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Risk of recurrence after antiepileptic withdrawal: Was it a good decision or not?

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Ozlem Yayici Koken[1], Ayse Aksoy[2], Ozge Kucur[3], Mehpare Kafali[4]

[1] Department of Pediatric Neurology, Ankara City Hospital, Ankara, Turkey
[2] Department of Pediatric Neurology, Ondokuz Mayis University, Samsun, Turkey
[3] Department of Pediatric Neurology, University of Health Sciences, Dr. Sami Ulus Research and Training Hospital, Ankara, Turkey
[4] Department of Pediatric Neurology, WM Medical Park Pendik Hospital, Istanbul, Turkey

Keywords
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Abstract

Background: The aim of this study was to identify the demographic-clinical variables affecting idiopathic epilepsy (IE) [called genetic generalized epilepsy (GGE)] recurrence and determine cut-off values that can be used in pediatric neurology practice for children with IE/GGE.

Methods: A total of 250 children and adolescents with IE/GGE were included and retrospectively evaluated. The patients' hospital records were examined in order to identify possible electro-clinical features affecting epilepsy recurrence.

Results: The overall rate of recurrence in the patients was 46%; the age at onset of seizures in recurrence group was lower (P = 0.040) and the age at last seizure was higher in the recurrence group (P < 0.001) than that in the non-recurrence group. Other factors found to be related to recurrence were the shorter duration of the seizure-free period (P = 0.030), shorter interval between the last seizure and antiepileptic drug (AED) withdrawal (P = 0.003), shorter duration of AED withdrawal (P = 0.005), and the existence of abnormalities on sleep electroencephalogram (EEG) during AED withdrawal (P = 0.010) and at the 6th month of withdrawal (P < 0.001). According to receiver operating characteristic (ROC) analysis, the risk of IE recurrence was higher in children who were younger than 3.6 years old (sensitivity: 65.6%, specificity: 62.7%), children with a seizure-free period that was shorter than 35.5 months (sensitivity: 89.6%, specificity: 32.8%), and children whose drug withdrawal period was shorter than 4.5 months (sensitivity: 56.3%, specificity: 71.6%).

Conclusion: This study defined some electro-clinical factors that could guide clinicians when deciding to withdraw AEDs with regard to recurrence risk after evaluating a homogenous population of children with a diagnosis of IE/GGE.

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Corresponding Author: Ayse Aksoy
Email: aysechild@gmail.com

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Introduction

Idiopathic epilepsy (IE), which is called genetic generalized epilepsy (GGE) in the current terminology, is one of the most common forms of childhood epilepsies. One of the most important points is the duration of antiepileptic drug (AED) use and the timing of discontinuation of therapy. The primary aim is to avoid recurrence. The recurrence risk of withdrawal is related with the duration of use, including 1) ensuring that the antiepileptics are taken for a period that does not increase the risk of recurrence and 2) withdrawing the medication using an appropriate protocol.

Factors related to the recurrence of IE/GGE after withdrawal of AEDs were the subject of many studies in the literature.[1-10] Age at onset of epilepsy, being female, a history of febrile or focal seizures, family history of epilepsy, duration of epilepsy before remission, seizure-free period before AED withdrawal, number of seizures and AEDs before remission, absence of a self-limiting epilepsy syndrome, concomitant developmental delay, and epileptiform abnormalities on electroencephalogram (EEG) before withdrawal were reported as independent factors for epilepsy recurrence.[1-9]

However, studies investigating the possible risk factors associated with IE/GGE recurrence in children and adolescents are very confusing. The aim of this study was to identify the demographic and clinical variables affecting IE/GGE recurrence and determine cut-off values that can be used in pediatric neurology practice for children and adolescents with IE/GGE.

Materials and Methods

This retrospective, descriptive, single-center study was conducted at the Department of Pediatric Neurology of University of Health Sciences, Dr. Sami Ulus Research and Training Hospital in Ankara, Turkey. The study was approved by the Regional Ethics Committee (Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital Clinical Studies, Ethical committee approval number: 2018-001) and the study was planned and conducted in accordance with the Declaration of Helsinki.

Hospital records were evaluated to find participants who had been diagnosed with IE/GGE using relevant International Classification of Diseases (ICDs) codes between 2009-2014. A total of 250 children and adolescents who were previously diagnosed with IE/GGE and followed-up for at least 5 years after withdrawal of AED and were between 8 and 18 years of age (129 boys and 121 girls) were included in the study.

