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Risk of Recurrence After Anti-Seizure Medication Discontinuation

Nöbet Önleyici İlaç kesimi Sonrası Rekürrens Riski

Firdevs Ezgi UÇAN TOKUÇ[1], Merve GÜRSOY HASOĞLAN[1], Fatma GENÇ[1], Meltem KORUCUK[1], Abidin ERDAL[2], Yasemin BİÇER GÖMCELİ[3]

[1]Republic of Turkey Ministry of Health Antalya Provincal Health Directorate University of Health Sciences Antalya Training and Research Hospital, Antalya, Turkey
[2]Department of Neurology, Health Ministry of Turkey Republic, Ankara Bilkent City Hospital, Ankara, Turkey
[3]Department of Neurology, Memorial Antalya Hospital, Antalya, Turkey

Öz

Uygun nöbet önleyici ilaç tedavisi ile epilepsi hastalarının yaklaşık 2/3'ünde nöbetsizlik sağlanabilmektedir. Uzun süreli nöbetsizlikten sonra hem hastalar hem de hekimler için ilaçların kesilmesi fikri ön plana çıkmaktadır. Biz de bu çalışma ile nöbet önleyici ilaç tedavisi kesilen hastalarda nöbet nüks oranlarını ve nüksü etkileyen faktörleri araştırmayı amaçladık. Çalışmaya 50 hasta dahil edildi. Hastaların 28'i (%56) kadındı, yaş ortalaması 41.28±14.58 yıl ve ortalama epilepsi süresi 15.20±9.90 yıldı. Hastaların 14'ünde (%28) nüks gözlendi. Nüks risk faktörleri incelendiğinde, nöbetsizlik süresi arttıkça nüks riskinin azaldığı tespit edildi. Çalışmamız nöbet önleyici ilaçların kesilmesinden sonra nüks riskinin ilaç kesim öncesi nöbetsizlik süresi uzadıkça azaldığını desteklemektedir. Ancak, ilacı bırakma kararının hasta bazında bireyselleştirilmesi gerektiği unutulmamalıdır.

Anahtar Kelimeler: Epilepsi, Nöbet Önleyici İlaç Kesimi, Nöbetsizlik, Nüks

Abstract

With appropriate anti-seizure medication, long-term seizure freedom can be achieved in about 2/3 of patients with epilepsy. After long-term seizure freedom, the idea of medication discontinuation arises for both patients and physicians. In this study, we aimed to investigate seizure recurrence rates and the factors affecting recurrence in patients whose anti-seizure medication treatment was discontinued. Fifty patients were included in the study. Twenty-eight (56%) patients were female, with a mean age of 41.28±14.58 years and a mean duration of epilepsy of 15.20±9.90 years. Recurrence was observed in 14 (28%) patients. When the recurrence risk factors were analyzed, it was observed that the risk of recurrence decreased as the seizure-free period increased. Our study supports that the risk of relapse after discontinuation of anti-seizure medications decreases as the seizure-free period is prolonged. However, it should not be forgotten that the decision to discontinue medication should be individualized.

Keywords: Epilepsy, Anti-Seizure Medication Discontinuation, Seizure-Free, Recurrence

