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Anti-seizure medication discontinuation in pediatric epilepsy patients in pediatric neurology practice: A single center experience

Hilal Aydin[1], Ozlem Kemer Aycan[2], Oguzhan Korkut[3], Betul Tosun[4]

[1]Balıkesir University Faculty of Medicine Department of Pediatric Neurology, Balıkesir, Türkiye
[2]Balıkesir University Faculty of Medicine Department of Pediatrics, Balıkesir, Türkiye
[3]Balıkesir University Faculty of Medicine Department of Pharmacology, Balıkesir, Türkiye
[4]Balıkesir Ataturk City Hospital, Clinic of Pediatrics, Balıkesir, Türkiye

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Abstract

The objective of this study was to investigate the relapse rate and associated factors following the discontinuation of antiseizure medication in pediatric patients diagnosed with epilepsy. This retrospective analysis included patients who were followed at the Pediatric Neurology Clinic of Balikesir Education and Research Hospital between August 2019 and June 2023, had received antiseizure medications for 12 to 48 months, and underwent gradual withdrawal of treatment.Clinical and demographic variables recorded included age at seizure onset, seizure type, etiology, family history of epilepsy, history of febrile seizures, presence of neurological comorbidities, number of antiseizure medications used, duration of treatment, number of seizures prior to remission, seizure-free period during treatment, age at the time of drug discontinuation, method of drug withdrawal, EEG findings prior to discontinuation, and time to seizure recurrence post-withdrawal. Among the 30 patients included in the study, 10 (33.3%) were female and 20 (66.7%) were male. The mean age was 8.8 ± 5.0 years (range: 3–18). The most common age of seizure onset was between 4-6 years (n = 9, 30%) and 12-14 years (n = 7, 23.3%). Focal seizures were identified in 3 patients (10%), while generalized seizures were observed in 27 patients (90%). The relapse rate after antiseizure medication (ASM) withdrawal was 3.3%. However, this rate should be interpreted with caution due to the limited sample size. The primary limitation of the study is its relatively small cohort, which may restrict the generalizability of the results. Despite this limitation, the study makes a novel contribution to the literature by concurrently evaluating both clinical and radiological parameters associated with seizure relapse following ASM withdrawal.

Keywords: Antiseizure medication, relapse, epilepsy

Introduction

Epilepsy is a neurological disorder defined by the occurrence of either (1) at least two unprovoked (or reflex) seizures occurring more than 24 hours apart, (2) a single unprovoked (or reflex) seizure with a ≥60% probability of recurrence within the next 10 years, or (3) the diagnosis of an epileptic syndrome with a known predisposition to seizures [1,2]. It may result from various genetic or acquired etiologies. Globally, epilepsy affects approximately 1% of the population and remains a significant public health concern [3]. The majority of cases manifest during childhood, with over 60% of diagnoses occurring in individuals under 18 years of age [3].

The primary goal of epilepsy treatment is to restore the balance between excitatory and inhibitory postsynaptic neuronal activity. Antiseizure medications (ASMs) achieve this by enhancing inhibitory mechanisms or suppressing excessive excitatory activity. It is well established that more than two-thirds of children newly diagnosed with epilepsy respond favorably to ASM therapy and achieve long-term remission [4,5]. The standard management of epilepsy involves the initiation of pharmacological treatment following the first seizure or diagnosis, followed by eventual withdrawal in

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Corresponding Author: Ozlem Kemer Aycan, Balikesir University Faculty of Medicine Department of Pediatric Neurology, Balikesir, Türkiye
Email: ozlemaycan@outlook.com

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selected cases [6]. However, the timing and method of both treatment initiation and discontinuation depend on numerous clinical factors, making them critical stages in the management process [7].

Once pharmacological treatment is initiated, several factors must be considered to optimize therapeutic outcomes. These include choosing the appropriate ASM based on seizure type or epilepsy syndrome, initiating monotherapy with a drug that has minimal side effects and drug interactions, and tailoring the choice based on the patient's age, mental status, comorbidities, and socioeconomic background. Gradual titration to therapeutic doses, maintaining consistency in drug administration, avoiding unnecessary medication changes, ensuring regular follow-ups every six months, monitoring plasma drug levels when necessary, and providing comprehensive education to families about the condition and its treatment all contribute to improved seizure control and treatment adherence [8].