Confirmation of the diagnosis of IE/GGE by 3 pediatric neurologists, using predefined diagnostic criteria, according to the definitions of the Commission on the Classification and Terminology of the International League Against Epilepsy (ILAE)[1] was required for inclusion. The patient was excluded from the study if three researchers could not reach a consensus or participants to the study were re-evaluated and give the diagnosis on which at least two pediatric neurologists agreed. Since the aim was to form a homogenous patient population, all patients suspected to be negative for IE/GGE were excluded from the study. Only children with IE/GGE were included in the study.

A participant diagnosed with IE was excluded if he/she or a parent: 1) had incomplete hospital records, 2) had a duration of follow-up after withdrawal of AED that was less than 5 years, 3) had concomitant situations such as global developmental delay, mental retardation, autism, or neurometabolic diseases, and 4) all had symptomatic epilepsies.

The possible factors related to seizure recurrence were analyzed according to age and sex. These factors were previous medical history including perinatal and childhood history, history of febrile seizures (FS) and family history of FS and epilepsy, history of status epilepticus (SE), seizure types, EEG findings; duration of disease and treatment, age at last seizure, duration of seizure-free period, duration of withdrawal of AED, EEG at diagnosis, pre-withdrawal EEG, and post-withdrawal EEG.

EEG recordings were routinely obtained from all patients as standard protocol at the time of diagnosis, before and after the initiation of AED withdrawal protocol, and after 6 months or 1 year following AED withdrawal. EEGs were classified as normal or abnormal (epileptic abnormalities). All patients underwent initial and serial waking and sleeping EEG recordings using a Nihon Kohden machine (Shinjuku-ku, Tokyo, Japan) that had 18 channels and the scalp electrodes were distributed according to the 10-20 system. The EEG consisted of a 30-minute digital tracing including a sleep trace of at least 20 minutes, 3 minutes of hyperventilation, and intermittent photic stimulation (IPS) at 1 to 20 Hz with the patient's eyes closed.

A seizure-free period of at least 2 consecutive years was the main criterion for AED withdrawal

in the clinic and all of the clinical features were evaluated before withdrawing the AEDs. The protocol for withdrawal was a stepwise 25% dose reduction. In patients receiving combination therapy, the dose of the second antiepileptic drug was reduced only after the first antiepileptic had been completely stopped. The patient population included patients who had stopped using their medication on their own or due to parental decision, violating the protocol.

Patients who were followed up for at least 5 years after AED withdrawal were included in the study. Patients were classified into 2 groups: those who had recurrence and those who did not. All demographic and clinical data of the 2 groups were compared to identify factors related to recurrence. In addition to identifying possible risk factors, the aim was to determine cut-off values for significant variables related to epilepsy recurrence.

Data analyses were performed using SPSS software (version 22, IBM Corporation, Armonk, NY, USA). The Kolmogorov-Smirnov test was used to determine the normal distribution of continuous variables. The Levene's test was used to evaluate the homogeneity of the variables. Continuous data were presented as mean ± standard deviation (SD). Categorical data were given as the percentage of the number of cases. Differences in normally-distributed variables between 2 independent groups were compared using the Student's t test, while the Mann-Whitney U test was applied for comparisons of data without normal distribution. Univariate multinomial logistic regression was applied to the risk factors thought to be related to recurrence. Risk factors with $P < 0.25$ on the univariate logistic regression were included in the multivariable logistic regression. The significance of every independent variable was analyzed using the Wald statistic.

The degree of explanation of the dependent variable by an independent variable was determined using the Nagelkerke R-squared statistic. Moreover, the model adaptation of the estimates was evaluated using the Hosmer and Lemeshow model adaptation test. Receiver operating characteristic (ROC) curve analysis was used to determine the cut-off points. $P < 0.05$ was accepted as statistically significant, while $0.10 < P < 0.05$ was accepted as borderline significant.

Results

A total of 250 patients were enrolled in the study. The average age of the patients was 155.7 ± 56.7 months, the total follow-up period was 98.0 ± 36.9 months, and 129 of the patients were boys.

Of the 250 patients for whom treatment was withdrawn, 135 remained seizure-free until the end of the study period (54%), while seizures recurred in 115 patients (46%). These 2 groups were evaluated to determine the risk factors related to recurrence by comparing the demographic and clinical characteristics, which are given in table 1.