Introduction

Although epilepsy is one of the most common chronic neurological diseases, long-term seizure freedom can be achieved in approximately 2/3 patients with appropriate anti-seizure medications (ASMs) (1). However, long-term use of ASMs has several adverse effects on many systems, including the kidneys, liver, central nervous system, and fertility, as well as negative impacts on the quality of life and economic status of patients (2). Consequently, after a long-term absence of seizures, the idea of discontinuing medication arises for both patients and physicians. Predicting the risk of seizure recurrence after discontinuation is the most important point in the decision and timing of medication discontinuation. In previous studies, it was claimed that medication discontinuation should be discussed with patients who have achieved seizure freedom for 2 to 5 years after treatment with ASMs. However, it was reported that the risk of recurrence after medication discontinuation should be carefully evaluated (3-7). As studies on recurrence rates after medication discontinuation increased, many new algorithms that may indicate the risk of recurrence were developed. It was emphasized in many studies that the risk of recurrence is never guaranteed to be zero (8). Additionally, to emphasize that epilepsy is not a disease that can be ultimately cured, the International League Against Epilepsy (ILAE) Task Force introduced a new definition. They suggested using the term 'resolved' to describe a situation where the individual no longer has active epilepsy. This terminology underscores that while the person might not currently experience epileptic events, there is no absolute assurance that the condition will not recur in the future. The task force further stated that the risk of recurrence can depend on multiple factors such as the type of epilepsy, age, syndrome classification, etiology, treatment, and various other factors (9). In recent studies, recurrence rates have been demonstrated to vary between 12% and 67% (10).

We aimed to investigate the seizure recurrence rates and the factors affecting recurrence in patients

	ORCID No
Firdevs Ezgi UÇAN TOKUÇ	0000-0002-0347-6026
Merve GÜRSOY HASOĞLAN	0000-0002-4035-4757
Fatma GENÇ	0000-0002-6062-3694
Meltem KORUCUK	0000-0002-0497-3980
Abidin ERDAL	0000-0003-3698-8201
Yasemin BİÇER GÖMCELİ	0000-0001-5043-0891

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Adres / Correspondence : Firdevs Ezgi UÇAN TOKUÇ
Republic of Turkey Ministry of Health Antalya Provincal Health Directorate University of Health Sciences Antalya Training and Research Hospital, Antalya, Turkey
e-posta / e-mail : ezgiucan@gmail.com

in whom treatment of ASMs was discontinued in our clinic. We want to underline the importance of continuous monitoring and individualized patient management even after a period of seizure freedom.

Material and Method

This study was approved by the ethics committee of Antalya Training and Research Hospital (2024/072). The files of all patients who were followed up in the epilepsy outpatient clinic of Antalya Training and Research Hospital between 2012 and 2023 were retrospectively reviewed. Patients with a definite diagnosis of epilepsy according to the ILAE 2014 definition of epilepsy (9), and who self-discontinued their medication for any reason, and all epilepsy patients whose anti-seizure medication was completely discontinued under physician control after 2 years or more of seizure-free status, were included in the study. Age, gender, age at onset, duration of the disease, seizure type, epilepsy type, family history, parental consanguinity, history of febrile convulsions, etiology of the disease, neurological examinations, cranial magnetic resonance imaging (MRI) findings, ASMs used, last discontinued ASMs, seizure-free period and electroencephalogram (EEG) findings before and after medication discontinuation were recorded.

Patients younger than 18 years of age, patients who had seizures during the discontinuation of ASMs, patients who voluntarily discontinued the medication but had not been seizure-free for a period of 1 year before discontinuation, patients who did not present to the hospital in the last 6 months after discontinuation and patients with a follow-up period of less than 1 year after drug discontinuation were excluded from the study.

Statistical Method

The data were analyzed with IBM SPSS V23. The conformity to the normal distribution was examined by the Shapiro-Wilk test. Yates correction, the Fisher-Exact test, and the Fisher-Freeman-Halton test were used to compare categorical variables between groups. Mann-Whitney U test was performed for the comparison of non-normally distributed data according to the binary group. The effect of independent variables on the recurrence time was analyzed by Cox regression analysis. Log Rank (Mantel-Cox) test was utilized to compare the duration of recurrence according to the number of seizure-free years. The results of the analyses were presented as mean±standard deviation and median (minimum- maximum) for quantitative data and frequency (percentage) for categorical data. The significance level was taken as $p<0.05$.

