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Archives of Epilepsy

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Archives of Epilepsy

## EDITORIAL

Dear Colleagues,

We all know that epilepsy is a disease with a high disability rate. Our journal frequently publishes articles addressing the emotional and social burdens experienced by individuals with epilepsy and their families in relation to the disease. Anxiety disorders are the most common mood disorder encountered by both patients and their relatives. Unpredictability is the main source of this anxiety. Even if patients have infrequent seizures, this anxiety can overwhelm them. I believe this issue should also be considered when determining disability rates.

Archives of Epilepsy invites you to submit your current and future publications in the field of epilepsy.

Wishing you good health and happy days, see you in 2026.

Best wishes

**S. Naz Yeni, M.D., Prof.**
**Editor-in-Chief**

Archives of Epilepsy

Original Article

# The Effect of Dapagliflozin on Absence Epilepsy in WAG/Rij Rats

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## Abstract

**Objective:** Epilepsy is the most common chronic brain disease that affects millions of people worldwide. In the present study, we investigated the effects of dapagliflozin, a sodium-glucose cotransporter-2 (SGLT2) inhibitor, which has been recently introduced as a new drug for diabetes mellitus, on seizure activity in Wistar Albino Glaxo from Rijswijk (WAG/Rij) rats with genetic absence epilepsy.

**Methods:** Twenty-eight adult male WAG/Rij rats were divided into the following groups: Group 1, control; Group 2, dapagliflozin (1 mg/kg); Group 3, dapagliflozin (5 mg/kg); Group 4, dapagliflozin (25 mg/kg). The tripolar electrodes were placed while the patient was under general anesthesia. After a recovery period, three hours of basal electrocorticography (ECoG) recording was taken. Following the basal ECoG recording, dapagliflozin at doses of 1, 5, and 25 mg/kg was injected intraperitoneally. After the dapagliflozin injections, researchers recorded ECoG for another three hours. In the recordings, the total number and duration of spike-and-wave discharges (SWDs), and average SWD amplitudes were used to evaluate seizures.

**Results:** Compared to the control group, the administration of 1 mg dapagliflozin significantly decreased the number and duration of SWDs. Both parameters of SWD increased significantly in the 25 mg dapagliflozin group. The number and duration of SWDs did not change significantly between 5 mg dapagliflozin and the control groups. There were no significant changes in the average SWD amplitude values of all groups.

**Conclusion:** The results of the present study provided electrophysiological evidence regarding the role of SGLT2 inhibitors in the modulation of genetic absence epilepsy seizures.

**Keywords:** Absence epilepsy, dapagliflozin SGLT2, SWD, WAG/Rij

## INTRODUCTION

Absence epilepsy, a subtype of idiopathic generalized epilepsy, accounts for 10-15% of pediatric cases and, despite its benign reputation, can persist into adulthood with associated cognitive deficits.[1,2] First-line treatments such as ethosuximide, valproic acid, and lamotrigine are effective in many cases, but drug resistance and adverse effects remain challenges.[3] This underscores the need for alternative therapies that also address underlying epileptogenic mechanisms.

The brain relies heavily on glucose metabolism for neuronal function, consuming nearly 20% of the body's total glucose.[4] Glucose uptake is mediated by facilitated glucose transporters (GLUTs) and sodium-glucose cotransporters (SGLTs).[5-7] Although SGLTs were initially identified in peripheral organs, recent findings confirm their presence in brain regions such as the hippocampus, cortex, and hypothalamus.[8] While SGLT2 is minimally expressed in the healthy brain tissue, it may be upregulated under pathological conditions, including epilepsy.[9]

Inhibition of SGLTs can limit intracellular glucose availability, potentially triggering energy imbalance and increased seizure susceptibility. Conversely, selective SGLT2 inhibition has shown neuroprotective effects in some models, possibly via enhanced ketogenesis, redox stabilization, and anti-inflammatory pathways.[10-12] Dapagliflozin, a selective SGLT2 inhibitor used for type 2 diabetes, has demonstrated both pro- and anti-epileptic effects in preclinical models. For example, phlorizin worsened seizures in the pilocarpine model,[13] while dapagliflozin reduced seizure activity and neuroinflammation in pentylenetetrazol (PTZ) and pilocarpine models.[9,14]

Wistar Albino Glaxo from Rijswijk (WAG/Rij) rats are a well-established genetic model of absence epilepsy, developing spontaneous spike-and-wave discharges (SWDs) akin to human absence seizures after three months of age.[15,16] This model provides a robust platform for evaluating anti-epileptic interventions targeting idiopathic generalized epilepsy.