With early and standardized treatment, seizure control is achievable in approximately 90% of pediatric epilepsy cases [9]. In children who remain seizure-free for a defined period, ASM therapy is typically tapered gradually under medical supervision. The reported relapse rates following ASM withdrawal in pediatric patients vary widely, ranging from 12% to 66% [3].

In the present study, we aimed to retrospectively evaluate the clinical characteristics and seizure recurrence rates among pediatric patients diagnosed with epilepsy who achieved at least a 24-month seizure-free period and subsequently underwent gradual withdrawal of ASM therapy. This study represents one of the few investigations from our country to examine seizure relapse after ASM discontinuation in childhood-onset epilepsy, based on clinically verified data.

Material and Methods

This retrospective study included pediatric patients diagnosed with epilepsy who were followed at the Pediatric Neurology Clinic of Balikesir University Hospital between August 2019 and June 2023. All included patients had received antiseizure medication (ASM) therapy for 12 to 48 months and subsequently underwent gradual medication discontinuation. The diagnosis of epilepsy was established by a pediatric neurologist based on clinical presentation, electroencephalography (EEG), and magnetic resonance imaging (MRI), in accordance with the International League Against Epilepsy (ILAE) classification [5].

Inclusion criteria were as follows: (1) diagnosis of epilepsy based on ILAE criteria, (2) age between 1 and 18 years, (3) normal baseline metabolicscreening results, and (4) ASM therapy had been fully discontinued.

Patients with incomplete or missing medical records were excluded from the study.

Patients whose etiology could be determined based on history, clinical findings, and neuroimaging were classified as symptomatic, whereas those with normal neurological examinations, normal cranial MRI, and no evidence of cognitive impairment were categorized as idiopathic.

A retrospective review of patient records was conducted to collect data on the following variables: age, seizure type, epilepsy etiology, family history of epilepsy, history of febrile seizures, presence of neurological impairment, number of ASMs used, duration of therapy, number of seizures prior to remission, seizure-free interval during treatment, age at ASM discontinuation, ASM tapering schedule, EEG findings prior to withdrawal, and time to seizure recurrence post-discontinuation.

All patients had both awake and sleep EEG recordings available from the time of diagnosis and prior to ASM withdrawal. For patients who remained seizure-free for at least two years and had normal or mildly abnormal EEG results, ASMs were tapered over a six-month period. In polytherapy cases, dose reduction was initiated with one ASM, followed by stepwise discontinuation of the remaining medications.

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 22.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were presented as mean ± standard deviation (SD), number (n), and percentage (%). The Mann–Whitney U test was used to compare non-normally distributed variables between two independent groups (Group 1: ASM treatment duration ≤2 years; Group 2: >2 years). A p-value < 0.05 was considered statistically significant. Additionally, Pearson correlation analysis was conducted to examine associations between treatment duration, family history of seizures, and polytherapy use.

This study was approved by the Clinical Research Ethics Committee of Balikesir University Faculty of Medicine on 22 November, 2023 (Approval No: 2023/165). As this was a retrospective study, informed consent from parents or legal guardians was not required.

Results

Between August 2019 and June 2023, a total of 500 patients were diagnosed with epilepsy according to the ILAE classification at the Faculty of Medicine, Balikesir University. Of these, 30 patients who underwent antiseizure medication (ASM) withdrawal met the inclusion criteria and were enrolled in the study. Among them, 10 patients (33.3%) were female and 20 (66.7%) were male. The mean age was 8.8±5.0 years (range: 3–18 years).

Age group distribution showed that the most frequent group was 2–6 years (n=13, 43.3%), followed by 6–12 years (n=9, 30%), 12–14 years (n=4, 13.3%), and 15–18 years (n=4, 13.3%) (Table 1). The most common age of seizure onset was between 4-6 years (n=9, 30%) and 12-14 years (n=7, 23.3%), whereas the least frequent was between 15-18 years (n=1, 3.3%).

