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Risk factors for seizure recurrence after antiepileptic drug withdrawal in children with epilepsy

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Abstract

Introduction and Objectives: The most common queries from families after an epilepsy diagnosis are, "When will the medication be discontinued?" and "Will it recur?". This study aims to evaluate the risk factors for seizure recurrence after antiepileptic drug (AED) withdrawal in children with epilepsy. **Methods:** Patients aged between one month and 18 years who were diagnosed with epilepsy, had been seizure-free for at least two years, and whose last two electroencephalogram (EEG) tests normal were included in the study. **Results:** The study encompassed a total of 297 patients. Seizures recurred in 43 individuals (14.5%) following the discontinuation of AEDs. The average length of time before seizure recurrence was five months (range: one to 18 months). No statistically significant relationship was observed between seizure recurrence and variables such as gender, age, seizure type, age at seizure onset, epilepsy etiology, abnormal initial EEG, cognitive impairment, or coexisting neurological conditions ($p = 0.158$, $p = 0.537$, $p = 0.184$, $p = 0.863$, $p = 0.744$, $p = 0.944$, $p = 0.702$, $p = 0.592$, respectively). Factors such as monotherapy or polytherapy, prior AED usage before discontinuation, and the length of time AEDs had been discontinued did not show a significant impact on seizure recurrence ($p = 0.297$, $p > 0.05$, $p = 0.155$, $p = 0.687$, respectively). **Conclusion:** In this study, seizure recurrence occurred in 14.5% of patients after AEDs were discontinued. The ability to predict seizure recurrence in individual patients seems challenging. Therefore, maintaining close monitoring during the first two years following AED discontinuation is deemed crucial for effective management.

Keywords: Antiepileptic drug. Children. Epilepsy. Seizure recurrence. Risk factor.

Fatores de risco para a recorrência de convulsões após a retirada de medicamentos antiepiléticos em crianças com epilepsia

Resumo

Introdução e Objetivos: As perguntas mais frequentes das famílias após um diagnóstico de epilepsia são "Quando é que a medicação será descontinuada?" e "Haverá recorrência?" Este estudo tem como objetivo avaliar os fatores de risco para a recorrência de crises após a retirada de "Fármacos antiepiléticos" (FACE) em crianças com epilepsia. **Métodos:** Foram incluídos no estudo doentes com idade entre 1 mês e 18 anos, diagnosticados com epilepsia e sem crises há pelo menos dois anos, que apresentaram os dois últimos os dois últimos EEG normais **Resultados:** O estudo abrangeu um total de 297 doentes, com recorrência de convulsões em 43 indivíduos (14,5%) após a descontinuação dos FACE. A duração média da recorrência das crises foi de 5 meses (intervalo: 1 – 18 meses). Não foi observada uma relação estatisticamente significativa entre a recorrência das crises e variáveis como o sexo, a idade, o tipo de crise, a idade de início das crises, a etiologia da

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epilepsia, o EEG inicial anormal, o défice cognitivo ou as condições neurológicas coexistentes (p = 0,158, p = 0,537, p = 0,184, p = 0,863, p = 0,744, p = 0,944, p = 0,702, p = 0,592, respetivamente). Fatores como a monoterapia ou politerapia, o uso prévio de FACE antes da descontinuação e a duração da descontinuação de DAE não mostraram impacto significativo na recorrência de convulsões (p = 0,297, p > 0,05, p = 0,155, p = 0,687, respetivamente). **Conclusão:** Neste estudo, a recorrência de convulsões ocorreu em 14,5% dos pacientes após a interrupção do uso de FACE. A capacidade de prever a recorrência de crises em doentes individuais parece desafiante. Por conseguinte, manter uma monitorização rigorosa durante os primeiros dois anos após a suspensão dos FACE é considerado crucial para um tratamento eficaz.

Palavras-chave: Fármaco. Crianças. Epilepsia. Recorrência de crises. Fator de risco.

