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Withdrawal of antiseizure medications in patients who are seizure-free

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Abstract

Objective: To evaluate the demographic data and resolved-relapse rates in clinical follow-up of patients whose antiseizure medications (ASM) were discontinued after a minimum of 2 years of seizure freedom. *Methods:* The files of 1985 patients followed in the epilepsy outpatient clinic were evaluated retrospectively. The inclusion criteria for patients were between 18 and 65 years old, followed up at an epilepsy outpatient clinic, and having discontinued ASM after at least 2 years of seizure freedom under the supervision of a neurologist. *Results:* A total of 56 patients were included in the study. The age of onset of seizures was 13.9±10.04 years, the age of onset of ASM was 15.87±9.69 years, and the age of quitting ASM was 24.58±11.54 years. The patients had a mean seizure-free period of 64.46±32.27 months before drug discontinuation and 43.73±38.87 months after drug discontinuation. The EEGs of 49 patients were normal in the EEGs performed after drug discontinuation, and seven patients had epileptiform discharges. Relapse was observed in 23.2% of patients after drug discontinuation. It was observed that 69% of the recurrences in 13 patients occurred within the first 2 months.
Conclusion: Although seizure recurrence probability is highest during the first 2 months after ASM discontinuation, it is still possible 6 years later in adults with inactive epilepsy. The time window without seizures before ASM discontinuation and follow-up EEGs afterwards may help in the prediction of seizure recurrence.

Keywords: Anti-seizure medications, withdrawal, recurrence, epilepsy

INTRODUCTION

Epilepsy is a chronic disease characterised by recurrent and unprovoked seizures affecting 1% of the population.[1] Seizures can be suppressed with appropriate antiseizure treatment at rates ranging from 65% to 85%.[2] Epilepsy is not always a lifelong disease. A patient is considered resolved if they have been followed up without seizures for 10 years and at least 5 years of this period should be medication-free, or the patient has passed the age range for an age-related epilepsy syndrome.[3] The adverse effects of antiseizure medications (ASM), such as behavioural and hormonal disorders and the desire of patients to be free of social life restrictions, provide the motivation for the discontinuation of ASM in individuals with epilepsy whose seizures are resolved.[4-6] When seizure-freeness is achieved under treatment, it is difficult to predict whether this is due to epilepsy resolved or treatment. This situation makes drug discontinuation controversial. Our study aimed to evaluate the relapse rates in the clinical follow-ups of patients whose ASM were discontinued after discussing with the patient with a minimum seizure freedom of 2 years.

METHODS

In our epilepsy outpatient clinic, epilepsy patients are followed regularly according to the clinical course of their disease. Seizure semiology is enquired from the patient and seizure observers; if possible, home videos of seizures are requested. A neurological examination is done, and if necessary, an IQ or cognitive test is performed. During follow up, the seizure course of patients is questioned, and treatment changes are planned when necessary. The patients who have an increase in the frequency of seizures during the course of the disease are hospitalised and followed up when necessary. In patients presenting with seizures, blood tests (biochemistry including electrolytes, thyroid function tests, hemogram, and if suspected, serologic test for infectious-, connective tissue-, metabolic-, immunologic diseases; genetic

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tests), routine awake EEG when possible with video recording, cranial MRI (1.5 Tesla) with epilepsy protocol [including T1(axial; without contrast), T2(axial and sagittal), FLAIR(axial and coronal), SWI(axial), DWI(axial), ADC(axial) and coronal STIR for hippocampal region)] or cranial computed tomography when MRI could not performed and, if necessary, sleep EEG when possible with video recording, EEG with sleep deprivation, cranial MRI with contrast, rarely cortical SSEP are taken. Routine awake EEG, which is described in the methods section, is performed every 6 months for patients without seizures. After ASM withdrawal, all patients are scheduled for follow-up every 6 months, and an EEG is performed during their visits for all compliant patients. This is the follow-up protocol of our clinic after ASM withdrawal because, in our country, the legislation regarding obtaining a driver's license for epilepsy patients makes this mandatory.

