PORTUGUESE JOURNAL OF PEDIATRICS

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ORIGINAL ARTICLE

Risk factors affecting the first unprovoked seizure recurrence in childhood: A retrospective cohort study

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Abstract

Introduction and Objectives: The decision of antiepileptic drug (AED) prescription following the first unprovoked seizure should be made considering the side-effects of the drug and the recurrence risk of seizure. The aim of this study was to define the seizure recurrence rate and risk factors among children with unprovoked seizures for the first time. **Methods:** A total of 102 paediatric patients who were followed up for a minimum of two years after their admission to the emergency department with first unprovoked seizure were evaluated retrospectively. **Results:** A total of 102 patients were included in this study. The vast majority of the patients were awake during the seizure (80.4%) and had a generalized type of seizure (91.2%). The median duration of patient follow-up was 36 months. The seizure recurred in 22 (21.6%) of the patients. The median time of seizure recurrence was three months (min-max: 2 days-3 years). Seizure recurrence was significantly higher in patients who had their first seizure between 7 and 11 years of age, during sleep ($p = 0.009$, $p = 0.02^5$, respectively). Seizure recurrence was higher among patients with a seizure duration longer than 5 minutes ($p = 0.008$). **Conclusion:** Due to the significant risk of seizure recurrence, patients with unprovoked seizures who experience seizures in sleep and last longer than 5 minutes should undergo a more thorough evaluation before considering antiepileptic drugs.

Key words: Antiepileptic drug. Children. Recurrence. Unprovoked seizure.

Fatores de risco que afetam a primeira recorrência de convulsão não provocada na infância

Resumo

Introdução e Objetivos: A decisão de prescrição do fármaco antiepileptics (AE) após a primeira crise não provocada deve ser tomada considerando os efeitos colaterais do medicamento e o risco de recorrência da crise convulsiva. O objetivo deste estudo foi definir a taxa de recorrência de crises e os fatores de risco entre crianças com crises não provocadas pela primeira vez. **Métodos:** Um total de 102 doentes pediátricos que foram acompanhados por um período mínimo de dois anos após sua admissão no pronto-socorro devido à primeira crise convulsiva não provocada foram avaliados retrospectivamente. **Resultados:** Um total de 102 doentes foram incluídos neste estudo. A grande maioria dos doentes estava acordada durante a crise (80,4%) e apresentou crise generalizada (91,2%). A duração média do acompanhamento dos doentes foi de 36 meses. A convulsão recorreu em 22 (21,6%) dos doentes. O tempo médio de recorrência das crises foi de três meses (min-max: 2 dias-3 anos). A recorrência das crises foi significativamente maior nos doentes que tiveram a primeira crise entre 7 e 11 anos de idade, durante o sono ($p = 0,009$, $p = 0,025$, respectivamente). A recorrência das crises foi maior entre os doentes com duração das crises superior a 5 minutos ($p = 0,008$). **Conclusão:** Devido ao risco significativo de recorrência de crises

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Received: 19-02-2025
Accepted: 30-03-2026
https://pjp.spp.pt

Available online: 09-06-52026
Port J Pediatr. (Ahead of print)
DOI: 10.24875/PJP.25000014

convulsivas, doentes com crises não provocadas que apresentam crises durante o sono e duram mais de 5 minutos devem ser submetidos a uma avaliação mais completa antes de considerar o medicamento antiepiléptico.

Palavras-chave: Droga antiepiléptica. Crianças. Recorrência. Crise não provocada.

Key Points

What is known:
- The first seizure may be an isolated one, or it may be an early finding of epilepsy.
- Recurrence risk factors and electroencephalography (EEG) findings are important for the diagnosis of epilepsy.
- The decision of antiepileptic drug (AED) prescription following the first unprovoked seizure should be made considering the side-effects of the drug and the recurrence risk of seizure.

What is added:
- It is difficult to predict which children with normal EEG findings will experience recurrent seizures after their first unprovoked seizure.
- Seizures occurring during sleep and seizures lasting longer than 5 minutes are the most important risk factors.