Key points

What is known

- Twenty to thirty percent of patients are likely to have seizures again after withdrawing AEDs.
- Several prognostic factors have been identified that may predict seizure recurrence, including the patient's gender, age at seizure onset, family history of epilepsy, type of seizure, neurological and psychiatric disorders, history of febrile seizures, EEG abnormalities, and abnormal MRI findings.
- The decision regarding antiepileptic drug (AED) prescription following the first unprovoked seizure should be made taking into consideration the side effects of the drug and the seizure recurrence risk.

What is added

- Seizure recurrence occurred in 14.5% of patients after AED discontinuation.
- There was no significant relationship between seizure recurrence and variables such as gender, age of seizure onset, seizure type, epilepsy etiology, cognitive status, comorbid neurological diseases, initial EEG findings, MRI abnormalities, timing of AED initiation, initial AEDs used, use of polytherapy, or duration of AED therapy.
- Although the first year following AED discontinuation is considered the highest risk period, close monitoring during the first two years after withdrawal is crucial.

Introduction

Epilepsy affects over 70 million people globally and is the most common neurological disorder in the pediatric age group. Anti-epileptic drugs (AEDs) help reduce epileptic activity in the brain and can prevent the recurrence of seizures even after the medication is discontinued[1]. However, the prolonged use of AEDs can lead to side effects, particularly in children. Thus, the critical question remains: when and how should treatment be discontinued after achieving seizure remission?

Twenty to thirty percent of patients are likely to have seizures again after ceasing AEDs, and they may then encounter further clinical and emotional challenges[2]. Several prognostic factors have been identified that may predict seizure recurrence, including the patient's gender, age at seizure onset, family history of epilepsy, type of seizure, neurological and psychiatric disorders, history of febrile seizures, electroencephalogram (EEG) abnormalities, and abnormal MRI findings[3]. Despite this, studies on factors affecting seizure recurrence are limited, and there is no consensus on the criteria for discontinuing AEDs. This underscores the need for further research on seizure recurrence and its risk factors[4].

The purpose of this study is to investigate the incidence and risk factors for seizure recurrence in epilepsy patients following the discontinuation of AED therapy.

Methods

The study involved patients ranging from one month to 18 years of age who were diagnosed with epilepsy and received follow-up care at the Pediatric Neurology Outpatient Clinic of Bursa Yuksek Ihtisas Training and Research Hospital between January 2017 and November 2021.

Regardless of EEG findings, individuals who have experienced two or more seizures clinically, with more than 24 hours between seizures, are diagnosed with epilepsy[5]. Patients who were seizure-free for at least two years, whose last EEG was normal, and who were monitored for at least two years after discontinuing the AEDs were included in this study. Patients with metabolic diseases, those who experienced seizures due to central nervous system infections, and those with a history of seizures in the neonatal period were excluded.

The seizure type was determined based on the family history and classified by the ILAE 2017 classification. The age, gender, age at seizure onset, type of first seizure, family history of epilepsy, mental status, EEG and cranial MRI findings, AEDs, duration of being

seizure-free, follow-up after medication withdrawal, and comorbid neurological diseases were noted. MRIs were classified as normal, non-specific, or abnormal. Mental status was assessed using the Denver II developmental test on children under six years of age, and intelligence tests (Stanford Binet or WISC (Wechsler Intelligence Scale for Children)) were conducted by a child psychiatrist on children over six years of age. Families were contacted by telephone to complete any missing information.

This study was performed in line with the principles of the Declaration of Helsinki. The study protocol was approved by the Institutional Ethics Committee with decision number 2011-KAEK-25 2022/01-13.

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 test and Fisher's exact test were used. The 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 of < 0.05 was accepted as statistical significance.