In our study, the files of 1985 patients who were followed up in the epilepsy outpatient clinic between 1999-2021 were reviewed. Age at the time of study, sex, history of febrile convulsions, family history of epilepsy, consanguinity between parents, age of seizure onset, learning disability, age of ASM onset, cranial magnetic resonance imaging, electroencephalogram (EEG) findings after ASM withdrawal to be evaluated as normal, focal or generalised epileptiform activity, abnormal findings of neurologic examinations, seizure type, age of ASM withdrawal and seizure-free time after ASM withdrawal were documented. All patients analysed were on monotherapy before withdrawal from antiseizure medication. We explore the criteria used to predict relapse, drawing upon insights from recent literature, including the study by Beghi *et al*. (2021).[7]

All EEGs taken during the follow-up period of our patients were recorded using silver cup electrodes placed according to the International 10-20 system for 20 minutes while the patient was awake and resting (Nicolet Version 5.91 Natus, Middleton, WI 53562). Hyperventilation for 3 minutes and 5-40 Hz photic stimulation (with 10-second intervals for 10 seconds; in the second half, the eyes were closed) were performed during EEG recordings.

The inclusion criteria for patients were as follows: being between 18 and 65 years old (because our clinic is an adult epilepsy service), following up at our epilepsy outpatient clinic, and having discontinued ASM after at least 2 years of seizure freedom under the supervision of a neurologist.

The exclusion criteria were discontinuation of ASM by the patient without discussing it with the physician. In our study, individuals under the age of 18 and those over the age of 65 were not included during file scanning.

Statistical analysis was performed using SPSS 20.0 software (IBM SPSS Statistics, Armonk, NY). The normal distribution of numerical data was analysed using Shapiro-Wilk and Kolmogorov-Smirnov tests. The student t-test was used to compare normally distributed continuous values. The chi-square tests were used to compare the significance of categorical data and the percentage ratios in the groups. Statistical significance was set at $p < 0.05$.

This study is approved by the Haydarpasa Numune Training and Research Hospital Ethics Committee (Date 28/02/2021, Protocol no: 3515).

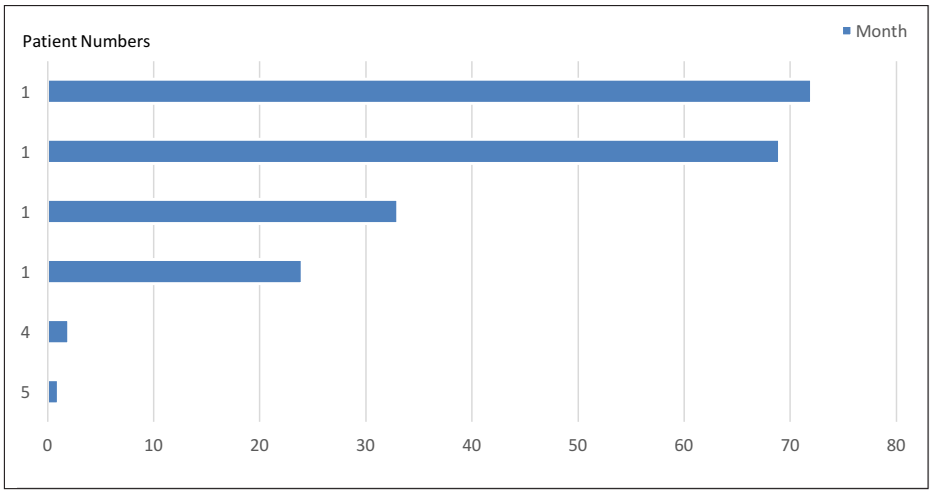
RESULTS

Sixty-one patients who were seizure-free were followed up without medication; two patients were excluded because of insufficient data, and three patients because of epileptiform discharges in EEG before ASM withdrawal. Although the presence of epileptiform activity in the EEG before drug discontinuation did not predict the risk of recurrence in a study by Beghi *et al*. in 2021, The Italian League Against Epilepsy identified this situation as a risk factor for relapse of seizure. Due to both the low number of individuals with epileptiform activity before medication withdrawal in our study and the conflicting literature on this issue, these patients were not included in our study.[7,8]

The study recruited 56 patients, 28 women and 28 men. The mean age of seizure onset of the patients was 13.90±10.04 years, the mean ASM onset age was 15.87±9.69 years, and the mean ASM withdrawal age was 24.58±11.54 years. In 64% (n=36) of the patients, the total number of seizures was between 1 and 5 during the follow-up period before discontinuation of ASM. The mean seizure-free follow-up time was 63.5±29.8 months before drug discontinuation and 43.4±36.9 months after ASM withdrawal (Table 1). All patients included in the study were receiving monotherapy before drug discontinuation. Seizure recurrence was observed in 23% of the patients whose drug was discontinued. Relapse occurred between 1 month and 6 years. Sixty-nine per cent of relapses occurred within the first 2 months of ASM withdrawal. When compared with the group without recurrence, the seizure-free time before ASM withdrawal (p=0.047) and interictal EEG