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Regarding seizure type, 3 patients (10%) had focal seizures, while 27 patients (90%) experienced generalized seizures. A positive family history of epilepsy was documented in 17 patients (56.7%). Neurological deficits were identified in 4 patients (13.3%) (Table 1).

Table 1. Demographic and clinical characteristics of patients with discontinued ASM therapy

Category	Category	n (%)
Sex	Female	10 (33.3)
	Male	20 (66.7)
Age at seizure onset	2–6 years	13 (43.3)
	6-12 years	9 (30)
	12-14 years	4 (13.3)
	15-18 years	4 (13.3)
History of febrile seizure	2-4 years	4 (13.3)
	4-6 years	9 (30)
	6-9 years	4 (13.3)
	9-12 years	5 (16.7)
	12-14 years	7 (23.3)
	15-18 years	1 (3.3)
Seizure Type	Focal	3 (10)
	Generalized	27 (90)
Family History of Seizure	Present	17 (56.7)
	Absent	13 (43.3)
Neurological Deficit	Present	4 (13.3)
	Absent	26 (86.7)
History of Febrile Seizure	Present	5(16.7)
	Absent	25(83.3)

The most frequently prescribed antiseizure medications (ASMs) among the study population were levetiracetam (n=19, 63.3%) and valproic acid (n=8, 26.7%). Monotherapy was employed in the vast majority of patients (n=29, 96.7%), while only one patient (3.3%) received combination therapy involving two ASMs.

At the time of diagnosis, electroencephalography (EEG) findings were normal in 16 patients (53.3%), demonstrated generalized epileptiform discharges in 8 patients (26.7%), and focal epileptiform discharges in 6 patients (20%) (Table 2).

In Group 1 (treatment duration: 0–2 years), there were 2 female and 1 male patients, while Group 2 (>2 years) included 8 females and 19 males. In Group 1, generalized seizures were observed in 2 patients and focal seizures in 1 patient. In Group 2, 25 patients had generalized seizures and 2 had focal seizures.

None of the patients in Group 1 had a positive family history of epilepsy, whereas 17 patients in Group 2 reported a family history. The mean age of patients was 6.00±5.19 years in Group 1 and 8.96 ±4.97 years in Group 2.

Regarding antiseizure medication (ASM) use, patients in Group 1 received sodium valproate (n=1) or levetiracetam (n=2). In Group 2, the prescribed ASMs included levetiracetam (n=17), sodium valproate (n=7), and phenobarbital (n=2).

The mean duration of treatment was 13.5±0.7 months in Group 1 and 40.0±12.68 months in Group 2.

Table 2. Antiseizure medications used by patients who discontinued ASMs, along with EEG and MRI characteristics

Variable	Category	n (%)
Antiseizure Medication	Valproic acid	8 (26.7)
	Levetiracetam	19 (63.3)
	Carbamazepine	1 (3.3)
	Phenobarbital	2 (6.7)
Pharmacotherapy	Monotherapy	29 (96.7)
	Polytherapy	1 (3.3)
EEG Findings (at diagnosis)	Normal	16 (53.3)
	Generalized	8 (26.7)
	Focal	6 (20)
EEG Findings (prior to medication discontinuation)	Normal	29 (96.7)
	Generalized	1 (3.3)
	Focal	0 (0%)
Treatment Duration	0-2 years	3 (10)
	More than 2 years	27 (90)
MRI	Abnormal	8 (26.6)
	Normal	22 (73.3)
Relapse after drug discontinuation	<1 year	1 (3.3)

The Pearson correlation analysis revealed a statistically significant negative correlation between the presence of a family history of seizures and the duration of antiseizure medication (ASM) treatment (r=-0.385, p=0.032). This suggests that patients with a family history of epilepsy tended to undergo shorter treatment durations, potentially due to earlier diagnosis and more proactive monitoring. However, no statistically significant correlation was found between family history and polytherapy use (r=0.155, p=0.405), nor between treatment duration and polytherapy use (r=-0.060, p=0.749). These results indicate that family history may play a unique role in influencing treatment length, independent of the complexity or intensity of pharmacotherapy.