Introduction

Seizure is an abnormal paroxysmal neuronal discharge manifested clinically with motor, sensory, autonomic, or behavioural impairments.[1] Epilepsy on the other hand, is a paroxysmal situation characterized with repeated seizures separated by interictal periods longer than 24 hours.[2] Approximately 10% of the population experience seizures at some time in their lifetime, and among these, the seizures recur in less than 50%.[3] The first seizure may be an isolated one, or it may be an early finding of epilepsy.

Recurrence risk factors and electroencephalography (EEG) findings are important for the diagnosis of epilepsy. The decision of antiepileptic drug (AED) prescription following the first unprovoked seizure should be made considering the side-effects of the drug and the recurrence risk of seizure.[4]

The aim of this retrospective study was to define the seizure recurrence rate and seizure recurrence risk factors among children who had presented to the paediatric neurology clinics or the paediatric emergency unit with unprovoked seizure for the first time.

Methods

In this retrospective cohort study, patients who presented to paediatric neurology outpatient clinics or paediatric emergency departments with complaints of unprovoked seizures for the first time between June 1, 2015, and June 1, 2019, were evaluated. Seizures without an identifiable event that could explain the seizure, such as fever, trauma, or infection, were considered unprovoked. Previously healthy children between 1 and 16 years old who presented with their first unprovoked afebrile seizure and no epileptiform abnormality detected on EEG, and who were followed up for a minimum of two years. were included after first seizure. The patients with underlying chronic neurological diseases, genetic or metabolic disorders, or provoked seizures caused by fever, trauma, or infection, and who had epileptiform abnormalities or epileptiform discharges, such as spikes, sharp waves, and spike-and-wave discharges in EEG were excluded from the study. Age and gender of the patients, seizure type, sleep/awakeness situation during seizure, duration of seizure, family history, neuroimaging findings, and seizure recurrence were evaluated. This study protocol was approved by the Institutional Ethics Committee (2011-KAEK-25 2019/08-08).

Statistical analysis

The categorical data were summarized using frequencies and percentages, and the continuous data were summarized using the mean, standard deviation (SD), and/or median. The Chi-square, Fisher's exact, Student's T and the Mann-Whitney U tests were used for the univariate analysis of seizure recurrence. For the multivariate analysis, the Chi-square and the Fisher's exact tests were used. The included multivariate analysis was performed using the possible factors determined in the previous analyses, and the independent predictors of seizure recurrence were evaluated using the logistic regression analysis. The Hosmer-Lemeshow test was used for model compliance. A p level <0,05 was accepted as statistical significance.

Results

Of 102 patients, 52.9% were males while 47.1% were females (male/female ratio 1,12:1). The median

Table 1. Demographic and clinical characteristics of the patients

Characteristics	n	%
Gender		
Male	54	52.9
Female	48	47.1
Age of seizure		
1-6 years	62	60.8
7-11 years	26	25.5
>12 years	14	13.7
Seizure condition		
Sleep	20	19.6
Awake	82	80.4
Seizure type		
Focal	9	8.8
Generalized	93	91.2
Duration of seizure		
<1 min	8	7.8
1-5 min	73	72.5
>5 min	21	19.6
Family history of seizure		
Present	13	12.7
Absent	89	87.3
Family history of FC		
Present	4	4
Absent	98	96
Neuroimaging findings		
Normal	57	72.4
Abnormal	10	12
Non-specific	13	15.6
Seizure recurrence		
Yes	22	21.6
No	80	78.4
Timing of seizure recurrence		
<6 months	14	64
7-11 months	6	27
>12 months	2	9

Table 2. Neuroimaging findings of the patients

Neuroimaging findings (n = 80)	n	%
Normal	57	72.4
Abnormal		
Increased intensity in bilateral posterior ventricles	10	12
Millimetric subependymal nodularity at bilateral ventricle level	5	6
Periventricular hyperintensity	1	1.2
Hypomyelinized areas in periventricular substantia alba	1	1.2
Hyperintense foci in substantia alba	1	1.2
Parahippocampal gyrus atrophy	1	1.2
Non-specific	13	15.6
Pineal gland cyst	4	4.8
Arachnoid cyst	2	2.4
Partial empty sella	2	2.4
Widening of left lateral ventricle	2	2.4
Chiari type 1	1	1.2
Choroid plexus cyst	1	1.2
Widened pericallosal vascular structure	1	1.2