Table 1: Demographic and clinical information of the patients

	Seizure recurrence after ASM withdrawal (n=13)	No seizure recurrence after ASM withdrawal (n=43)	p
Sex			0.52
Female	5 (38.4%)	23 (53.4%)	
Male	8 (61.6%)	20 (46.6%)	
Seizure type			0.50
Focal onset	3 (23%)	16 (37.2%)	
Generalised onset	10 (77%)	27 (62.8%)	
History of febrile convulsions			0.70
Yes	3 (23%)	8 (18.6%)	
No	10 (77%)	35 (81.4%)	
Family history of epilepsy			0.34
Yes	4 (30.7%)	21 (48.8%)	
No	9 (69.3%)	22 (51.2%)	
Abnormal findings of neurologic examinations			0.41
Yes	1 (7.6%)	1 (2.3%)	
No	12 (92.4%)	42 (97.7%)	
Consanguinity between parents			0.999
Yes	2 (15.3%)	9 (20.9%)	
No	11 (84.7%)	34 (80.1%)	
Learning Disability			0.999
Yes	1 (7.6%)	3 (6.9%)	
No	12 (92.4%)	40 (93.1%)	
Cranial magnetic resonance imaging anomaly			0.37
Yes	3 (23%)	5 (11.6%)	
No	10 (77%)	38 (98.4%)	
Age of seizure onset (years)	11.92±10.86	14.64±9.83	0.122
Age of ASM onset (years)	15.46±9.71	16.00±9.80	0.770
Age of ASM withdrawal (years)	22.23±9.52	25.30±12.09	0.393
Total number of Seizures before ASM withdrawal			0.673
1-5	9 (69.2%)	29 (67.4%)	
6-10	1 (7.7%)	8 (18.6%)	
11-15	1 (7.7%)	3 (7%)	
>15	2 (15.4%)	3 (7%)	
Seizure-free period after ASM withdrawal (month)	25.30±30.36	49.30±39.73	**0.11**
Seizure-free period before ASM withdrawal (month)	49.92±16.02	68.86±37.71	**0.047**
EEG findings after ASM withdrawal			**<0.001**
Normal	7 (53.8%)	42 (97.7%)	
Focal discharge	1 (7.7%)	-	
Generalised discharge	5 (38.5%)	1 (2.3%)	



ASM: Antiseizure Medications

Figure 1. Seizure time after ASM withdrawal in recurrence group

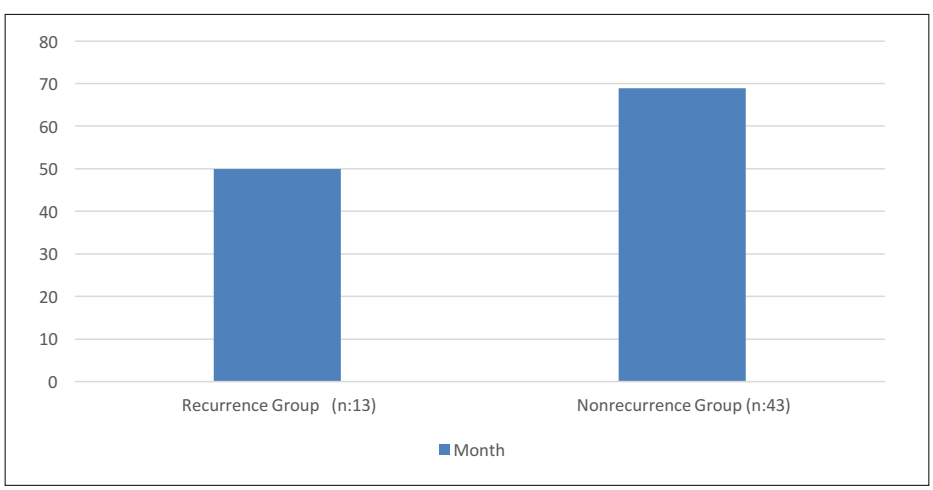
findings after ASM withdrawal ($p<0.001$) were found to be statistically significant in predicting relapse of seizures (Table 1).

Abnormal findings in neurologic examinations, consanguinity between parents, history of febrile convulsions, family history of epilepsy, learning disability, seizure onset age, and seizure types were not found statistically significant in predicting the risk of seizure relapse (Table 1).