In this study, we evaluated the acute, dose-dependent effects of dapagliflozin on absence seizures in WAG/Rij rats using *in vivo* electrocorticography (ECoG) recordings. To our knowledge, this is the first report examining SGLT2 inhibition in this genetic model, aiming to clarify the dualistic impact of dapagliflozin on seizure modulation and to explore SGLT2 as a metabolic target in epilepsy.

## METHODS

### Animals

In this study approved by Gaziosmanpaşa University Animal Experiments Local Ethics Committee (approval no: 2019 HADYEK-57, date: 22.01.2020), 28 male WAG/Rij rats weighing 270±10 g were used for the experiments. Rats were housed in a fixed-temperature room (23±4 ºC) in a 12-hour light/12-hour dark cycle (the light turned on at 7 a.m. and turned off at 7 p.m.) with free access to food and drink. The following experimental groups were created with random assignment of seven rats in each group:

1. Control group (saline 2 mL/kg, intraperitoneal)

2. Dapagliflozin (1 mg/kg, intraperitoneal, 0.5 mL)

3. Dapagliflozin (5 mg/kg, intraperitoneal, 0.5 mL)

4. Dapagliflozin (25 mg/kg, intraperitoneal, 0.5 mL)

### Drug

Dapagliflozin (≥98% purity, high-performance liquid chromatography, purified grade) was purchased from Sigma-Aldrich (Merck Germany, catalog no: SML2804) and freshly dissolved in sterile 0.9% saline for intraperitoneal administration, in accordance with previously published protocols using purified research-grade dapagliflozin in rodent epilepsy models.[14,17]

The doses of dapagliflozin (1, 5, and 25 mg/kg) were selected based on previous studies investigating the neuroprotective and anti-epileptic effects of SGLT2 inhibitors in rodent models,[9,14,17] as well as standard preclinical protocols for assessing dose-dependent responses. Dapagliflozin (intraperitoneal) was administered once, immediately following the completion of baseline ECoG recordings, to evaluate its acute effects on absence seizure activity. Intraperitoneal injection was chosen as the administration route because it ensures consistent systemic drug delivery and is widely used in experimental epilepsy models. Dapagliflozin exhibits partial blood-brain barrier (BBB) permeability under physiological conditions, achieving brain/plasma ratios of approximately 30-50%.[18]

### Surgical Procedures

WAG/Rij rats were anesthetized with ketamine (90 mg/kg, intraperitoneal) and xylazine (10 mg/kg, intraperitoneal). With the help of a stereotaxic instrument, tripolar ECoG recording electrodes (Plastic Products Company, 333/2A) were placed in rats under anesthesia in accordance with the Paxinos and Watson atlas. For ECoG recording, electrodes were placed at the following coordinates: anteroposterior (AP) +2.0, lateral (L) +3.5 (frontal region); AP -6.0, L +4.0 (parieto-occipital region); and a reference electrode on the cerebellum. After placement, the electrodes were fixed to the skull using cold dental acrylic. Following the stereotaxic surgery, the animals were kept in individual cages and allowed a week to recover.[15,19]

### ECoG Recording and Drug Administration

After placing tripod electrodes for ECoG recording, the rats were allowed to recover for a week. After the recovery period, ECoG recordings were made in WAG/Rij rats, which moved freely in a noise-isolated room. First, the animals were accustomed to a recording cage (50×50×50 cm). After stereotaxic implantation of electrodes and a 7-day postsurgical recovery period, baseline ECoG recordings were performed for 180 minutes during the lights-on period (09:00 to 12:00) to minimize circadian rhythm effects. After completion of the baseline recording, the animals were allowed to rest for 24 hours without intervention. On the following day, between 9:00 and 12:00, dapagliflozin (1 mg/kg, 5 mg/kg, or 25 mg/kg) or sterile saline (control group) was administered intraperitoneally. Immediately after injection, a second EcoG recording session was initiated and continued for another 180 minutes. This procedure was applied consistently to all rats across the experimental groups (Figure 1).

### Evaluation of ECoG Records

ECoG signals were recorded online using the PowerLab 16/35 data acquisition system (ADInstruments, Australia). In WAG/Rij rats, ECoG recordings were analyzed both before and after the administration of dapagliflozin, in the treatment groups and physiological saline in the control group. The primary parameters assessed were the number, duration, and amplitude of spontaneously occurring SWDs.

SWDs were identified based on their characteristic morphology: sharp, asymmetric, large-amplitude spikes followed by slow waves, in accordance with previously established criteria. Data were analyzed using LabChart v7.3.7 software (ADInstruments, Australia), which enables quantification of the frequency and amplitude of epileptiform discharges.