Results

In this study, of the 297 patients included, 147 were males (49.5%) and 150 were females (50.5%) (male/female ratio: 0.98). The mean age at the onset of the first seizure was 60 months (range: 2 – 180 months). The initial seizure type was classified as focal in 95 patients (32%) and generalized in 202 patients (68%). A family history of epilepsy among first-degree relatives was noted in 18 patients (6%). A structural cause of the seizures was found in 14 (4.7%) of the patients and a genetic cause in one (0.3%). Status epilepticus was the presentation in five patients (1.7%), cognitive impairment was observed in 40 patients (13.5%), and comorbid neurological disorders were present in 24 patients (8%). The initial EEG revealed abnormalities in 192 patients (64.7%) and cranial MRI findings were abnormal in 12 patients (4%). The demographic characteristics of the patients are presented in Table 1.

Table 1. Demographic data of patients

	n	%
Gender		
Female	150	50.5
Male	147	49.5
Family history of epilepsy		
Yes	18	6
No	279	94
Seizure type		
Focal	95	32
Generalized	202	68
Etiology of epilepsy		
Unknown	282	95
Structural	14	4.7
Genetic	1	0.3
First EEG findings		
Normal	105	35.3
Abnormal	192	64.7
MRI findings		
Normal	267	90
Nonspecific	18	6
Abnormal	12	4
Cognitive status		
Normal	257	86.5
Abnormal	40	13.5
Comorbid neurological diseases (n = 24)		
Cerebral Palsy	15	5.1
NMGG	9	3
Time from first seizure to initiation of AEI		
0-2 month	214	72
3-12 month	74	25
>12 month	9	3
Number of seizures after initial AEI (n = 102)		
1-5	87	29.2
6-10	11	3.7
>10	4	1.3
AEI used before seizure control		
Monotherapy	254	85.5
Polytherapy	43	14.5
Duration of AEI Use		
2-5 year(s)	279	94
> 5 year(s)	18	6
Duration of AEI Discontinuation		
< 3 month	37	12.5
3-6 month	252	84.8
> 6 month	8	2.7

A total of 43 patients (14.5%) experienced a seizure recurrence after discontinuing AEDSs. The median length of time until seizure recurrence was five months (range: 1 – 18 months). Among patients who experienced seizure recurrence, 26 (60.4%) were female and 17 (39.6%) were male (p = 0.158). The median age of patients who experienced seizure recurrence was 12 years (range: 6 – 18 years). In the group with seizure

recurrence, 37 patients (86%) had their first seizure at age ≤ 10. Among patients with seizure recurrence, 10 (23.3%) had focal seizures, and 33 (76.7%) had generalized seizures (p = 0.184). There were 36 patients (83.7%) with a time interval of less than two months between the first seizure and the onset of AEDs in the group with seizure recurrence. There was no statistically significant difference in the time interval between the first seizure and starting AEDs (p = 0.137). In the group with seizure recurrence, 14 patients (32.6%) experienced one to five seizures after starting AEDs, four patients (9.3%) experienced 6 – 10 seizures, and one patient (2.3%) experienced more than 10 seizures. There was no statistically significant difference in the number of seizures after starting AEDs in relation to seizure recurrence (p = 0.095).

While 39 patients (90.7%) who had seizure recurrence received monotherapy, four (9.3%) received polytherapy. No statistical difference was found in terms of seizure recurrence between monotherapy and polytherapy (p = 0.297). In the patients with seizure recurrence, 38 patients (88.4%) were on AEDs for 2 – 5 years, while five patients (11.6%) were on AEDs for more than five years. There was no statistically significant difference between the groups in terms of the duration of AED use (p = 0.155). In eight patients who were receiving multiple drug therapy and showed an initial history of difficult-to-control seizures, medication was tapered for more than six months. In addition, medication was tapered for more than three months in patients receiving multiple drug treatments who initially had difficulty controlling seizures, attended follow-up appointments at longer intervals, and those whose families were anxious about discontinuing medication. In the group with seizure recurrence, it was observed that five patients (11.6%) had tapered their AEDs in under three months, while 36 patients (83.7%) between three and six months, and two patients (4.7%) more than six months. No statistically significant difference was found in terms of the duration of AED tapering (p = 0.687). While the average seizure-free period prior to discontinuation in the group with seizure recurrence was 2.5 years (min – max: 2 – 7 years), it was three years (min – max : 2 – 9 years) in the group without seizure recurrence. It was found that the pre-discontinuation seizure-free period was higher in the group without seizure recurrence (p = 0.001). Demographic characteristics of the patients are shown in table 2.