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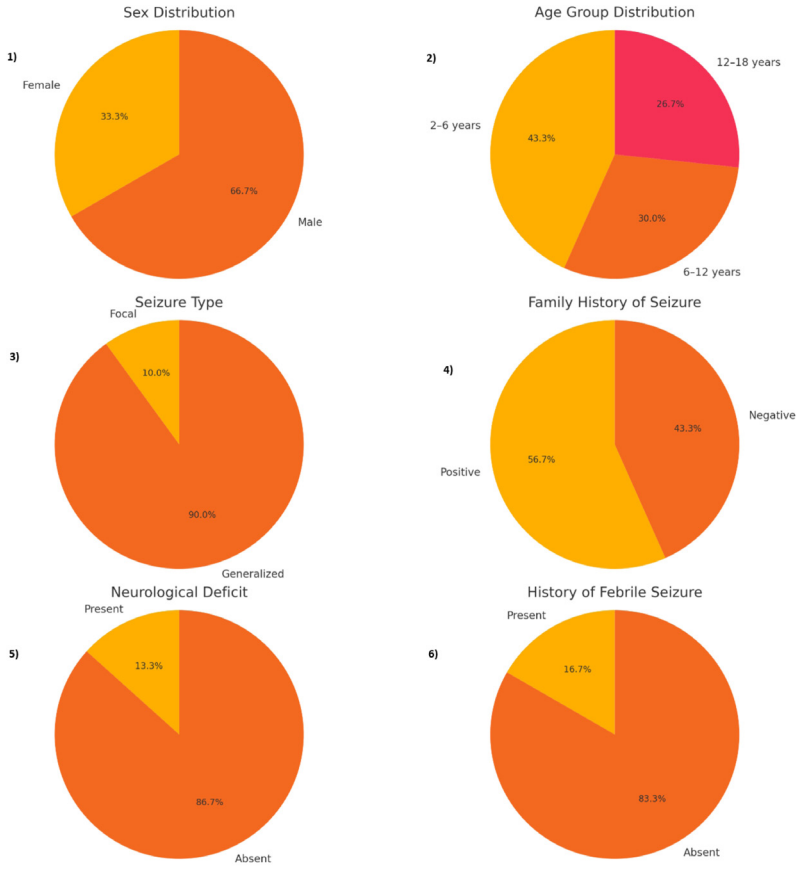

1. The majority of patients were male (66.7%), while females constituted 33.3% of the cohort
2. Patients were mostly in the 2–6 years age group (43.3%), followed by 6–12 and 12–18 years groups.
3. The majority of patients (90%) experienced generalized seizures, with only 10% having focal seizures.
4. A positive family history of seizures was present in 56.7% of patients.
5. Neurological deficits were relatively rare, observed in only 13.3% of the patients.
6. Only 16.7% of the patients had a history of febrile seizures.

Figure 1. Pie charts were used to visually present the distribution of key findings in a clear and interpretable manner

Table 3. Demographic and clinical characteristics by treatment duration

Variable	Group 1 (0–2 years)	Group 2 (>2 years)	p
Sex (Female / Male)	Female:2 Male:1	Female:8 Male:19	0.243
Seizure type (Generalized / Focal)	Generalized:2 Focal:1	Generalized:25 Focal:2	0.151
Family history (Yes / No)	Yes:0 No:3	Yes:17 No:10	0.035*
Age (mean ± SD)	6±5.19 years	8.96±4.97 years	0.168
Polytherapy use (Yes / No)	Yes:0 No:3	Yes:1 No:26	0.743
Neurological deficit (Yes / No)	Yes: 1 No:2	Yes:3 No:24	0.275
ASM preference	Valproate (n=1), Levetiracetam (n=2)	Valproate (n=7), Levetiracetam (n=17), Phenobarbital (n=2) Carbamazepine (n=1)	0.627
Treatment duration (mean ± SD)	13.5±0.7 months	40±12.68 months	0.020*
Febrile seizure history (Yes / No)	Yes: 0 No: 3	Yes: 5 No: 22	0.432