In the data analysis menu, the "spike shape" feature was used to set detection thresholds, allowing the software to differentiate SWDs from baseline cortical activity. Each automatically identified event was visually inspected to ensure it exhibited the hallmark SWD morphology. The total number and duration of SWD clusters, as well as the average spike amplitude (peak-to-peak), were calculated automatically.

Percent changes were calculated relative to the three-hour baseline recordings obtained prior to drug or saline administration. For each parameter (number, duration, and amplitude of SWDs), the percentage change was computed using the formula:

$$\frac{\text{Average number, duration and amplitude of SWDs after dapagliflozin or saline administration}}{\text{Average number,duration and amplitude of SWDs before dapagliflozin or saline administration}} \times 100$$

**MAIN POINTS**

- Low-dose dapagliflozin (1 mg/kg) significantly reduced the number and duration of spike-and-wave discharges (SWDs) in Wistar Albino Glaxo from Rijswijk rats.
- High-dose dapagliflozin (25 mg/kg) markedly increased both the number and duration of SWDs, suggesting a pro-epileptic effect.
- Mid-dose dapagliflozin (5 mg/kg) had no significant effect on seizure parameters.
- SWD amplitude remained unchanged across all treatment groups.
- The findings demonstrate that dapagliflozin has dose-dependent, bidirectional effects on absence seizure activity, highlighting its potential and risk in epilepsy treatment.

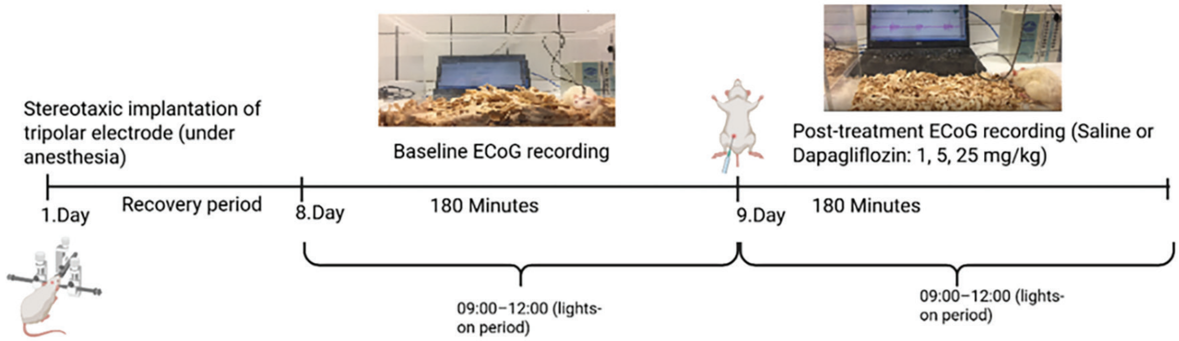


**Figure 1.** Experimental timeline of the study. Baseline and post-treatment ECoG recordings were performed in WAG/Rij rats following stereotaxic implantation of tripolar electrodes. Recordings were conducted during the lights-on period (09:00-12:00) on days 8 and 9. Dapagliflozin was administered intraperitoneally (1, 5, or 25 mg/kg) immediately before the second recording session
ECoG: Electrocorticography, WAG/Rij: Wistar Albino Glaxo from Rijswijk

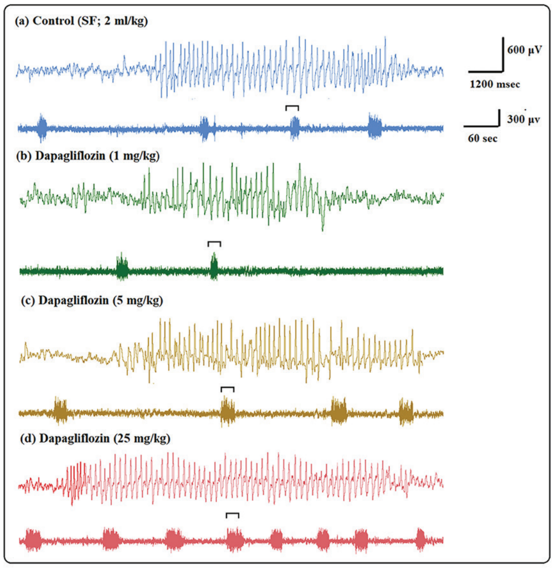


**Figure 2. (a)** control, **(b)** dapagliflozin (1 mg/kg), **(c)** dapagliflozin (5 mg/kg) and dapagliflozin (25 mg/kg) groups. Some representative ECoG recordings between 80th and 90th minutes (bar 300 millivolt (mV), 60 seconds (sec); bar 600 microvolts (µV), 1200 milliseconds (msec)
ECoG: Electrocorticography

### Statistical Analysis

Parameters of baseline SWDs were calculated for each rat, including total number of SWDs, cumulative SWDs duration (seconds), and mean amplitude (µV). Following treatment, the same parameters were re-evaluated during the post-treatment ECoG recording. To control for inter-subject variability, each rat's post-treatment values were expressed as a percentage of its own baseline value. This normalization allowed for accurate group-level comparisons of treatment effects.