DISCUSSION

In our study, seizure recurrence was observed in 23% of the patients; relapses occurred frequently in the first 2 months, signifying the importance of close follow-up of patients in the early period (Figure 1). The period without seizures was shorter for patients who experienced seizures after withdrawing from ASM compared to those who remained seizure-free ($p=0.047$) (Figure 2). In other studies, an increased risk of seizure recurrence was reported in the first year following ASM withdrawal.[9,10] Despite the fact that patients reported being seizure-free for more than 5 years on average before ASM withdrawal, seizure recurrence was observed in approximately one-quarter of the patients during the ASM-free follow-up period. This shows that being seizure-free under ASM is not sufficient to predict seizure recurrence.

Patient-specific approaches are currently recommended for ASM withdrawal in case of a



ASM: Antiseizure Medications

Figure 2. Seizure-free time before ASM wihtdrawal (months)

seizure-free period exceeding 2 years in patient groups known to be at low risk of recurrence.[11] Although there are articles in the literature stating that a long period of remission reduces the risk of relapse, there are also studies showing that there is no significant relationship between the risk of remission and the risk of relapse.[12] The average seizure-free follow-up period before ASM withdrawal was found to be approximately in the seizure recurrence group 4.16 years, and in the no recurrence group 5.7 years, respectively (Table1). As recommended in the literature, a seizure-free monitoring period of 2 years before ASM withdrawal is suggested.[12] However, it is noteworthy that in our patients, this duration seems to be notably longer, potentially reducing the risk of seizures recurring. The files of two patients with seizure recurrence of more than 6 years later were reviewed. There was no distinctive feature in the history of these patients, and it was learned that one of the patients had a seizure triggered by emotional stress, and the other had a spontaneous relapse.

In our study, which included patients who did not have epileptiform discharge in the EEG taken before ASM withdrawal, the presence of epileptiform discharge in the follow-up EEGs after ASM withdrawal was found to be statistically significant in predicting the risk of seizure relapse ($p<0.001$). In different studies, including both paediatric and adult patient groups, it was observed that epileptiform discharges in EEG follow-ups after ASM withdrawal increased the risk of relapse.[11]

In the literature, it has been observed that a learning disability increases the risk of seizure recurrence in prospective studies with paediatric populations.[13,14] Our study results revealed that learning disability made no significant difference in increasing the risk of relapse, which might be due to having an adult patient population. The results of our study about family history of epilepsy and history of febrile seizures were in line with the guidelines of the Italian League Against Epilepsy (2013), which stated that having a family history of epilepsy or a history of febrile seizures were not contraindications to ASM withdrawal.[8]

It has been stated that the age of seizure onset in adolescence and adulthood carries a higher risk of seizure relapse compared with childhood.[11,15] It has also been reported that symptomatic epilepsy syndromes that begin in the newborn and early childhood and accompanying pathologies such as cerebral palsy may have a higher risk of relapse compared with idiopathic epilepsy syndromes that begin in childhood.[15] In a meta-analysis including 10 studies, the age at onset of epilepsy associated with seizure recurrence is U-shaped with elevated risk in the newborn and first year of life decreases with childhood and begins to increase by adolescence.[15] Due to the age range of the patient population included in our study, it was thought that the age of seizure onset was not significant in predicting the risk of relapse.

In our study, in which the patient groups were divided into seizure types with focal or generalised onset, there was no statistically significant difference in the risk of relapse between the patient groups with focal or generalised onset seizures. However, it has been reported in the literature that focal-onset seizures have a higher risk of relapse.[16-18]

The limitations of our study are that the study was retrospective, the number of patients was not large, and our patient group mostly consisted of adolescent and adult-onset epilepsy. On the other hand, the strengths of this study are that the study population consisted of patients who remained seizure-free on ASM for a long time and that these patients continued to be followed for a long time after ASM withdrawal.

In conclusion, seizure relapses were observed in 23% of the patients whose ASM were withdrawn. Although the first 2 months, in particular, are a high-risk period for seizure recurrence after ASM withdrawal, recurrence can also be seen after 6 years. The seizure-free period before ASM withdrawal and follow-up EEGs after ASM withdrawal are important in predicting relapse. In individuals with epilepsy whose seizures are in remission with ASM, individual ASM withdrawal should be considered.

DISCLOSURE

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Conflict of interest: None.

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