A young age at first seizure, older age at last seizure, shorter duration of the seizure-free period, shorter time between the last seizure and AED withdrawal, shorter duration of AED-free period, and the existence of epileptic abnormalities on EEG at the 6th month of withdrawal were found to be related to a higher risk of recurrence. Table 1 summarizes this data by comparing the 2 groups.

Sex, history of FS in the patient or family, prematurity, history of SE, type of seizure, number of seizures both before and after AED initiation, mono- or polytherapy, duration of AED use, and the existence of epileptic abnormalities on EEG at the time of diagnosis were not established to be risk factors.

The average duration of tapering was 5.2 ± 2.2 months for the whole study population. In 13 patients (5.2%), it was shorter than a month. This group consisted of patients who stopped using AEDs on their own or as a result of their parents' decision. With regards to tapering off, success was achieved with 23 patients (9.2%) in 1-3 months, with 144 patients (57.6%) in 3-6 months, with 62 (24.8%) patients in 6-9 months, and with 8 (3.2%) patients in 9-12 months.

In 115 patients with recurrence, the highest incidence was in the first 4 months after completion of the tapering protocol. Recurrence was observed during the tapering period in 12 patients, and of these patients, 10 had seizures, while 2 had EEG abnormalities. In 103 patients who had recurrence after completion of withdrawal, 53 presented with seizures, while only 50 patients had seizures and EEG abnormalities. Multiple attempts were made at AED withdrawal for 9 patients, and thus, multiple recurrences were observed. Only the first electroclinical features were taken into consideration for the purposes of this study. Twelve patients who had epileptiform anomalies in sleeping and waking EEGs recorded just before the beginning of AED withdrawal protocol were seizure-free for 19.6 ± 3.2 months, but all had recurrences.

Table 1. Demographic and clinical findings and comparison of two groups with or without recurrence

Variable	Group without recurrence (n = 135)	Group with recurrence (n = 115)	P
Sex (M/F)	72/63	57/58	0.552
Prematurity [n (%)]	16 (11.9)	10 (8.7)	0.667
History of FS [n (%)]	23 (17.0)	25 (21.7)	0.347
Family history of epilepsy [n (%)]	34 (25.2)	18 (15.7)	0.021
Family history of FS [n (%)]	19 (14.8)	17 (14.8)	0.823
Age at first seizure (month) (mean ± SD)	57.6 ± 44.7	42.7 ± 33.8	0.041
Age at last seizure (month) (mean ± SD)	67.6 ± 13.2	99.9 ± 58.4	< 0.001
History of SE [n (%)]	14 (10.4)	12 (10.4)	0.968
Number of seizures before AED initiation [n (%)]			
1	30 (22.2)	23 (20.0)	0.413
≥ 2	105 (77.8)	92 (80.0)	
Duration of AED use (month) (mean ± SD)	41.9 ± 24.5	35.6 ± 28.5	0.457
Monotherapy [n (%)]	132 (97.8)	107 (93.0)	0.173
Polytherapy [n (%)]	3 (2.2)	8 (7.0)	
Number of seizures in the first 6 months following AED initiation [n (%)]			0.982
0	92 (68.1)	76 (66.1)	
1-10	38 (28.2)	35 (30.5)	
≥ 10	5 (3.7)	4 (3.5)	
Number of seizures 6 months after AED initiation [n (%)]			0.783
0	106 (78.5)	88 (76.5)	
1-10	28 (20.8)	26 (22.6)	
≥ 10	1 (0.7)	1 (0.9)	
Seizure-free interval before withdrawal of AED (month) (mean ± SD)	32.2 ± 13.2	27.4 ± 11.1	0.033
Duration between the last seizure and AED withdrawal (month) [n (%)]			0.003
0-1	2 (1.5)	7 (6.1)	
2-12	5 (3.7)	13 (11.3)	
12-24	28 (20.7)	32 (27.8)	
24-36	92 (68.1)	56 (48.7)	
> 36	9 (6.7)	7 (6.0)	
Duration of AED withdrawal (month) (mean ± SD)	5.7 ± 2.3	4.5 ± 2.0	0.005
Epileptiform abnormalities on EEG [n (%)]			
At time of diagnosis			
Awake	63 (46.7)	50 (43.4)	0.808
Sleep	59 (43.7)	51 (44.3)	0.316
At withdrawal			
Awake	0 (0)	12 (10.4)	0.001
Sleep	1 (0.7)	12 (10.5)	0.013
In 6th month of AED withdrawal			
Awake	9 (6.7)	24 (20.9)	< 0.001
Sleep	11 (8.1)	22 (19.1)	> 0.001
Time until relapse (month) (mean ± SD)	-	4.7 ± 2.3	
Time until relapse (month) [n (%)]			
0-4	-	48 (41.7)	
4-12		27 (23.5)	
12-24		17 (14.7)	
≥ 24		13 (11.3)	