Results

The medical records of 3200 patients who were followed up in the epilepsy outpatient clinic of Antalya Training and Research Hospital between 2012 and 2023 were analyzed. Fifty patients who had discontinued anti-seizure medication and met the appropriate criteria were included in the study. Twenty-eight (56%) of the patients were female, with a mean age of 41.28±14.58 years and a mean duration of epilepsy of 15.20±9.90 years. Recurrence was observed in 14 (28%) patients. Nine (18%) patients discontinued their medication on their own, and recurrence developed in 55.5% of these patients. This group constituted 35.7% of the patients with recurrences. Recurrence was observed in 10 (71.5%) patients within the first year and 80% of these patients had recurrence within the first 6 months. While 3 (21.4%) patients developed recurrence within the 2nd year, 1 (7.1%) patient had recurrence within the 3rd year.

Patients were divided into two groups: those with recurrence and those without recurrence, and no difference was observed between age, gender, epilepsy type, duration of epilepsy, presence of etiology, presence of pathology on cranial MRI, and EEG abnormalities both during and after discontinuation (Table 1).

The effect of independent risk factors on recurrence was analyzed by Cox regression analysis with univariate and multiple models. When the results of the univariate model were analyzed, the risk of recurrence was 24.96 times higher in generalized epilepsy compared to focal epilepsy ($p=0.009$). The risk of recurrence increased 1.379 times as the seizure-free period decreased ($p=0.023$). In the multiple model, the risk of recurrence increased 1.488 times as the seizure-free period decreased ($p=0.034$). Other variables had no statistically significant effect ($p>0.050$) (Table 2).

The recurrence time did not differ when the seizure-free periods were divided into 2 groups: >5 years and ≤5 years ($p=0.516$). The mean recurrence time was 76.455 months in the 5 years or less group and 91.165 in the >5 years group (Table 3) (Figure 1).

Table 1. Comparison results according to recurrence.

	Recurrence		Total	Test	p
	Available (n=14)	N/A (n=36)	(n=50)	statistics	
Age	40.07±13.14 37.00(24.00-67.00)	41.75±15.26 38.50(22.00–70.00)	41.28±14.58 37.50(22.00-70.00)	237.000	0.746[a]
Gender					
Female	6 (42.9)	22 (61.1)	28 (56)	0.723	0.395[b]
Male	8 (57.1)	14 (38.9)	22 (44)		
Etiology					
Yes	6 (42.9)	20 (55.6)	26 (52)	0.242	0.623[b]
No	8 (57.1)	16 (44.4)	24 (48)		
Etiology					
Perinatal injury	1 (16.7)	1 (5)	2 (7.7)		
Febrile convulsions	2 (33.3)	2 (10)	4 (15.4)		
CNS Infection	0 (0)	2 (10)	2 (7.7)		
Head Trauma	3 (50)	8 (40)	11 (42.3)	4.460	0.718[d]
SAH-CVD	0 (0)	3 (15)	3 (11.5)		
Brain Tumor	0 (0)	2 (10)	2 (7.7)		
Other	0 (0)	2 (10)	2 (7.7)		
Age at Epilepsy Diagnosis (years)	21.00±15.05 17.00	28.00±16.47 25.00	26.04±16.25 22.50	174.000	0.092[a]
Duration of epilepsy (years)	19.07±9.37 16.00	13.69±9.81 11.00	15.20±9.90 13.50	163.500	0.056[a]
Epilepsy Type					
Focal	9 (64.3)	25 (69.4)	34 (68)		
Generalized	1 (7.1)	0 (0)	1 (2)	2.350	0.406[d]
Unclassified	4 (28.6)	11 (30.6)	15 (30)		
History of Status Epilepticus					
Yes	1 (7.1)	4 (11.1)	5 (10)	---	1.000[c]
No	13 (92.9)	32 (88.9)	45 (90)		
Cranial MRI Findings					
Lesion available	5 (35.7)	16 (44.4)	21 (42)	0.059	0.808[b]
Lesion N/A	9 (64.3)	20 (55.6)	29 (58)		
Used medication					
Monotherapy	12 (85.7)	28 (77.8)	40 (80)	----	0.704[c]
Polytherapy	2 (14.3)	8 (22.2)	10 (20)		
ASM					
Levetiracetam	6 (42.9)	12 (33.3)	18 (36)		
Carbamazepine	3 (21.4)	10 (27.8)	13 (26)		
Oxcarbazepine	0 (0)	5 (13.9)	5 (10)		
Valproate	3 (21.4)	4 (11.1)	7 (14)	6.141	0.550[d]
Lamotrigine	1 (7.1)	3 (8.3)	4 (8)		
Topiramate	0 (0)	1 (2.8)	1 (2)		
Zonisamide	0 (0)	1 (2.8)	1 (2)		
Phenytoin	1 (7.1)	0 (0)	1 (2)		
Duration of epilepsy until remission (years)	13.21±7.43 11.50	10.08±8.16 6.50	10.96±8.02 8.50	173.000	0.087[a]
Duration of use of Discontinued ASM (years)	8.21±4.51 9.50	7.61±5.45 5.50	7.78±5.16 7.00	217.500	0.454[a]
Duration of seizure-free (years)	3.71±2.74 3.50	6.33±4.49 5.00	5.6±4.25 4.50	163.000	0.053[a]
EEG on discontinuation of ASM					
Abnormal	4 (28.5)	5 (13.9)	9 (18)	0.649	0.422[d]
Normal	10 (71.5)	31 (86.1)	41 (82)		
EEG after discontinuation of ASM					
Abnormal	3 (21.5)	3(9.1)	6 (12)	0.631	0.427[d]
Normal	11 (78.5)	33 (91.9)	44 (88)		
Previous DiscontinuationAttempt					
Yes	2 (14.3)	1 (2.8)	3 (6)	---	0.186[c]
No	12 (85.7)	35 (97.2)	47 (94)		
Reason for Discontinuation					
Seizure freedom	9 (64.3)	32 (88.9)	41 (82)	---	0.094[c]
Self- discontinuation	5 (35.7)	4 (11.1)	9 (18)		

