

# Importance of Long-term EEG in Seizure-free Patients with Normal Routine EEG

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## Abstract

**Objective:** Withdrawal of anti-seizure medicine (ASM) may be considered in epilepsy patients when seizure control is achieved. Predicting the risk of recurrence after discontinuing ASM. We compared routine electroencephalography (EEG) and long-term EEG (LTEEG) findings in seizure-free epilepsy patients with planned drug discontinuation. Hence, we aimed to emphasize the relationship between interictal electrophysiological findings and clinical features to assess the superiority of LTEEG over routine EEG in medication termination.

**Methods:** Fifty-eight patients diagnosed with epilepsy and under the follow-up epilepsy outpatient clinics of our tertiary center with normal EEG and at least a two-year seizure-free period were included. LTEEG was performed in all these patients. Age, sex, seizure onset age, type and frequency, risk factors for epilepsy, anti-seizure medications, neurological examination, and electrophysiological and magnetic resonance imaging (MRI) findings were retrospectively recorded.

**Results:** The study group consisted of 36 females (62.1%) and 22 males (37.9%). Their mean age was 38.67 (21-70) years. The mean duration of seizure freedom was 4.8 years. Neurological examination was abnormal in 9 patients, and MRI detected an anomaly in 22 patients (37.9%). Epileptiform anomalies on LTEEG were observed in 27 (46.6%) of 58 patients. LTEEG anomalies and seizure frequency were correlated with a statistically significant relationship.

**Conclusion:** LTEEG may reveal interictal epileptiform anomalies even in patients with long-term seizure-free epilepsy with a normal routine EEG. On the basis of our results, we would like to emphasize the value of LTEEG to reevaluate a better treatment strategy in seizure-free patients.

**Keywords:** Seizure-free, routine EEG, long-term EEG

## INTRODUCTION

Epilepsy is one of the most common neurological diseases worldwide. It is known as a chronic disease, but not always lifelong treatment is required. Anti-seizure medications (ASMs) are effective in approximately 65-85% of patients with epilepsy.<sup>1,2</sup>

According to the International League Against Epilepsy, epilepsy is considered resolved for individuals in two main scenarios. First, for patients who previously had an age-dependent epilepsy syndrome, resolution occurs when they surpass the applicable age range for that particular syndrome. Second, resolution is also recognized for individuals who have remained seizure-free for the last 10 years and have been off antiseizure medications for at least the last 5 years. However, “resolved” does not equate to “remission” or “cure”. It indicates 10 years seizure-free and 5 years without antiseizure medications.<sup>3</sup>

In adult patients with epilepsy, medication can be tapered off and drug withdrawal could be planned after a seizure-free period of at least 2 years, considering the side effects of their chronic use.<sup>4-7</sup> The widely accepted belief that it is prudent to wait for a minimum of two years is founded on a subjective benchmark, and it is necessary to augment this guideline by recognizing that the risk diminishes with each successive seizure-free year.<sup>2</sup> There are no definite guidelines concerning the optimal timing of ASM withdrawal. By discontinuing ASMs, long-term toxicity, drug-drug interactions, cognitive or other side effects, teratogenicity, the ongoing need for and costs of monitoring and follow-up care, and affirmation of being sick can be avoided. However, epilepsy is a highly heterogeneous disease, and some patients experience seizure recurrence during ASM reduction, whereas others experience relapse after drug withdrawal.

Relapse rates have been reported as 20-60% in different studies.<sup>4,8-10</sup> Resuming medication does not always control seizures in a substantial proportion of patients. Several predictors of seizure recurrence after ASM withdrawal have been reported electroencephalography (EEG) abnormalities are known risk factors for seizure recurrence after drug withdrawal.<sup>5,6,11,12</sup> However, there are limited studies on long-term EEG (LTEEG) in these patients.

This study aimed to investigate interictal epileptiform anomalies observed during LTEEG in seizure-free epilepsy patients with normal routine EEG and to reveal the relationship between these findings and clinical features.

## METHODS

We retrospectively reviewed the data of patients who were followed up in our outpatient clinic with a diagnosis of epilepsy. In this study, patients aged 18 to 80 years with focal epilepsy of symptomatic or unknown etiology and idiopathic generalized epilepsy with primary generalized tonic-clonic seizure were included. Although patients with juvenile myoclonic epilepsy have a good prognosis, a majority require ongoing treatment because of high relapse rates. Patients with mesial temporal sclerosis generally belong to the group of drug-resistant epilepsy and were therefore excluded from our study. In addition, reflex epilepsy patients were excluded. To gather information on individuals with intellectual disabilities, interviews were conducted with their parents as needed, and informed consent forms were obtained from their guardians.