FS: Febrile seizure; AED: Antiepileptic drug; SE: Status epilepticus; EEG: Electroencephalogram; SD: Standard deviation

Two patients who stopped taking AEDs due to the decisions of their families had recurrences in 3.4 ± 1.1 months after stopping AEDs, two patients had recurrences during the cessation protocol, and 8 patients had epileptic seizures which were classified as recurrences in 9.7 ± 2.1 months after the completion of the cessation protocol. Cessation was attempted for a second time in one of these patients during follow-up, but recurrence occurred once more.

Table 2. Univariate and multivariate logistic regression analysis to determine risk factors for recurrence

	Univariate logistic regression analysis				Multivariate logistic regression analysis (backward LR 1 step)			
	Wald statistic	**OR**	**95% CI**	**P**	**Wald statistic**	**OR**	**95% CI**	**P**
Sex	0.353	1.163	0.707-1.913	0.552				
Prior diagnosis of SE	0.002	1.017	0.450-2.297	0.968				
Age at first seizure	5.914	0.991	0.983-0.998	0.015	11.785	0.961	0.940-0.983	0.001
Age at last seizure	12.475	1.011	1.005-1.018	< 0.001	9.502	1.031	1.011-1.051	0.002
Duration of seizure-free period	8.447	0.967	0.946-0.989	0.004	3.532	0.953	0.906-1.002	0.060
Duration of AED withdrawal	8.114	0.772	0.645-0.922	0.004	3.815	0.794	0.630-1.001	0.051
Duration of recurrence	1.571	1.041	0.977-1.109	0.310				

Statistically significant P-values are in bold; variables with P > 0.25 in the univariate analysis were excluded from multivariate analysis. Nagelkerke R-squared: 0.394 Hosmer and Lemeshow P: 0.327

OR: Odds ratio; CI: Confidence interval; SE: Status epilepticus; AED: Antiepileptic drug; LR: Likelihood ratio

9 (69.2%) out of 13 patients who had abnormalities in sleeping EEG recorded before the withdrawal had recurrences, while three of these patients did not have recurrences. 15 patients with normal EEGs before withdrawal had anomalies in EEGs recorded 6 months after withdrawal.

Factors related to epilepsy recurrence were evaluated using univariate logistic regression. Table 2 summarizes the results of the univariate and multivariate regression analysis. Factors believed to increase the risk of recurrence were included in the univariate logistic regression analysis. Variables that were found to have P < 0.25 as a result of the univariate analysis (age at first seizure, age at last seizure, duration of seizure-free period, and duration of weaning from AED) were included in the multivariate analysis. The backward likelihood ratio (LR) method was applied for the multivariate analysis.

The risk of recurrence increased by 3.9% for every unit of decrease in the age of onset [Odds ratio (OR): 1-0.961 = 0.039], while the risk increased by 2.9% for every unit of increase in the age of last seizure. A 1-unit decrease in the duration of the seizure-free period (OR: 1-0.953 = 0.047) caused a 4.7% increase in the risk of recurrence (borderline significant). A 1-unit decrease in the duration of tapering protocol (OR: 1-0.794 = 0.206) caused a 20.6% increase in the risk of recurrence (borderline significant) (Tables 2 and 3).

The ROC curve analysis of the potential predictors for the risk of recurrence is shown in figure 1 and table 3. The risk of recurrence was higher in patients who experienced first seizure at an age younger than 43.5 months (sensitivity: 64.6%, specificity: 62.7%), had a seizure-free period of less than 35.5 months (sensitivity: 89.6%, specificity: 32.8%), and had duration of AED withdrawal of less than 4.5 months (sensitivity: 56.3%, specificity: 71.6%).