Table 3. Comparison of demographic and clinical characteristics between patients with and without seizure recurrence

	Seizure recurrence				
	Absent		Present		
	n	%	n	%	p
Age of first seizure					
1-6 years	54	67.5	8	12.9	0.009
7-11 years	15	18.8	11	42.3	
>12 years	11	13.8	3	21.4	
Gender					
Male	42	52.5	12	54.5	0.865
Female	38	47.5	10	45.5	
Duration of seizure					
≤ 5 min	68	84	13	16	0.008
> 5 min	12	57.1	9	42.9	
Neuroimaging findings					
Normal	39	68.5	18	31.5	0.280
Abnormal	9	90	1	10	
Non-specific	12	92.4	1	7.6	
Family history of seizure					
Present	10	76.9	3	23.1	0.887
Absent	70	78.7	19	21.3	
Family history of FC					
Absent	77	78.6	21	21.4	0.497
Present	3	75	1	25	
Type of seizure					
Focal	8	88.9	1	11.1	0.424
Generalized	72	77.4	21	22.6	
First seizure					
Sleep	12	60	8	40	0.025
Awake	68	82.9	14	17.1	

age at the first seizure was 48 months (min-max:12-192 months). The vast majority of the patients were awake during the seizure (80.4%) and had a generalized type of seizure (91.2%). The sociodemographic and clinical characteristics of the patients have been presented in Table 1. Among patients undergoing neuroimaging (n:80, 78.4%), 12% revealed abnormal findings (Table 2). The remaining 22 patients could not undergo neuroimaging due to unsuitability to MRI under anaesthesia or due to patient or family non-compliance (21.6%).

The median duration of patient follow-up was 36 months (min-max: 24-120 months). During the follow-up, recurrent seizures were observed in 22 (21.6%) of the patients. The median time of seizure recurrence

Table 4. Predictors of recurrence risk after a first unprovoked seizure (age)

Risk factor (multivariate analysis)	%95 CI	P	Partial Eta square
Age		0.009	0.092
1-6 years	0.029-0.229		
7-12 years	0.268-0.578		
>12 years	0.003-0.425		

R squared = .092 (adjusted R squared = .073)

was 3 months (min-max: 2 days-3 years). Control EEG was performed on the 22 patients with seizure recurrence. Among these, 4 had epileptic abnormality. AED was begun for 21 patients with seizure recurrence during the follow-up. One patient was not given medicine because there was a three-year interval between two seizures.

Seizure recurrence was significantly higher in patients who had their first seizure between 7 and 12 years of age. In the logistic regression analysis performed here, seizure recurrence is significantly more common in patients over 7 years of age than in patients younger than 7 years old. (B = -1.291, SE = 0.53, p=0.01). And also, seizure recurrence was significantly higher in patients who had their first seizure between 7 and 12 years of age (p = 0.009, 95% CI = 0.268-0.578, Adjusted R Squared = .073). Comparison of demographic and clinical characteristics between patients with and without seizure recurrence was given in Table 3. Seizure recurrences were higher among patients who had their first seizure during sleep (p = 0.025). There was no significant relationship between seizure recurrence and seizure type (p = 0.424). Seizure recurrence was higher among patients with a seizure duration longer than five minutes (p = 0.008). The risk factors affecting seizure recurrence have been presented in Table 4.

Logistic regression analysis revealed that having a seizure longer than 5 minutes increased the risk of seizure recurrence by 3.63-fold, compared to those with a duration of seizure of shorter than 5 minutes, which was statistically significant. It was observed that the risk of seizure recurrence increased by 2.45 times in patients who had two seizures on the same day; however, this increase was not statistically significant.