The data were analyzed statistically using SPSS 20.0 (IBM Corp., Armonk, NY, USA). First, the Kolmogorov-Smirnov test was applied to determine whether the data had a normal distribution. In the analysis of normally distributed data, the statistical difference among the groups was determined using one-way ANOVA followed by Tukey's post-hoc test. For the post-hoc test, $p<0.05$ was considered significant. GraphPad Prism version 7.0 (GraphPad Software, San Diego, CA, USA) was used for the graphics in statistical evaluations.

## RESULTS

### The Total Number of SWDs

In the baseline ECoG recordings, no significant differences in the total number of SWDs were detected among the groups (63.57±5.39, 65.14±6.99, 61.84±2.31, and 60.29±3.62 for the control, dapagliflozin 1 mg/kg, 5 mg/kg, and 25 mg/kg groups, respectively; $p>0.05$; Figures 2 and 3).

The total number of SWDs significantly decreased in the dapagliflozin 1 mg/kg group (35.71±2.45) compared to the control group (66.40±7.05) ($p<0.01$). No significant difference was observed between the dapagliflozin 5 mg/kg group (76.17±5.55) and the control group ($p>0.05$). However, the total number of SWDs was significantly higher in the dapagliflozin 25 mg/kg group (134.1±7.19) compared to the control group ($p<0.001$), the 1 mg/kg group ($p<0.001$), and the 5 mg/kg group ($p<0.001$) (Figures 1 and 2).

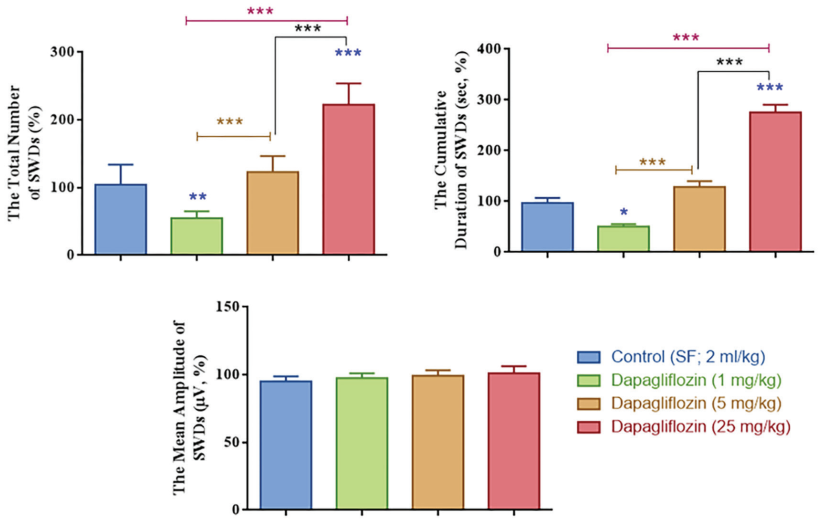


**Figure 3.** Effects of 1, 5, and 25 mg/kg dapagliflozin administration on **(a)** the total number, **(b)** the cumulative duration, and **(c)** the mean amplitude of SWDs in WAG/Rij rats with genetic absence epilepsy. SWD parameters were calculated from 180-minute ECoG recordings following treatment and normalized to each rat's own baseline values. Data are presented as percentage change (%), expressed as mean±SEM. Administration of 1 mg/kg dapagliflozin significantly reduced the total number and cumulative duration of SWDs compared to the control group (*$p<0.05$; **$p<0.01$). The 5 mg/kg dose showed no significant effect on SWD number, duration, or amplitude relative to controls ($p>0.05$). In contrast, 25 mg/kg dapagliflozin significantly increased both total SWD number and cumulative duration compared to the control, 1 mg/kg, and 5 mg/kg groups (***$p<0.001$). There were no significant differences in the mean amplitude of SWDs among the groups ($p>0.05$)

SWDs: Spike-and-wave discharges, WAG/Rij: Wistar Albino Glaxo from Rijswijk, ECoG: Electrocorticography, SEM: Standard error of the mean

The total number of SWDs was measured numerically, normalized to baseline values, and presented as a percentage in Figures 2 and 3.