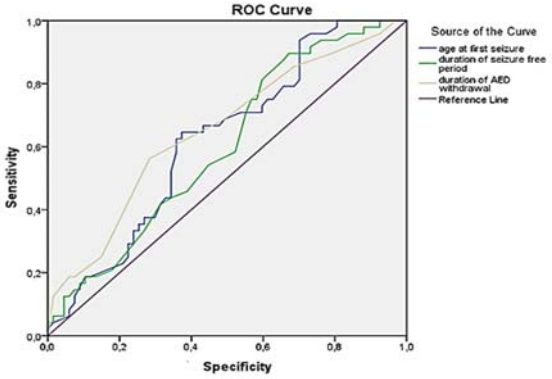


Figure 1. Graphed receiver operating characteristic (ROC) analysis results

Table 3. Receiver operating characteristic (ROC) analysis results

	AUC	**SE**	**P**	**95% CI**		**Cut-off**	**Sensitivity (%)**	**Specificity (%)**
Age at first seizure	0.623	0.052	0.025	0.521	0.725	43.5	64.6	62.7
Duration of seizure-free period	0.601	0.053	0.067	0.498	0.704	35.5	89.6	32.8
Duration of AED withdrawal	0.651	0.052	0.006	0.549	0.753	4.5	56.3	71.6

AUC: Area under the curve; CI: Confidence interval; AED: Antiepileptic drug; SE: Standard error

Discussion

The results of this study show that 46% of the pediatric patients with a diagnosis of IE/GGE had recurrences following AED withdrawal. Recurrences occurred most frequently in the first 4 months after completion of the tapering protocol and a younger age at the onset of seizures, older age at the time of last seizure, shorter duration of seizure-free period, shorter interval between AED withdrawal and the last seizure, shorter duration of AED tapering, and the existence of EEG abnormalities at the time of AED withdrawal and at the 6th month following withdrawal were risk factors for recurrences.

The recurrence rate of epilepsy in children and adolescents was investigated in many studies, which showed that the frequency of seizure recurrence after AED withdrawal was 12% to 56%.[2-8] The heterogeneity of the patient populations is striking in all of these studies. The effect of underlying etiology of epilepsy on recurrence rates is an undeniable fact. Therefore, while creating the study group, the aim was to minimize the differences by selecting patients diagnosed with IE/GGE. Similarly, there were significant variations in the risk of recurrence following AED withdrawal reported in studies investigating pediatric patients diagnosed with IE. Murakami et al.[8] reported a rate of 8.3% in patients with partial IE and 17.9% in patients with generalized IE who were weaned off AED following a 3-year seizure-free period. The overall rate of recurrence was 46% in the current study, which is strikingly high. This may have been caused by the fact that a large group of patients with IE that had long-term follow-up (5-8 years) was evaluated. Another possible reason could be the fact that patients who stopped taking AED medication in an inappropriate way, as a result of patient or parent noncompliance, were also included in the study.

However, contrary to the literature, positive family history of epilepsy was more frequent in the non-recurrence group, although this difference was not statistically significant. In other words, it was observed that a family history of epilepsy was more frequent in patients without recurrence.[4,9,11-14] This result led us to believe that adherence to treatment was higher in patients with positive family history since they had a higher level of knowledge about the disease. Despite contrary data in the literature, prior febrile convulsion was not a risk factor for recurrence.[4,15-17] Since two manuscripts published in our country did not define prior febrile convulsion history as a risk factor, it may be possible that epigenetic and environmental factors play a role.[16,17] According to the literature, early response to treatment is associated with prognosis.[18] Indirect evidence for this is the fact that the number of seizures observed in patients receiving polytherapy or after initiation of AED as a factor that necessitates polytherapy is not associated with the risk of recurrence. In addition, it was observed that some factors that were reported with increased risk of recurrence, such as sex, prematurity, history of FS in the family, and history of SE (at the time of diagnosis or during follow-up) did not have an effect on the risk of recurrence in patients with IE/GGE.

In the current study, the age at onset of seizures was significantly lower in the recurrence group compared to the non-recurrence group ($P = 0.041$), while the age at last seizure was higher ($P < 0.001$). The risk of recurrence was reported as 31%-33% for seizures with an onset age of younger than 10-12 years and twice this number for seizures with an onset age older than 10-12 years.[10,19] Verrotti et al.[4] reported that being older than 6 years at the onset of epilepsy was a risk factor for recurrence, while Altunbasak et al.[16] associated being 2 years or younger at the onset of epilepsy with better prognosis. Furthermore, ROC analysis revealed that the risk of relapse would increase if the first epileptic seizure happened below a 43.5-month threshold in our study. Researchers have not been able to confirm this in major studies investigating the risk factors associated with recurrence after AED withdrawal due to small and heterogeneous study populations.[4,15]