In this study, we included patients who underwent prolonged EEG for drug withdrawal. All patients were seizure-free for at least 2 consecutive years, their last routine EEGs were normal, and LTEEG was performed with a minimum of 3 to 8 hours. For each patient, the main demographic and clinical variables, age, gender, age of seizure onset, seizure type and frequency before treatment, risk factors for epilepsy, neuroradiological findings, ASMs, and seizure-free time were recorded. EEG features are coded as normal, slow, or epileptiform. Epileptiform anomalies were determined as a spike; sharp, multiple spikes; spikes and slow wave; sharp and slow wave; multiple spikes and slow waves. The relationship between primary variables and epileptiform variations in LTEEG was investigated.

The protocol of this study was approved by the Ethics Committee of the University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital on 06.06.2022 with the number 2022-11-10.

### Statistical Analysis

The study criteria were defined as mean, standard deviation, frequency, and percentage values. Chi-square and Fisher's exact tests were used to compare frequencies and percentages between groups. To evaluate the means of variables with normal distribution, the t-test was used to compare two different groups, and the one-way ANOVA method was used to compare the means of more than two groups. Spearman's correlation, multivariate logistic regression, and Cox regression analyzes were performed to

investigate the correlations between the variables and their model. In the interpretations, the limit of significance was taken as  $p=0.05$ . The Statistical Package for the Social Sciences (version: 22.0) package program was used for biostatistical analysis.

## RESULTS

We enrolled 58 patients. Epileptiform anomalies in the VEM were detected in 27 (46.6%) of 58 patients. Of these, six had generalized and 21 had focal findings. The generalized discharges were from patients diagnosed with idiopathic generalized epilepsy. The clinical and electrophysiological results of 27 patients with abnormal LTEEG findings and 31 patients with normal LTEEG findings were compared. Thirty-six (62.1%) patients were female and 22 (37.9%) were male. The mean age was 38.67 years (21-70). The mean seizure-free period was 4.8 years (2-10). Abnormal neurological examination findings were found in 9 patients. These included varying degrees of mental retardation and paresis. Magnetic resonance imaging (MRI) abnormalities were detected in 22 (37.9%) of 58 patients with encephalomalacia areas of previous trauma, cortical developmental anomalies, cavernoma, encephalitis sequelae, previous venous infarction, and sequela changes due to cerebral mass operations. Only eight of the patients were under dual drug therapy, while the others were receiving monotherapy. The clinical and electrophysiological characteristics of patients with abnormal LTEEG findings and those of patients with normal LTEEG findings were documented and compared (Tables 1, 2).

A significantly higher rate of LTEEG abnormality was found in patients with high seizure frequency before the seizure-free period (odds ratio=3.05, confidence interval: 1.002-9.27) ( $p=0.046$ ). No correlation was found between other study parameters ( $p>0.05$ ). However, interictal epileptiform anomalies are seen more often in females and patients with abnormal MRI findings, but these results are not statistically significant.

## DISCUSSION

Although epilepsy is a common chronic disease, two-thirds of cases achieve effective seizure control under ASMs. Discontinuation of treatment after at least two years of seizure-free period could be planned in adult patients with epilepsy.<sup>4-7</sup> However, the recurrence risk after withdrawal must be carefully evaluated. In addition, after seizure relapse occurs, 20% of these patients' seizures cannot be controlled immediately with anti-seizure treatment.<sup>13</sup> The reoccurrence of seizures may additionally have negative consequences in the individual, social, and professional lives of the patient. Therefore, it is essential to determine the risk of relapse after drug discontinuation in seizure-free patients. Studies have shown that symptomatic epilepsies, some epilepsy syndromes (juvenile myoclonic epilepsy, reading epilepsy, juvenile absence epilepsy, generalized epilepsy characterized by primary generalized tonic-clonic seizures with abnormal EEG findings), abnormal findings on neurological examination, duration of epilepsy, and seizure frequency before drug treatment are factors that increase the risk of relapse.<sup>8,10,11,14</sup> In addition, abnormal EEG findings during drug withdrawal are significant risk factors for seizure recurrence. Before and within a year after drug discontinuation, abnormal EEG findings are important because they predict seizure recurrence.<sup>15-17</sup> In a meta-analysis conducted on 2349 patients, EEG abnormalities

### MAIN POINTS

- Interictal abnormalities in long-term EEG (LTEEG) were found to be significantly higher than those in routine EEG in seizure-free epilepsy patients.
- A significantly higher rate of LTEEG abnormality was found in patients with high seizure frequency before the seizure-free period.
- Seizure recurrence following drug withdrawal was related to the seizure frequency to reaching the seizure-free period with medication.
- The patient group showed higher rates of abnormalities in LTEEG, reflecting the higher rate of symptomatic epilepsy.