[a]Mann-Whitney U test, [b]Yates correction, [c]Fisher-Exact test, [d]Fisher-Freeman-Halton test, mean±s. deviation, median (minimum - maximum), frequency (percentage). CNS: Central Nervous System, SAH: Subarachnoid Haemorrhage, CVD: Cerebrovascular Disease, MRI: Magnetic Resonance Imaging, ASM: Anti-seizure Medication, EEG: Electroencephalogram

Table 2. Analysing the risk factors affecting the duration of recurrence by Cox regression analysis

	Univariate		Multiple	
	HR (95%CI)	p	HR (95%CI)	p
Age at Epilepsy Diagnosis	0.977 (0.939 – 1.016)	0.241	0.989 (0.912 – 1.073)	0.795
Seizure Frequency	1.006 (0.995 – 1.017)	0.295	1.007 (0.989 – 1.026)	0.429
Epilepsy Type (Reference: Focal)				
Generalized	24.96 (2.198 – 283.453)	**0.009**	3.932 (0.025 – 613.591)	0.595
Unclassified	1.061 (0.326 – 3.453)	0.921	1.147 (0.158 – 8.322)	0.892
History of Status Epileptikus (Reference: None)	0.631 (0.081 – 4.912)	0.660	0.879 (0.084 – 9.204)	0.915
ASM (Reference: Monotherapy)	0.58 (0.13 – 2.596)	0.476	0.322 (0.04 – 2.581)	0.286
Duration of epilepsy until remission	1.042 (0.981 – 1.108)	0.183	1.063 (0.92 – 1.227)	0.406
Duration of use of Discontinued ASM	1.014 (0.919 – 1.119)	0.777	1.133 (0.916 – 1.4)	0.250
Duration of seizure freedom	0.725 (0.55 – 0.956)	**0.023**	0.672 (0.465 – 0.971)	**0.034**
Reason for Discontinuation (Reference: seizure freedom)	2.83 (0.945 – 8.475)	0.063	3.39 (0.645 – 17.805)	0.149