Among those experiencing seizure recurrence, the first EEG findings were normal in 15 patients (34.9%) and abnormal in 28 patients (65.1%) (p = 0.944). Cranial MRI findings were normal in 40 patients (93%) in the

Table 2. Demographic characteristics of patients with and without recurrent seizures

	Recurrent Seizures				P value
	Yes (n = 43)		No (n = 254)		
Gender					
Female	26	60.4	124	48.8	0.158[a]
Male	17	39.6	130	51.2	
Seizure type					
Focal	10	23.3	85	33.5	0.184[a]
Generalized	33	76.7	169	66.5	
Seizure onset age					
≤10 year(s)	37	86	216	85	0.863[a]
>10 year(s)	6	14	38	15	
Time from first seizure to initiation of AEI					
0-2 month(s)	36	83.7	178	70.1	0.137[a]
3-12 month(s)	7	16.3	67	26.4	
>12 month(s)	0	0	9	3.5	
AEI used before seizure control					
Monotherapy	39	90.7	215	84.6	0.297[a]
Polytherapy	4	9.3	39	15.4	
Number of seizures after AEI					
1-5	14	32.6	73	28.7	0.095[b]
6-10	4	9.3	7	2.8	
>10	1	2.3	3	1.2	
Seizure-free	24	55.8	171	67.3	
Duration of AEI Use					0.155[c]
2-5 year(s)	38	88.4	241	94.9	
> 5 year(s)	5	11.6	13	5.1	
AEI discontinuation					
< 3 month	5	11.6	32	12.6	0.687[a]
3-6 month	36	83.7	216	85	
> 6 month	2	4.7	6	2.4	
First EEG					
Normal	15	34.9	90	35.4	0.944[a]
Abnormal	28	65.1	164	64.6	
MRI					
Normal	40	93	227	89.4	0.746[c]
Nonspecific	2	4.6	16	6.3	
Abnormal	1	2.4	11	4.3	
Etiology of epilepsy					
Unknown	42	97.7	240	94.5	0.744[c]
Structural	1	2.3	13	5.1	
Genetic	0		1	0.4	
Cognitive status					
Normal	38	88.4	219	86.2	0.702[a]
Abnormal	5	11.6	35	13.8	
Comorbid neurological diseases					
Yes	2	4.6	22	8.7	0.548[d]
No	41	95.4	232	91.3	

a: Chi-Square Test.
c: Fisher-Freeman-Halton Test.
d: Fisher's Exact Chi-square Test.

group with seizure recurrence, and the impact of cranial MRI findings on seizure recurrence was not observed (p = 0.746). In the group with seizure recurrence, the cognitive status of patients was normal in 38 patients (88.4%). There was no statistically significant difference in terms of cognitive status between the groups with and without seizure recurrence (p = 0.702).

In the group with seizure recurrence, 42 patients (97.7%) had idiopathic epilepsy. There was no statistically significant difference between the groups in terms of epilepsy etiology (p = 0.744). Among the patients with seizure recurrence, two patients (4.6%) had spastic hemiparesis. There was no statistically significant difference between the groups in terms of seizure recurrence based on the presence of comorbid neurological diseases (p = 0.548). The demographic characteristics of patients with and without seizure recurrence are presented in Table 2. The results of multivariate logistic regression analysis showed that the risk of seizure recurrence in patients who discontinued AEDs over a period longer than six months increased by 5.25 times as compared to the group of patients who discontinued medication in less than three months (p < 0.001) (Table 3).