### The Cumulative Duration of SWDs

In the baseline ECoG recordings, no significant differences in the cumulative duration of SWDs were detected among the groups (442.3±16.89, 448.4±37.88, 418.1±24.65, and 405.7±27.95 seconds for the control, dapagliflozin 1 mg/kg, 5 mg/kg, and 25 mg/kg groups, respectively; $p>0.05$) (Figures 2 and 3).

The cumulative duration of SWDs was significantly reduced in the dapagliflozin 1 mg/kg group (227.4±22.27 seconds) compared to the control group (430.2±43.42 seconds) ($p<0.05$). The dapagliflozin 5 mg/kg group (538.5±48.09 seconds) showed no significant reduction compared to the control group ($p>0.05$). Conversely, the dapagliflozin 25 mg/kg group (1,117±62.04 seconds) exhibited a significant increase in cumulative SWD duration compared to the control group ($p<0.001$), the 1 mg/kg group ($p<0.001$), and the 5 mg/kg group ($p<0.001$) (Figures 2 and 3).

The cumulative duration of SWDs was measured numerically, normalized to baseline values, and presented as a percentage in Figures 2 and 3.

### The Mean Amplitude of SWDs

In the baseline ECoG recordings, no statistically significant differences were observed in the mean amplitude of SWDs among the groups (control: 661.8±13.20 µV; dapagliflozin 1 mg/kg: 634.8±31.29 µV; 5 mg/kg: 646.7±31.28 µV; 25 mg/kg: 647.6±24.52 µV; $p>0.05$). Following treatment, the mean SWD amplitudes remained statistically unchanged between the control group (629.0±25.02 µV) and the dapagliflozin-treated groups (1 mg/kg: 619.2±23.28 µV; 5 mg/kg: 642.6±25.67 µV; 25 mg/kg: 654.4±34.53 µV; $p>0.05$). Amplitude measurements were obtained by averaging the peak-to-peak voltages of individual SWD events over the 180-minute recording period. Values were normalized to each subject's baseline amplitude and expressed as percentage change in Figures 2, 3; Tables 1, 2.

## DISCUSSION

In the present study, the low dose of dapagliflozin (1 mg/kg) suppressed absence seizures, while the high dose (25 mg/kg) showed an enhancing effect on absence seizures. A moderate dose of 5 mg/kg on the other hand, was found to have no effect on absence seizures.

Changes in neuronal energy metabolism are known to cause epileptic seizures.[20] GLUT type 1 deficiency syndrome was first described in 1991 in children with developmental retardation and infancy seizures.[21,22] Generalized SWDs have been observed in electroencephalography recordings of affected individuals, particularly during fasting states.[23] Glucose analogue $^{18}$F-florodeoksiglukoz ($^{18}$F-FDG), is an indirect marker of neuronal activity and allows absolute measurement of cerebral glucose metabolism.[24] In studies with $^{18}$F-FDG-positron emission tomography, it was shown that FDG absorption in epileptic foci increased during ictal activity, that is, during seizures, and decreased during the interictal period.[24] Experimental models have also demonstrated increased glucose utilization in epileptic foci.[25,26] Inhibition of SGLT causes lower glucose entry into the cell and, as a result, lower adenosine triphosphate (ATP) production. ATP is the energy source for performing various cell functions, including the operation of sodium-potassium and chloride pumps, and the preservation of resting membrane potential.[27] Therefore, SGLTs may be necessary for the survival of neurons under low glucose concentrations or anoxia.[8]

**Table 1.** SWD parameters recorded from baseline ECoG before SF and dapagliflozin injections

| Groups | The total number of SWDs | The cumulative duration of SWDs (sec) | The mean amplitude of SWDs (µV) |
|---|---|---|---|
| Control (SF; 2 mL/kg) | 63.57±5.38 | 442.3±16.89 | 661.8±13.20 |
| Dapagliflozin (1 mg/kg) | 65.14±6.99 | 448.4±37.88 | 634.8±31.29 |
| Dapagliflozin (5 mg/kg) | 61.84±2.30 | 418.1±24.65 | 646.7±31.28 |
| Dapagliflozin (25 mg/kg) | 60.29±3.62 | 405.7±27.95 | 647.6±24.52 |

Data are presented as mean±standard error of the mean.
ECoG: Electrocorticography, SWDs: Spike-and-wave discharges, SF: Saline formulation

**Table 2.** SWD parameters recorded from ECoG after SF and dapagliflozin injections

| Groups | The total number of SWDs | The cumulative duration of SWDs (sec) | The mean amplitude of SWDs (µV) |
|---|---|---|---|
| Control (SF; 2 mL/kg) | 66.40±7.04 | 430.2±43.42 | 629±25.02 |
| Dapagliflozin (1 mg/kg) | 35.71±2.44,[b] | 227.4±22.27,[a] | 619.2±23.28 |
| Dapagliflozin (5 mg/kg) | 76.17±5.55,[d] | 538.5±48.09,[d] | 642.6±25.67 |
| Dapagliflozin (25 mg/kg) | 134.1±7.18,[c,d,e] | 1117±62.04,[c,d,e] | 654.4±34.53 |