**Table 1.** The clinical and electrophysiological results of patients with abnormal LTEEG findings and normal LTEEG findings

		Total (n=58)	LTEEG normal (n=31)	LTEEG abnormal (n=27)	x <sup>2</sup> / t	p
		Frequency (%) Mean±SD	Frequency (%) Mean±SD	Frequency (%) Mean±SD		
Age		38.67±13.51	39.39±14.02	37.85±13.12	-0.43	0.67
Gender	Female	36 (62.1)	17 (54.8)	19 (70.4)	1.48	0.224
	Male	22 (37.9)	14 (45.2)	8 (29.6)		
Seizure type	GTC	6 (10.3)	3 (9.7)	3 (11.1)	Fisher	0.596
	Focal	52 (89.7)	28 (90.3)	24 (88.9)		
Examination	Normal	49 (84.5)	27 (87.1)	22 (81.5)	0.35	0.556
	Abnormal	9 (15.5)	4 (12.9)	5 (18.5)		
MRI findings	Normal	36 (62.1)	21 (67.7)	15 (55.6)	0.91	0.34
	Abnormal	22 (37.9)	10 (32.3)	12 (44.4)		
Seizure frequency	1-9	23 (39.7)	16 (51.6)	7 (25.9)	3.98	0.046*
	>10	35 (60.3)	15 (48.4)	20 (74.1)		
Febrile convulsion	None	54 (93.1)	29 (93.5)	25 (92.6)	0.02	0.886
	Positive	4 (6.9)	2 (6.5)	2 (7.4)		
Family history	None	52 (89.7)	28 (90.3)	24 (88.9)	0.03	0.858
	Positive	6 (10.3)	3 (9.7)	3 (11.1)		
Follow-up (year)		12.10±5.15	12.32±5.33	11.85±5.04	-0.34	0.732
Age at seizure onset		18.98±12.44	19.40±14.69	18.52±9.6	-0.27	0.792
Seizure-free years		4.90±2.26	4.81±2.32	5±2.24	0.32	0.748

\*Significant at the p&lt;0.05 level.

SD: Standard deviation, LTEEG: Long-term electroencephalography, MRI: Magnetic resonance imaging, GTC: Generalised tonic clonic seizure

**Table 2.** The electrophysiological results of patients with abnormal LTEEG findings and normal LTEEG findings

	Normal (n=31)	Primary generalised discharges (n=6)	Focal discharges (n=21)	F	p
	Mean±SD	Mean±SD	Mean±SD		
Age	39.39±14.02	33.67±11.74	39.05±13.51	0.45	0.637
Follow-up	12.32±5.33	12.67±4.18	11.62±5.32	0.15	0.859
Age at seizure onset	19.40±14.69	13.83±7.52	19.86±9.86	0.57	0.567
Seizure-free years	4.81±2.32	5.33±2.42	4.90±2.23	0.13	0.876

SD: Standard deviation, LTEEG: Long-term electroencephalography

detected during drug discontinuation were defined as a red flag in determining recurrence.<sup>12</sup> Routine EEG is insufficient to reveal epileptiform anomalies with disadvantages such as short duration, easy emergence of artifacts and false negativity. We investigated interictal epileptiform abnormalities in LTEEG in seizure-free epilepsy patients scheduled to discontinue the medication. Abnormal findings in LTEEG were found in 27 (46.6%) of 58 patients with normal routine EEGs included in our study, which is a relatively high rate.