Discussion

Epilepsy is a disease of the brain defined by any of the following conditions: at least two unprovoked (or reflex) seizures occurring more than 24 hours apart, one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years, and diagnosis of an epilepsy syndrome[5]. It is possible that the first afebrile seizure is the last, or it may be an early sign of epilepsy. The low-risk group has been defined as single seizure, normal EEG findings and absence of a neurological disorder. It has been demonstrated that AEDs reduce the risk of seizure recurrence within two years to a negligible level[6]. The decision to prescribe AEDs is difficult after a single seizure. Drug side effects and the risk of seizure recurrence should be considered. Although risk factors have been described in different studies, the criteria for predicting seizure recurrence are unclear. If the child is conscious and has normal vital signs after first afebrile seizure, the “Wait and see” option should be considered according to the recommendations of ILAE[7]. It has been mentioned that the general recurrence rate varies between 14% and 65% among children with the first unprovoked seizure, and recurrence was observed within the first two years in 88% of the children[4,8,9]. In our study, the median duration of follow-up was 36 months (min-max: 24-120 months), and seizure recurrence was observed in 21.6% of the patients. Of these, 64% occurred within the first six months. The exclusion of patients with neurological problems and the inclusion of only patients with normal EEG in the study were thought to be the most important reasons for the lower recurrence rate compared to the literature.

In our study, seizure recurrence is significantly more common in patients aged over 7 years of age. The mean age of the first seizure was 6.8 years in the study of Shinnar[8]. In the study of Winckler et al.[10] on 109 children, the mean age of seizure was observed to be 6 years with the highest incidence occurring between 7 and 12 years of age. Another study detected a significant relation between the age of late onset (≥11 years) and the risk of recurrence[11]. There are various studies on the effects of focal seizures on seizure recurrence[10,12,13]. Focal findings on the EEG were related to the risk of recurrence[11]. In our study, no significant relation was determined between the seizure type and recurrence (p = 0.424).

A higher risk of recurrence has been reported for seizures lasting more than 5 minutes[14]. There are studies showing that there is no relationship between seizure duration and risk of recurrence; however, there are also studies showing that the risk of seizure recurrence is higher in patients whose first seizure lasted more than 5 minutes[15,16]. In our study, recurrence was observed more frequently in the patients with a duration longer than 5 minutes (p = 0.008). Seizure recurrence was observed to be higher among patients who had seizure while sleeping (p = 0.025). Seizure during sleep was demonstrated to increase the risk of recurrence by 3-fold. In a 2004 study, seizures experienced while awake were reported to be dominant; however, they had no significance for the risk of recurrence[11]. It significantly increases the risk of recurrence of seizures that occur during sleep[17,18].

In the absence of an emergency, MRI should be preferred as the neuroimaging method for patients presenting to the hospital with a first afebrile seizure[7]. Significant MRI findings in children diagnosed with epilepsy are reported at rates ranging from 11.3% to 16%[19,20]. MRI abnormalities have been found to significantly increase the risk of seizure recurrence[21]. In this study, abnormal findings were detected in 12.5% of the patients. No significant relation was detected between the abnormal findings in neuroimaging and the risk of seizure recurrence (p = 0.280).

Different opinions have been reported on the relationship between the presence of a family history of febrile seizures and seizure recurrence. Some studies demonstrate that family history of seizure is not a risk factor for seizure recurrence, as well as studies demonstrating that it is[11,20,22]. According to Ghiasian et al.'s [23] study, idiopathic epilepsy patients tend to have a very high incidence of epilepsy and seizures in their first-degree relatives. In our study, no significant relation was determined between a family history of seizure and febrile seizure, and seizure recurrence (p = 0.887, p = 0.285, respectively).

The main limitations of the study are that it was single-centred, retrospective, and that the seizure type could be determined based on the data available by the family. The lack of genetic and metabolic studies is another limitation of this study.

In summary; In this study including children with normal EEG findings, seizure recurrence was observed in 21.6% of the patients. Risk factors were identified as having the first seizure after 7 years of age, having the seizure while asleep, and having a seizure duration longer than 5 minutes. Considering the risk factors for seizure recurrence in patients with normal EEG following the first unprovoked seizure, it would be appropriate to decide to start AED on a patient basis.

Author Contribution

A. Ekici: conceptualization, Data curation, Formal Analysis, Investigation, Z. Beyza Kuşku: methodology, Validation, Visualization, Writing – review & editing.

Funding

None.

Conflicts of interest

None.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely obtained and anonymized clinical data, so informed consent was not necessary. Relevant guidelines were followed.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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