Table 3. Risk factors affecting seizure recurrence

	Multivariate logistic regression model	
	OR (95%GA)	p
Gender (male)	0.677 (0.35:1.31)	0.244
Seizure type (generalized)	1.24 (0.61:2.54)	0.551
History of epilepsy (none)	0.81 (0.26:2.56)	0.717
Epilepsy etiology (structural)	2.52 (0.78:8.12)	0.121
First EEG findings (abnormal)	1.05 (0.54:2.05)	0.897
MRI findings (abnormal)	2.68 (0.82:8.75)	0.104
AEI discontinuation period (< 3 month) 3-6 month > 6 month	0.81 (0.33:2.01) 5.25 (1.04:26.60)	0.653 0.045
Drug treatment before seizure control (polytherapy)	1.11 (0.47:2.64)	0.810
Seizure onset age	0.98 (0.91:1.06)	0.619

In the multivariable logistic regression model, the following categories were designated as reference categories: for the gender variable, "female"; for the seizure type variable, "focal"; for the epilepsy history variable, "present"; for the epilepsy etiology variable, "unknown"; for the initial EEG findings variable, "normal"; for the MRI findings variable, "normal"; for the AEI (Antiepileptic Intervention) discontinuation duration variable, "< 3 months"; and for the AEI used before seizure control was achieved variable, "monotherapy".
OR: Odds ratio; CI: Confidence interval.

Discussion

With an incidence of 5 – 10/1,000 people, epilepsy is one of the most common neurological diseases and is becoming more common among children[6]. A critical concern for parents following diagnosis is determining the appropriate time to discontinue AEDs. The risk of seizure recurrence is a significant consideration in the decision to cease medication[7]. Consequently, after a patient achieves remission with AED therapy, the gradual discontinuation of the medication should be considered on an individual basis following a seizure-free period of at least two years. The possibility of a seizure occurring is still the biggest concern when considering ceasing AED use. Currently, there is no consensus regarding the withdrawal of AEDs[8].

In studies examining seizure recurrence following discontinuation of AEDs, varying outcomes have been reported, attributable to the heterogeneity of patient groups. The recurrence rates during follow-up post-AED discontinuation in patients diagnosed with epilepsy range from 11 to 52%[9,10]. In our study, we found a 14.5% seizure recurrence rate during the mean follow-up time of two years (range: 2 – 2 years) following the termination of AEDs. Out of the 200 participants in the study, 27% had a recurrence after ceasing their AED treatment[9]. Verrotti et al.[11] reported a recurrence rate of 28.6% both during the AED tapering phase and after discontinuation. Our study's relatively low recurrence rate may be attributed to all patients with normal EEG results in the last two EEGs prior to AED discontinuation and the exclusion of patients with metabolic diseases from the study.

Regarding gender distribution, our study reported a male/female ratio of one, finding no significant effect of gender on seizure recurrence (p = 0.158). Similar findings have been reported, with the observation that gender did not affect relapse rates[7,8]. Conversely, some studies suggest that female sex is a risk factor for relapse, although the reasons for this remain unclear[12]. In a study, female sex was identified as a significant risk factor in univariate analysis, with the hypothesis that physiological hormonal changes in women might be contributing to this risk[12]. Additionally, the age at which epilepsy begins has been considered a risk factor in numerous studies. Dooley et al.[13] found that seizure onset at age 10 or older was a significant risk factor for seizure recurrence. Similar results suggesting the impact of epilepsy onset after the age of 10 for relapse were reported[12]. In contrast, our study did not find a statistically significant difference in seizure recurrence based on the age of onset (p = 0.863). However,

it was determined that an onset of seizures under the age of two was a favorable prognostic factor[14].

The risk of a seizure recurrence after ceasing AED use has been linked to the etiology of epilepsy. It was found that the recurrence rate for structural–metabolic and unknown etiology groups was significantly higher compared to the genetic group[10]. Nevertheless, there was no statistically significant difference ($p = 0.744$) in the etiology of epilepsy between the groups in our study. This could be because metabolic diseases were excluded and 95% of patients had an unknown etiology. In some studies, the etiology of epilepsy has not been identified as a possible risk factor[9,14].