Note: ASM = antiseizure medication; SD = standard deviation. Group 1 includes patients treated for ≤2 years; Group 2 includes those treated for >2 years. The Mann-Whitney U test was used for comparisons. A p-value < 0.05 was considered statistically significant

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Table 4. Pearson correlation coefficients between clinical variables

Variables Compared	Correlation Coefficient (r)	p-value
Family History vs. Treatment Duration	-0.385	0.032
Family History vs. Polytherapy	0.155	0.405
Treatment Duration vs. Polytherapy	-0.06	0.749

Discussion

When considering the discontinuation of antiseizure medications (ASMs), several clinical and demographic factors must be taken into account, including age at seizure onset, seizure frequency and type, family history of epilepsy, presence of neurological deficits, EEG findings, and overall patient compliance [10]. The withdrawal of ASMs not only reduces healthcare costs but also improves the patient's quality of life, particularly given the potential long-term adverse effects associated with chronic ASM use. These side effects may include cognitive impairment, cosmetic issues, ataxia, tremor, and sedation [11,12].

Approximately 70% of individuals with epilepsy do not experience seizure recurrence following ASM treatment, highlighting the importance of identifying appropriate candidates for medication withdrawal [1,3]. In a previous study involving 80 pediatric patients who underwent ASM discontinuation between 2009 and 2019, seizure recurrence was observed in 19 patients (23.75%) during a two-year follow-up period. The mean time to recurrence was reported as 11.09 ± 7.57 months. Although the recurrence rate at three years was 4.9%, 13 patients were followed for more than four years—with the longest follow-up extending to seven years—and no recurrences were observed beyond the fourth year, indicating that the majority of recurrences tend to occur within the first two years post-discontinuation [13].

In addition, a positive family history of epilepsy has been identified as a significant risk factor for recurrence following ASM withdrawal [14].

In our study, a statistically significant negative correlation was observed between family history of seizures and treatment duration ($r = –0.385$, $p = 0.032$), indicating that patients with a positive family history tended to undergo shorter courses of antiseizure medication (ASM) therapy. This finding may reflect the influence of earlier diagnosis and increased clinical vigilance in families with known epilepsy, potentially contributing to more efficient management and faster achievement of seizure control.

A similar association was reported by Dooley et al. [14], who found that a familial predisposition to epilepsy was linked to more proactive treatment strategies and favorable clinical outcomes in pediatric patients.

In contrast, other studies have associated a positive family history with an elevated risk of seizure recurrence following ASM withdrawal. Ghiasian et al. [15], for instance, demonstrated a significantly higher relapse rate in patients with a familial history of epilepsy, thereby supporting a more cautious approach to drug discontinuation. Likewise, Zhao et al. [13] emphasized that genetic susceptibility may contribute to seizure recurrence despite gradual tapering of therapy.

These conflicting findings highlight the complexity of interpreting family history as a prognostic indicator in pediatric epilepsy. While it may confer benefits in early detection and treatment, it may also signal a higher intrinsic risk for relapse. Therefore, further large-scale, prospective studies are needed to clarify the impact of familial predisposition on both treatment duration and long-term seizure outcomes.

In a study by Pavlovic et al., 95.4% of seizure relapses occurred within the first two years following antiseizure medication (ASM) withdrawal, with more than half (54.5%) occurring within the first six months. Additionally, 18.8% of relapses were reported during the tapering phase itself [16]. Similarly, Çeleğen et al. found that 40% of patients experienced seizure recurrence within the first year of drug discontinuation [17]. Across the literature, reported relapse rates following ASM withdrawal range from 10% to 70% [18]. In our study, only one patient (3.3%) experienced seizure recurrence, which occurred four months after treatment cessation.

Currently, there is no consensus regarding whether or when ASM therapy should be discontinued in pediatric or adult patients in remission. The average relapse risk—reported to be approximately 23.7%—continues to raise concerns among clinicians [19]. As a result, the timing and tapering method of ASM withdrawal remain sources of hesitation and variability in clinical practice. According to prior studies, ASM tapering can be performed gradually over a period of up to two years or more rapidly within 3–6 months [20]. In the present study, all ASM tapering protocols were conducted over a standardized 6-month period.

