (7,10,16).

In our study, treatment was statistically significant factor for seizure recurrence that in treated children recurrence rate was 39.4% while non-recurrence rate was 60.6% and in untreated children recurrence rate was 7.5% though non-recurrence rate was 92.5% ( $p=0,001$ ) (Table 1). Under AET, recurrence risk was lower than non-recurrence risk (39.4% vs. 60.6%) which concludes that treatment could lower recurrence risk but could not completely eliminate the recurrence risk entirely (4,10).

Seizure recurrence rate was 45% in 815 children followed for 3 years without AET (17). Seizure recurrence rates in 283 children, 84% of whom did not receive AET, were 26%, 36%, 40% and 42% in 12, 24, 36 and 48 months, respectively (18). The study concluded that AET initiation did not alter recurrence risk and ultimately, noted that seizure could not recur even in follow-up without AET (18). In our study no recurrence was observed in the majority (92.5%) of children who were followed up without treatment for 1 year. Seizure may not recur in follow up without AET, so the decision of AET initiation for the first unprovoked seizure should definitely be questioned (7,15,18). The decision to initiate AET should be individualized (4,7,10,16). If the risk of recurrence is expected to be high after the first seizure, epilepsy is considered in the diagnosis and treatment is started without wasting time to protect the central nervous system from the damage of subsequent seizures (4,5,10,19).

## EEG

Guidelines suggest that EEG is crucial in the assessment of first epileptic seizure for determining the risk of recurrence, to identify underlying epilepsy syndrome and to subclassify seizure type (3,5,7-10,20-24). The examination time of EEG is another curious question because, the timing of EEG may affect the accuracy of EEG in demonstrating epileptic activity (5,7,8,22,24). If the EEG is taken in the early period, the chance of catching sight of pathologic waves increases (5,10,19,22). But, it should be kept in mind that EEG demonstrates exaggerated discharges in the very early time period and after this higher excitability interval, excessive signaling activities will ease (5). Therefore, care should be taken in early EEG evaluation that early abnormal activities can be temporary (5).

In 169 children, epileptiform discharge was confirmed in 65.2% of EEGs performed within 12 hours and in 28.1% of the EEGs taken afterwards ( $p< 0.001$ ) (22). In 300 patients 59 (20%) of whom children, epileptiform changes were higher in EEGs taken within 24 hours compared to the next timeframe (51% vs. 34%) (19). In another study, no statistical difference was found in terms of pathologic epileptic activities between EEGs performed urgently in 48 hours (37%) and EEGs delayed after 48 hours (40%) (8). In a study with 108 children, EEG was taken in the first 96 hours and 63% of them were abnormal (24). EEG abnormality was noted as a risk factor in terms of recurrence (24). Examination time of EEG was classified in 7 groups and each period was analyzed for EEG abnormalities, though no correlation was present (24).

In a study, according to EEG findings taken in the emergency room, 27.8% of 90 children who had new-onset seizures were diagnosed with epilepsy (21). A review evaluated the impact of EEG test on confirming the diagnosis of epilepsy and children analysis indicated 57.8% sensitivity, 69.6% specificity (23). The seizure recurrence rate and so epilepsy probability in children with abnormal EEG was 66%, while in children with normal EEG was 38%. (23). But, antiepileptic treatment factor that would affect the result of EEG test was not evaluated (23).

Our pathological EEG rates were 40.8% in early and 40.6% in late EEG. In pathological EEGs, antiepileptic treatment was started in 60% of the early recordings and 57.7% of the late recordings. Of pathological EEG, seizure recurrence rates were 33.3% and 46.7% under treatment, while they were 12.5% and 0% in follow-up without treatment (in early and late results, respectively) (Table 4).

## Neuroimaging

Guidelines highlight neuroimaging monitoring after the first unprovoked seizure if essential, and MRI is the recommended procedure since lesions may be overlooked on CT and also MRI produces clearer, more detailed images compared to CT scan (4,7,9,10,25,26). MRI is the most accepted assessment that help to determine the risk of recurrence of the first epileptic seizure and classify epilepsy subtypes and discern patients in need of AET (9,20,25,26).

In a retrospective study with 96 children who had their first afebrile seizure, 92 CT and 4 MRI neuroimaging were performed within 48 hours after the seizure and 33% (32 out of 96) of them were pathological (27). Seizures recurrence was observed in 19% (6 out of 32) of pathological results (27).

A prospective study with 411 children of whom 218 (53%) had taken neuroimaging, seizure recurrence rate was 78% (35 out of 45) in patients with pathological results and 56% (97 out of 173) with normal results (26).

In the neuroimaging guide which includes 18 prospective and retrospective studies, it is stated that approximately 50% of neuroimaging findings were abnormal in the localized new-onset seizure, 15-20% were effective in etiological differentiation, and 2-4% has shown need of urgent medical intervention (25).

We had taken 57 CR MRIs and 19.3% of them were pathological. Antiepileptic was initiated in 45.5% of pathological scans. In patients with pathological scans, seizure recurrence rate was 60% under treatment and 16.7% without treatment (Table 4).

### Study limitations

The biggest limitation of current study was our limited number of patients. Our insufficient sample size prevented the data distributions from reaching statistical significance. Second limitation of our study was its retrospective nature and could not extract more descriptive data. Third, this research was carried out in a single hospital located in the western region of Turkiye which may limit its national generalizability, and it is clear that large multicenter series are needed for useful results that broadly reflect national data. Finally, considering that our study is a 1-year observation, obviously long term observational studies are requisite to interpret seizure recurrence and treatment decision.

### Conclusions

In our study, children who had their first unprovoked seizure were evaluated for seizure recurrence according to whether they received antiepileptic treatment or not. It is generally accepted that treatment should be initiated in patients with a high risk of recurrence, because it was thought to be the first seizure of epilepsy. Careful consideration should be given when immediately starting antiepileptic treatment after the first afebrile seizure in children. It should be kept in mind that seizure recurrence may not occur during follow-up without treatment after the first unprovoked seizure, because we found that in most of our untreated children seizure did not recur in 1 year follow-up.

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