In our study, a family history of epilepsy was present in 6% of patients. None of the patients with seizure recurrence had a family history of epilepsy. A family history of epilepsy and seizure recurrence were not shown to be significantly correlated in studies[13,15]. There are various studies showing the impact of comorbid neurological diseases on relapse[13,16]. According to a meta-analysis by Shinnar et al.[17], neurological disorders are an important risk factor for relapse. In the study by Bouma et al.[18], when neurological disorders were evaluated together with mental retardation, the risk of relapse was found to be significant. However, depending on the prevalence of concomitant neurological disorders, there was no statistically significant difference observed between the groups in our study regarding seizure recurrence ($p > 0.05$). This may be due to the small number of patients with neurological diseases.

The role of EEG in terms of the risk of relapse after discontinuing AEDs is debatable. In our study, no relationship was found between EEG abnormalities and seizure recurrence ($p > 0.05$). Similarly, no connection was identified between EEG abnormalities and relapse by Shinnar et al[17]. Çeleğen et al.[7] stated in their study that a normal EEG in patients with remission reduces the risk of seizure recurrence. On the other hand, Kılınç et al.[19] demonstrated a close relationship between initial EEG abnormalities and seizure recurrence. It has been suggested that the effects of epilepsy type on seizure recurrence may be more significant than EEG abnormalities. The importance of epileptiform abnormalities in the EEG before discontinuing antiepileptic drugs is still a subject of debate.

In a meta-analysis, it was found that an abnormal EEG before drug discontinuation increased the risk of recurrence by a factor of 1.45. In our study, patients with normal findings in the last two EEGs had their antiepileptic drugs discontinued. Therefore, the impact on seizure risk could not be evaluated. According to Verotti et al.[11], there was no correlation between seizure recurrence and EEG results at the time of diagnosis and prior to AED withdrawal. They suggest that although improvement may be seen in the EEGs of epilepsy patients during treatment, this does not always mean that epilepsy has been completely cured, as the epileptiform abnormalities in the EEG may be suppressed.

In our study, 4% of the patients had abnormal MRI findings and in our study, abnormal MRI findings were not found to be a risk factor for the frequency of relapse. The lack of individuals with hippocampal atrophy and sclerosis and the small number of patients with abnormal MRI results in the group experiencing seizure recurrence may be the reason for this. According to Cardoso et al.[20], the presence of hippocampal atrophy and sclerosis in MRI increases the risk of relapse. Kılınç et al.[19] and Wirrell et al.[3] have determined that abnormal MRI findings are significantly associated with high risks of subsequent seizure recurrences.

The number of seizures prior to AED treatment, the time elapsed between the start of the first seizure and the start of AED treatment, the number of seizures following the initiation of AED treatment, the total number of AEDs before remission, and the response time to treatment were all taken into consideration as measures of the severity of epilepsy[21]. It was discovered that a seizure's pre-control count plays a significant role in its likelihood of recurring[14,22]. Nevertheless, according to reports, none of these variables significantly increases the probability of recurrence[9,14]. The number of seizures after starting AEDs and the interval between the first seizure and the start of AEDs were not found to be significant risk factors in our study ($p > 0.05$).

In our study, 9.3% of patients with recurrent seizures and 15.4% of patients without recurrent seizures were on polytherapy, but no statistically significant effect of polytherapy on seizure recurrence was found ($p > 0.05$). In the study by Çeleğen et al.[7], patients with epilepsy using polytherapy were found to have a risk factor for seizure recurrence. In another study, people using two or more AEDs had a 2.53-fold increased incidence of seizure relapse[23]. Both univariate and multivariate analyses revealed that polytherapy markedly raised the probability of recurrence[21]. Polytherapy was shown not to significantly affect the chance of recurrence in one study[8]. They further attributed this, in accordance with our data, to the inadequate number of patients in the relapse and remission groups receiving polytherapy.