Another factor influencing treatment outcomes is the type of therapy—monotherapy versus polytherapy. In a cohort of 188 patients, Wang et al. reported that relapse rates were twice as high among those receiving polytherapy compared to those on monotherapy [21]. Their study also found no significant association between relapse and variables such as age, sex, perinatal history, or imaging abnormalities. However, abnormal EEG findings prior to drug withdrawal were significantly associated with increased relapse risk. Notably, polytherapy regimens most frequently included combinations such as valproate with lamotrigine or carbamazepine.

Our findings differ in this regard, as only one patient in our cohort received polytherapy and no seizure recurrence was observed in that case. Similarly, Çeleğen et al. found that 20% of patients in the relapse group had received polytherapy, in contrast to just 5.3% in the non-relapse group—a statistically significant difference ($p = 0.036$) [16].

EEG abnormalities have also been consistently linked to

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increased relapse risk. A meta-analysis concluded that features such as slowing, spike-wave discharges, and paroxysmal activity significantly increased the likelihood of seizure recurrence after ASM withdrawal [22]. In our study, the single patient who experienced relapse had a focal EEG abnormality prior to tapering.

Other identified risk factors include polytherapy, febrile seizures, and high pre-treatment seizure frequency. Verrotti et al. reported a relapse rate of 28.6% in a cohort of 187 pediatric patients and found that relapse was more likely in children with a history of febrile seizures, polytherapy, and recurrent seizures prior to treatment [23]. However, other studies have found no significant association between prior febrile seizures and relapse risk [24].

Epilepsy etiology has also been evaluated as a predictor of relapse. Several studies suggest that children with structural abnormalities—such as congenital malformations, brain tumors, or imaging-detected lesions—are at higher risk of seizure recurrence compared to those with idiopathic epilepsy [24,25]. For instance, Çeleğen et al. observed significantly higher relapse rates among patients with symptomatic epilepsy [17]. Conversely, Specchio et al. found no association between epilepsy etiology and relapse risk [26].

According to the Italian League Against Epilepsy, ASM withdrawal is not recommended in patients with abnormal neuroimaging findings [27]. Interestingly, in our study, none of the patients with MRI abnormalities experienced relapse. Furthermore, existing literature indicates that focal seizure types may be more prone to relapse than generalized seizure types [28], which aligns with the EEG findings in our single relapse case.

Conclusion

In the present study, we evaluated clinical data and recurrence patterns in pediatric patients diagnosed with epilepsy, who were regularly followed in our clinic from its establishment to the present, with a particular focus on those who underwent antiseizure medication (ASM) withdrawal.

Currently, there is no clear consensus in the literature regarding the association between ASM discontinuation and variables such as age, sex, age at seizure onset, family history of epilepsy, history of febrile seizures, or EEG findings before or after treatment. However, the prevailing evidence suggests that patients receiving polytherapy and those with abnormal EEG or MRI findings are at increased risk of seizure recurrence following drug withdrawal.

It is generally recommended that ASM therapy be continued for at least two years in patients who achieve seizure control. Furthermore, when discontinuation is considered, the tapering process should be performed gradually over a minimum of three months to reduce the risk of relapse.

The primary limitation of this study is the relatively small sample size (n = 30), which restricts the generalizability of the findings and limits the statistical power to detect significant associations. Additionally, the single-center and retrospective design may reduce the external validity of the results and introduce potential biases related to data completeness and accuracy.

Another important limitation is the low number of relapse cases—only one patient experienced seizure recurrence—which prevented meaningful subgroup analyses and limited the ability to identify potential predictors of relapse.

To overcome these limitations, future studies should adopt multicenter, prospective designs with larger cohorts. Such studies would improve the robustness of statistical analyses and contribute to the development of evidence-based guidelines for antiseizure medication withdrawal in pediatric epilepsy management.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
This study was approved by the Clinical Research Ethics Committee of Balikesir University Faculty of Medicine on 22 November, 2023 (Approval No: 2023/165).

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