Data are presented as mean±standard error of the mean. [a]: $p<0.05$, [b]: $p<0.01$, [c]: $p<0.001$ compared to the control group, [d]: $p<0.001$ compared to the dapagliflozin 1 mg/kg group, [e]: $p<0.001$ compared to the dapagliflozin 5 mg/kg group.
ECoG: Electrocorticography, SWDs: Spike-and-wave discharges, SF: Saline formulation

In conditions such as epilepsy, ischemia, and hypoglycemia, increased expression of SGLT1 and SGLT2 proteins in the plasma membrane of neurons may play a protective role when energy supply decreases (e.g., during ischemia and hypoglycemia) or when energy consumption increases, during epilepsy.[8,9] A study by Melo et al.[13] lends support to this situation. They showed that inhibition of SGLT by phlorizin increased the severity of pilocarpine-induced limbic seizures, and neurodegeneration in the hippocampus increased 24 hours after seizures were created.[13] Similarly, absence seizures were observed to increase after SGLT2 inhibition with high doses of dapagliflozin in the present study. The inhibition of SGLT2 with high doses of dapagliflozin may have increased absence seizures by causing less glucose entry to the cell.

Under physiological conditions, dapagliflozin exhibits partial BBB permeability, achieving brain/plasma ratios of approximately 30-50%.[18]

Pathological conditions like epilepsy can impair BBB integrity, potentially increasing central nervous system drug penetration.[28,29] In WAG/Rij rats, PTZ-induced seizures have been shown to elevate both BBB permeability and SWDs activity.[30] In this context, enhanced brain access of high-dose dapagliflozin may have resulted in excessive SGLT2 inhibition or metabolic imbalance, promoting neuronal hyperexcitability and absence seizures. Conversely, low-dose administration may have maintained homeostasis, attenuating oxidative stress and inflammation without inducing energy deficit

Oxidative stress and neuroinflammation are increasingly recognized as key contributors to epileptogenesis in absence epilepsy. Elevated oxidative markers and increased lipid peroxidation have been reported in WAG/Rij rats compared to non-epileptic controls.[31,32] Additionally, pro-inflammatory cytokines such as interleukin (IL)-1β and tumor necrosis factor-α have been shown to exacerbate SWD occurrence, while targeting inflammatory pathways (e.g., IL-6 inhibition) attenuates seizure activity.[33,34]

Recent studies suggest that SGLT2 inhibitors possess anti-inflammatory and antioxidant properties. Liu et al.[9] demonstrated that dapagliflozin (10 mg/kg) attenuated microglial activation and oxidative injury in a pilocarpine epilepsy model 9. Similarly, Abdelaziz et al.[35] showed that empagliflozin reduced lipid peroxidation and enhanced antioxidant defenses while modulating neuroplasticity pathways (brain-derived neurotrophic factor-tropomyosin receptor kinase B) in PTZ-induced seizures. Consistent with these findings, our results suggest that low-dose dapagliflozin (1 mg/kg) may have suppressed absence seizure activity by ameliorating oxidative stress and neuroinflammation, although direct molecular analyses were not conducted in this study. Future investigations incorporating biomarker assessments will be essential to confirm these proposed mechanisms.

Moreover, dapagliflozin has been reported to enhance dopamine levels and improve motor function in experimental Parkinson's models.[12] Considering that dopaminergic deficits are implicated in the pathophysiology of absence epilepsy and that dopamine agonists reduce, while dopamine antagonists exacerbate SWDs, it is possible that low-dose dapagliflozin exerted beneficial effects via dopaminergic modulation as well.

## CONCLUSION

This study provides the first preclinical evidence that dapagliflozin, a selective SGLT2 inhibitor, exerts dose-dependent and bidirectional effects on absence seizure activity in a genetic model of epilepsy. The findings emphasize the critical role of dosage in modulating seizure susceptibility. Furthermore, the lack of data regarding SGLT2 expression and function in thalamocortical circuits, which are the central pathways involved in absence seizures, highlights an important area for future investigation.

### Ethics

**Ethics Committee Approval:** In this study approved by Gaziosmanpaşa University Animal Experiments Local Ethics Committee (approval no: 2019 HADYEK-57, date: 22.01.2020).