There is a great deal of disagreement over whether long-term AED usage affects the prognosis of epilepsy or merely suppresses seizures to permit spontaneous remission. It was concluded that there was no difference in AED treatment durations between two and five years[17]. It was found that the frequency of recurrence followed a downward trend in patients receiving treatment for more than two years. In a study, univariate analysis revealed that durations of AED use shorter than 4.5 years were not significantly associated with the risk of recurrence[12]. Similarly, our study found no statistically significant difference in recurrence rates between patients on AEDs for 2 – 5 years and those for more than five years ($p > 0.05$).

Before ceasing AEDs, it is generally expected that both adults and children will have been seizure-free for at least two years. The mean time without a seizure before stopping an AED was found to be 2.5 years (range: 2 – 7 years) for patients who had a seizure recurrence and three years (range: 2 – 9 years) for those who did not in our study. The results also showed a strong association between the length of seizure-free period and the risk of recurrence, with significantly lower recurrence rates when seizure-free time exceeded three years[10]. The longer seizure-free period in the group without seizure recurrence was statistically significant ($p = 0.001$)[22,24,9]. However, there was no evidence of a significant correlation between the duration of the seizure-free interval and the possibility of a recurrence[25]. Additionally, it has been observed that patients who stop taking AEDs for fewer than six months have an increased risk of relapse[15,26].

The patients who withdrew from AEDs in under three months had a much greater likelihood of recurrence[7]. However, although this difference was not statistically significant, the study by Ramos-Lizana et al.[15] reported that the risk of recurrence within four years increased by 8% in the group with a tapering period of 4 – 6 weeks, although this difference was not statistically significant. Mastropaolo et al.[27] emphasized the importance of a tapering period of at least six months. This supports previous studies advocating for a quicker tapering of medications[28]. Altunbaşak[14] reports that the recurrence rate was 16.5% for patients whose medication was tapered over a period longer than five months, whereas it was 38.9% for those whose medication was tapered gradually over a period of two to five months. In our study, only eight patients (2.7%) had their medication tapered for more than six months as per the multivariate logistic regression analysis. Patients who tapered medication for longer than six months were those receiving polytherapy and who initially had difficulty controlling seizures. These patients were already clinically suspected of having a high risk of seizure recurrence. In the light of this data, we found that slow drug weaning did not prevent seizure recurrence if a higher incidence was clinically anticipated.

In our study, the mean value of the seizure recurrence period was five months (min – max: 1 – 18 months). A total of 65.1% of cases with seizure recurrence were observed within the first six months, while 23.3% were observed after 12 months. Our study's findings, which show that almost all recurrence happened within the first two years following medication cessation, are in line with those of other research projects[12,28]. Close observation is therefore necessary, particularly in the first six months following the termination of AEDs, though the first two years following treatment discontinuation are thought to be very important[8].

The retrospective design of our study, lack of detailed epilepsy classification, and small number of included patients are limitations of the study.

In summary, we found a seizure recurrence rate of 14.5%, with approximately one-third of these recurrences occurring within the first year following discontinuation. We found no significant relationship between seizure recurrence and variables such as gender, age of seizure onset, seizure type, epilepsy etiology, cognitive status, comorbid neurological diseases, initial EEG findings, MRI abnormalities, timing of AED initiation, initial AEDs used, use of polytherapy, or duration of AED therapy. Predicting the likelihood of which patients may experience seizure recurrence appears to be challenging based on our findings. Further studies involving a larger cohort and examining additional risk factors are necessary to improve our ability to predict seizure recurrence. Although the first year following AED discontinuation is considered to be the highest risk period, close monitoring during the first two years after the discontinuation of medication is crucial.

Author contributions

H. Meteris and A. Ekici made substantial contributions to the conception or design of the research, the acquisition, analysis, or interpretation of data; or the creation of new software used in the work; H. Meteris and A. Ekici approved the version to be published; and all authors agree to be held accountable for all aspects of the research in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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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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