Other factors related to recurrence were a shorter duration of seizure-free period ($P = 0.033$) and shorter time period between the start of AED tapering and the last seizure ($P = 0.003$). There are many studies that aimed to find the ideal duration of seizure-free period before AED withdrawal, while minimizing the risk of recurrence. Some studies supported the notion that, while taking patient- and family-dependent risk factors into consideration, a minimum seizure-free period of 2 years must be achieved before withdrawing AEDs; in other words, withdrawing AEDs after being seizure-free for 2 years decreases the risk of recurrence.[11-13] In a meta-analysis investigating the risk factors for recurrence following AED withdrawal in patients with epilepsy, AED withdrawal was reported to be performed at a

median of 33 months (range: 3-385 months) after the last seizure.[14] In our study, the seizure-free period prior to AED withdrawal was shorter in the group with recurrence. The ROC analysis revealed that AED withdrawal after 35.4 months without seizures lowered the risk of recurrence. In other words, approximately, 3 years without seizures led to a decreased risk of recurrence.

Other factors related to recurrence in IE/GGE were the existence of epileptic abnormalities in sleeping EEG while weaning from AED (P = 0.013) and at the 6th month following withdrawal (P < 0.001). The role of epileptic anomalies in EEG is subject to debate in terms of the decision about AED withdrawal. However, given the fact that recurrence was observed in 69.2% of the patients who had epileptic activity in EEGs recorded prior to AED withdrawal and in 68.5% of the patients who had epileptic activity in EEGs recorded in the sixth month after AED withdrawal, it can be inferred that the existence of epileptic activity in EEGs recorded before and 6 months following the withdrawal of AEDs is associated with a higher risk of recurrence. There are studies stating that, similar to ours, epileptic abnormalities in EEG recorded at the time of diagnosis are not associated with recurrence, while such abnormalities in EEG recorded at the time of withdrawal indicate a higher risk of recurrence.[4,6,16] AED treatment suppresses epileptic activity in EEG. Since withdrawal of AED abolishes this suppression, an increase in epileptic activity which was not completely suppressed or a recurrence of epileptic activity which was previously suppressed can be expected.[4,20] Thus, based on our results and the literature, patients should be evaluated via EEG both at the time of decision to withdraw AEDs and during follow-up.

Another important topic is the optimal duration of AED dose tapering. Methodologies differed in studies investigating dose tapering in the pediatric patients. Although there are studies that associated a shorter tapering duration with increased risk of recurrence,[9,11] studies stating the contrary can also be found.[17] In this study, the tapering period was shorter in the recurrence group when compared to the non-recurrence group (P = 0.005). The risk of recurrence was higher in patients who had AED tapering periods that were shorter than 4.5 months. Indeed, 7 of the 10 patients who stopped using AED medications on their own or as the result of their parents' decision had recurrences within the first 4 months. Recurrence was usually observed during or immediately after the AED tapering protocol. The rate of recurrence after 2 years in the literature was similar to the results of the current study.[4,9]

Conclusion

In this study, the aim was to determine the impact of demographic and clinical factors on the recurrence of IE/GGE in childhood. The most important limitation of the study is its retrospective design; as a result, the updated epilepsy classification system could not be used. A younger age at onset of seizures, older age at the time of last seizure, shorter duration of seizure-free period, shorter interval between AED withdrawal and the last seizure, shorter duration of AED tapering, and the existence of EEG abnormalities at the time of AED withdrawal and at the 6th month following withdrawal were found to be correlated with an increased risk of recurrence. The results of this study support the notion that AED withdrawal should be carried out after at least 3 seizure-free years, over a 4.5-month period. Hence, EEG recordings should be planned both before and following AED withdrawal and the decision should be reevaluated in cases where epileptic abnormalities are found. Contrary to the literature, no correlation was found between sex, history of FS, history of febrile and epileptic seizures in the family, prematurity, history of SE, type of seizures, number of seizures before AED initiation, number of seizures after AED initiation, duration of AED therapy, and the existence of abnormalities on EEG at the time of diagnosis and the risk of recurrence. The decision to stop or continue AEDs is an important one that has to be made by taking all of the above factors into consideration and AED tapering protocols require close cooperation between patients, parents, and clinician.

Conflict of Interests

The authors declare no conflict of interest in this study.

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