HR (95% CI): Hazard rate (95% confidence interval). ASM: Anti-seizure Medication

Discussion

In our study, the relapse rate was 28% after discontinuation of ASMs. In previous studies, a wide range of relapse risk after discontinuation of ASMs has been reported, ranging from 12% to 67% (11). In a recent study by Li et al. this rate was found to be 29.8%, similar to our study. They also argued that the high risk of recurrence was related to the use of multiple ASMs and EEG findings after seizure freedom (10). In a previous study conducted in our country in which recurrence rates after discontinuation of ASMs were analyzed, this rate was observed to be 19.3% (12). Moreover, in a study conducted by Vurucu et al., the recurrence rate was found to be 19.2%, and it was argued that the recurrence rate was relatively low, and this was due to patients with low-risk factors in the study population (13). The slightly higher recurrence rates in our study may be due to the inclusion of patients who self-discontinued their medication. We thought that this situation was significant because it reflected real-life data.

Table 3. Comparison of the duration of recurrence based on the number of seizure-free years

	Average survival time (months) (95% CI)	P
Number of seizure-free years		
≤5	76.455 (60.126–92.783)	0.516
>5	91.165 (67.481–114.848)	
Total	86.009 (71.007–101.011)	

*Log Rank (Mantel-Cox) test

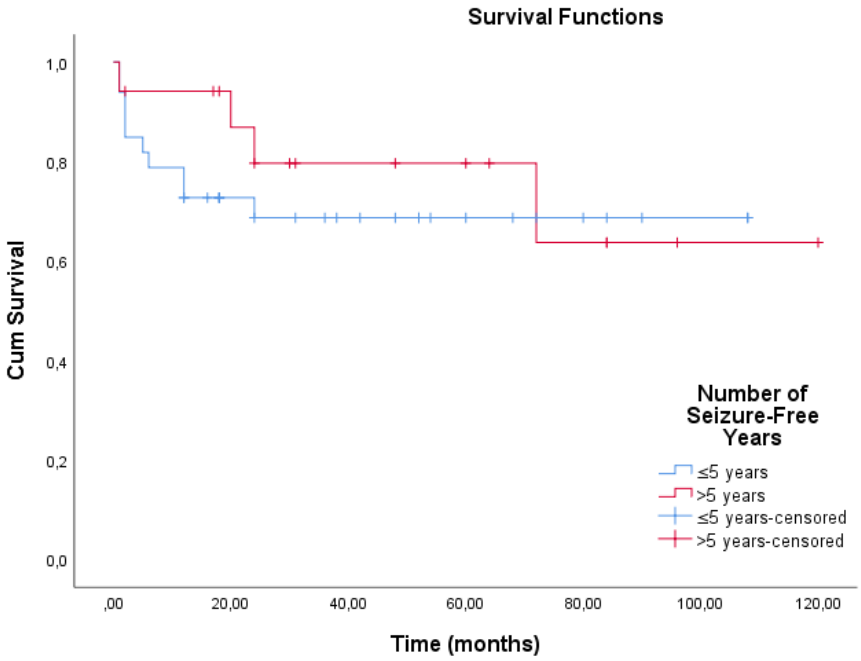

Figure 1. Kaplan Meier univariate analysis of the relationship between seizure-free years and duration of recurrence

The National General Practice Study of Epilepsy in the United Kingdom identified a 3-year recurrence risk of 44% after a seizure-free period of 6 months, 32% after 12 months, and 17% after 18 months. Although there is insufficient data on the risk of seizure recurrence after a long period of seizure-free and medication-free life, it has been reported that delayed recurrences are rare after 5 years and that the annual risk of seizures is probably very low 10 years after discontinuation of anti-seizure medication (9). Also, in many studies, it has been shown that the period with the highest risk of seizure is in the first 2 years (14,15). In our study, this rate was observed to be higher in the first year, and the risk rate was considerably higher, especially in the first 6 months.