**Informed Consent:** Animal experiment.

## Footnotes

**Financial Disclosure:** The author declared that this study received no financial support.

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Archives of Epilepsy

Original Article

# Rumination and Cognitive Distortion Levels in Temporal Lobe Epilepsy, Psychogenic Non-epileptic Seizures and Healthy Control Groups

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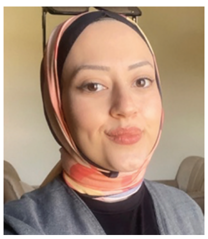

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**Abstract**

**Objective:** It is known that various psychopathologies, as well as the current neurological conditions of patients with epilepsy and psychogenic non-epileptic seizures (PNES), affect the disease process. In this study, we aimed to investigate the relationship between cognitive distortions, ruminative thinking, anxiety, and depression in patients with temporal lobe epilepsy (TLE) and compare them with PNES and healthy control groups.

**Methods:** Between September 2021 and April 2022, 300 volunteers were randomly sampled among individuals who applied to the Department of Neurology, Erciyes University Gevher Nesibe Faculty of Medicine and were included in the research process. The 300 volunteers in the research sample were assigned to 100 volunteers for each group. The self-assessment scales used in the research were personal information form, Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), Ruminative Thought Style Questionnaire (RTSQ), and Cognitive Distortion Inventory (CDI).

**Results:** BDI, BAI, RTSQ, and CDI values were found to be lowest in the control group and highest in the TLE patient group. BDI scores were found to be higher in the TLE group than in both PNES and the control groups ($p<0.001$), while BAI, RTSQ, and CDI scores were similar in the TLE and PNES groups ($p>0.05$), but higher than in the control group.

**Conclusion:** Our study found that the scores of all scale types in the TLE group were higher than in the PNES patients. We think that this situation is due to neural dysfunctions related to epilepsy, the recurrent seizures experienced by TLE patients, and the neurological, psychological, and social devastation caused by seizure anticipation.

**Keywords:** Anxiety, cognitive distortions, depression, psychogenic non-epileptic seizures, rumination, temporal lobe epilepsy

## INTRODUCTION

Among all types of epilepsy, temporal lobe epilepsy (TLE) is one of the types most associated with psychiatric comorbidities.[1] Psychiatric comorbidity in TLE has been associated with decreased quality of life, impaired cognitive functions, poor seizure control, and hippocampal sclerosis (HS).[2] Psychogenic non-epileptic seizures (PNES) are thought to occur as a dissociative response to various internal or external stimuli.[3] PNES has a complex relationship with emotional disorders. Rates of anxiety disorders and depression are higher in PNES patients than in the general population and in patients with epilepsy.[4] Catastrophic thoughts and rumination are higher in these patients than in patients with epilepsy.[5]

Ruminative thinking style is characterized by the individual constantly thinking about his or her negative experiences. Ordinary individuals can also have ruminative thoughts, but when these thoughts become so severe that they disrupt daily life, they become a pathological condition.[6] One of the main characteristics of obsessive-compulsive disorder (OCD) is that ruminative thinking reaches pathological dimensions. However, over the years, rumination has been associated with many disorders other than OCD, such as depression, anxiety, post-traumatic stress disorder, and eating disorders.[7] The risk of OCD is high in TLE. Obsessive thoughts accompany 10-22% of TLE cases. The structural brain changes that are most common in TLE are discussed among the causes of this condition.[8]

Cognitive distortion is the use of faulty and dysfunctional thought patterns in information processing. According to Beck, cognitive distortions effectively create and maintain mental disorders. The thought patterns here are negative, non-abstract, and prejudiced. Beck proposed that depression results from an individual's cognitive distortion processes. Today, cognitive distortion theory has been linked to the development of not only depression but also many other psychiatric disorders. Studies on this subject relating to epilepsy patients are insufficient in the literature.[9,10]

The aim of this study was to examine the relationship between cognitive distortions, rumination, anxiety and depression in patients with TLE and PNES and to compare the obtained data between the patient groups and the healthy control groups. Here, our first hypothesis is that all psychiatric scales will be higher in the PNES group than in both the TLE and control groups. Our second hypothesis is that rumination, cognitive distortions, depression and anxiety will be related to each other.

## METHODS

### Participants

Our study included 300 individuals who applied to the Erciyes University Faculty of Medicine Gevher Nesibe Hospital, Clinic of Neurology, Division of Epilepsy between November 2021 and March 2022. Of the patients included in our study, 100 were diagnosed with TLE according to the International League Against Epilepsy (ILAE) diagnostic criteria, and 100 were PNES patients that we followed and whose PNES attacks were proven by video electroencephalography (EEG) monitoring. Attacks of patients with PNES were recorded using a 48-hour video EEG examination.