EEG, particularly prolonged EEG monitoring, is often used to predict the risk of ASM withdrawal. Few studies have compared routine EEG and LTEEG in seizure-free epilepsy patients planned for drug withdrawal. In one of these studies, both electrophysiological investigations, routine EEG, and LTEEG were performed in seizure-free patients. They found the rate of an interictal anomaly in LTEEG to be 28.6% in patients with normal routine EEG.<sup>18</sup> In other studies, the rate of epileptiform anomaly in routine EEG was reported as 10-20%.<sup>19,20</sup> Furthermore, the relapse risk was higher in patients with interictal epileptiform anomalies,

and it was suggested to continue drug therapy. Although routine EEG was normal, evidence of abnormal neurological examination and epileptiform discharges in LTEEG is higher in trauma or other symptomatic epilepsy. Our study showed that symptomatic patients with epilepsy were probably more rated in LTEEG with interictal epileptiform anomalies, albeit statistically not significant. In another study that excluded symptomatic epilepsies, LTEE revealed unusual findings in 16 seizure-free patients out of 78 who formerly showed normal routine EEG.<sup>21</sup> On follow-up, 27% had relapsed yearly, which is lower than that in other studies. As a result, LTEEG is suggested in seizure-free patients planned for ASM withdrawal, even if the routine EEG is normal. Our patient group showed higher rates of abnormalities in LTEEG, reflecting the higher rate of symptomatic epilepsy included in our study.

In our study, patients with frequent seizures before the seizure-free period had significantly higher LTEEG abnormalities. Seizure recurrence following drug withdrawal was related to the seizure frequency to reaching the seizure-free period with medication.<sup>22-24</sup> Seizure frequency indicates seizure severity.

On the other hand, abnormal findings in LTEEG were found at a higher rate in women. While the rate of female gender was 54% in the group with normal LTEEG results, this rate was 70% in those with abnormal LTEEG. This difference could be explained by the coincidentally higher rates of female patients participating in our study. However, in some studies, higher rates of EEG abnormalities were found in females.<sup>5,20</sup>

In this study, we could not find an association between age, seizure onset, duration of epilepsy, febrile convulsion, family history, and LTEEG abnormalities. This could be explained by the limited patient number.

Our epilepsy patients achieved sufficient seizure control in an attempt to discontinue ASM. Therefore, most patients were under monotherapy (50 of 58 patients). We observed that the rate of detection of an interictal epileptiform anomaly in the LTEEG of these seizure-free epilepsy patients was high. In a retrospective investigation, data on these epilepsy patients showed that 24 of 58 had relapses in their seizures during the previous drug reduction phase or when treatment was interrupted for any reason. Altogether, it is considered that although epilepsy seems “finished” in appearance, it contains many complex pathophysiological processes in its nature, and the existing “epilepsy” continues. With a pessimistic interpretation, seizure freedom is asserted as symptomatic success due to ASM. However, discontinuation of ASM should be recommended in long-term seizure-free patients. The essential aspect here is to predict the risk of seizure relapse after drug discontinuation. Although LTEEG may be normal, discontinuing medication can be challenging, especially in mentally retarded patients and patients with symptomatic epilepsy, and each patient should be individually evaluated by the physician. In these patients, it may be preferable to continue with lower doses of medication rather than complete cessation of medication.

Our objective is to expand the research by creating subgroups of more seizure-free epilepsy patients. We believe that a prospective study that follows up on seizure recurrence in treatment-withdrawn epileptic patients with normal and abnormal LTEEG would be valuable.

In our study, interictal abnormalities in LTEEG were found to be significantly higher than those in routine EEG in seizure-free epilepsy patients. However, LTEEG may not be a feasible option in all centers because it may not always be accessible or cost-effective. Nonetheless, it is recommended to perform LTEEG in patients with symptomatic epilepsy and those with frequent seizures before achieving seizure freedom, especially if there are MRI findings. Our study also showed a higher incidence of abnormalities in the LTEEG of the group with frequent seizures and the symptomatic group.

### Study Limitations

The small number of patients and the fact that all patients could not undergo LTEEG for 8 h or longer are the limitations of the study.

### CONCLUSION

Our study showed that LTEEG is more sensitive in detecting epileptic discharges. Symptomatic patients with epilepsy were probably more rated in LTEEG with interictal epileptiform

anomalies, albeit statistically not significant. Patients with frequent seizures had significantly higher LTEEG abnormalities. Our study results emphasize that LTEEG is beneficial in the treatment planning of seizure-free epilepsy patients.

### Ethics

**Ethics Committee Approval:** The protocol of this study was approved by the Ethics Committee of the University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital on 06.06.2022 with the number 2022-11-10.

**Informed Consent:** Consent form was filled out by all participants.

**Peer-review:** Externally and internally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: A.C.D., B.M., F.E., H.D.A., Concept: A.C.D., B.M., Design: A.C.D., B.M., F.E., H.D.A., Data Collection or Processing: A.C.D., B.M., Analysis or Interpretation: A.C.D., Literature Search: A.C.D., F.E., Writing: A.C.D., B.M., F.E., H.D.A.

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