In many studies, in order to compare the link between the timing of discontinuation and recurrence rates, seizure-free periods before medication discontinuation were classified as 2 years, 2–5 years, and 5 years. It was reported that the longer the remission period was maintained, the lower the risk of relapse after discontinuation, although no difference was observed between the periods (4,16). In our study, when we classified the patients as below 5 years and above 5 years, we observed that there was no significant difference between the two groups in terms of recurrence, but the recurrence rate decreased as the seizure-free period increased in compliance with other studies.

In a study conducted by Bouma et al. on a pediatric population, an inverse correlation was found between the duration of ASM use and the risk of relapse (17). In another study, evidence was presented that previous use of multiple ASMs, the presence of abnormal EEG during discontinuation, and the presence of a structural lesion in the etiology of epilepsy increased the risk of recurrence (10,18-22). On the other hand, Benhadis et al. argued that female patients should be more careful because of the high risk of recurrence in the presence of abnormal EEG after medication discontinuation (23). In our study, the risk of recurrence was statistically significantly higher in patients with generalised epilepsy, and no relation was found with any of the previously described risk factors such as gender, epilepsy duration, age at onset, or abnormal EEG findings.

Although data on seizure control in patients with relapse after medication discontinuation are limited, while seizures can be controlled again in 64-91% of patients, there are data on difficulty in seizure control and development of drug-resistant seizures at rates ranging from 7 to 19%, however, no predictive factor has been shown for this situation (24-26). In the Medical Research Council Antiepileptic Medication Discontinuation Study, it was shown that the risk of seizure recurrence was similar between patients who relapsed after discontinuation of ASMs and patients who relapsed while continuing treatment. Therefore, it has been argued that the detected resistances are perhaps related to the natural course of the disease (27). In our study, seizures were not resistant to treatment in any patient with a recurrence. The seizures of all patients were controlled after the initiation of treatment. In addition, in a study by Cho et al. evaluating 104 patients who underwent anti-seizure medication discontinuation for the second time, it was observed that 41.3% of the patients were seizure-free for at least 2 years. Therefore, it is argued that relapse after discontinuation of anti-seizure treatment does not mean that the treatment will last for life, and that drug discontinuation may be tried again at a later time, but it should be kept in mind that the threshold for a cessation attempt may be slightly higher in such cases (28,29).

This study has several limitations. Firstly, the small number of patients is one of the limitations. The reason for the lower number of patients with medication discontinuation may be due to the fact that our center is a tertiary epilepsy center and therefore, especially medication-resistant epileptic patients are referred. Additionally, multicentre randomised controlled studies with a large sample size may lead to more precise results. The fact that retrospective nature of the study is another limitation. Although patients were followed up for at least one year, not all patients had equal follow-up periods. Considering that the rate of discontinuation of ASMs may also affect seizure recurrence, no evaluation could be made in this regard since we did not have information about the discontinuation periods of the medication in some patients.

Conclusion

In conclusion, our study supports that the risk of relapse after discontinuation of ASMs decreases as the seizure-free period is prolonged. However, it should not be forgotten that the decision to discontinue medication should be individualized. When making a decision, the risk of relapse should be evaluated and shared with the patient or the patient's relatives. The patient's work and social life, the expectation of a license, drug interactions, side effects, and even the risk of teratogenicity should all be taken into consideration and discussed with the patient. A joint decision should be reached together with the patient.

Conflict of interest statement

In our study, there is no financial conflict of interest with any institution, organization, person and there is no conflict of interest between the authors.

Ethics Committee Approval: This study was approved by the human ethics committee of Antalya

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