The number of patients to be included in the study was determined by G*Power analysis. Accordingly, under the condition that the G*Power analysis results are: alpha=0.05, power=0.90, and the effect size is 0.395, at least 87 volunteers for each group should participate in the study.

All TLE patients underwent video EEG examination, and their hippocampal magnetic resonance imaging (MRI) was examined. Although interictal EEG abnormalities were present in all patients included in the study, ictal seizures were not recorded in any patient. Sixty-one patients with TLE displayed HS on hippocampal MRI. The inclusion criteria for participants with TLE were as follows: 1) diagnosed with TLE according to ILAE criteria, 2) normal MRI findings or unilateral/bilateral HS evidence consistent with EEG findings, 3) no evidence of a secondary extrahippocampal lesion that may contribute to seizures, 4) followed for at least 1 year, 5) between 18 and 65 years old, 6) possessing literacy skills. The exclusion criteria were as follows: 1) having mental retardation, 2) having a psychotic disorder, having dementia, having visual impairment, 3) alcohol or substance abuse.

The PNES group was selected from literate patients aged 18-65 years who had PNES, referred to as one of the sub-dimensions of conversion disorders according to DSM-5, who did not have an epileptic seizure, and whose PNES attack was recorded in a 48-hour video EEG examination.

The study included 100 healthy controls matched for age and gender. The control group consisted of healthy volunteers between the ages of 18-65, who were without any neurological or psychiatric diagnosis, not using neurological or psychiatric medication, and literate.

### Scales Used in the Study

#### Basic Demographic Data Form

This form was created to obtain information about the patient's age, gender, region of residence, education status, employment status, income status, marital status, family history, and concomitant disease history and consists of 14 questions in total.

#### Beck Depression Inventory

The Beck Depression Inventory (BDI) is a 4-point Likert-type self-report scale developed by Beck to measure the severity of depression. The answers given in the scale, which consists of 21 questions in total, are evaluated in the range of 0-3; and a total score range of 0-63 is reached. The score range of 0-9 is grouped as no depression; 10-16 is mild depression; 17-29 is moderate depression; 30-63 is severe depression.[11] Validity and reliability studies regarding the use of the scale in a Turkish sample were conducted by Hisli[12]. As a result of Hisli's[12] studies, the split-half test reliability coefficient of the BDI was 0.74 and the validity coefficient ranged between 0.47 and 0.63.

#### Beck Anxiety Inventory

The BAI, developed by Beck et al.[13] is designed to determine anxiety levels and consists of 21 questions requiring a 7-point Likert-type assessment. Each item in the scale is evaluated in the range of 0-3 to obtain a total score. The total score is expected to be between 0 and 63 points. The individual's anxiety level is interpreted according to the total score. The range of 0-7 points indicates minimal anxiety, 8-15 points indicates mild anxiety, 16-25 points indicates moderate anxiety, and 26-63 points indicates severe anxiety. Validity and reliability studies on the use of the scale in a Turkish sample were conducted by Ulusoy et al.[14] The alpha value indicating the internal consistency of the scale was reported as 0.93.

#### Ruminative Thought Style Scale

Ruminative Thought Style Questionnaire (RTSQ), developed by Brinker and Dozois[15] to determine individuals' uncontrolled, repetitive, and harmful thinking tendencies, is a 7-point Likert-type self-report scale consisting of 20 items. The total score obtained by the individual's self-assessment is expected to be between 20 to 140 points. The individual's ruminative thinking tendency can be interpreted according to the total score obtained.[16] Validity and

**MAIN POINTS**

- Depression was higher in patients with temporal lobe epilepsy (TLE), compared to the psychogenic non-epileptic seizure (PNES) patient group and the control group.
- Anxiety, ruminative thinking, and cognitive distortions were similar in the TLE and PNES groups, but were significantly higher in these groups than in healthy individuals.
- There was a significant positive relationship between cognitive distortions, depression, anxiety, and rumination across all three groups.

reliability studies regarding the use of the scale in a Turkish sample were conducted by Karatepe[16]. The Cronbach alpha internal consistency coefficient of the scale was reported as r=0.907, and the sample adequacy in terms of data validity was reported as 0.881.

**Cognitive Distortions Scale**

The Cognitive Distortions Scale (CDS) is a self-report scale consisting of 10 questions and 10 sub-dimensions developed by Covin et al.[17] to determine the types and frequencies of dysfunctional cognitive interpretations. The intensity of cognitive distortion can be interpreted by taking the average of the two sub-dimensions determined for each type of cognitive distortion in the scale.[17] Validity and reliability studies regarding the use of the scale in a Turkish sample were conducted by Ardaniç[18]. Ardaniç[18] reported the Cronbach's alpha internal consistency coefficient of the scale in a Turkish sample, to be 0.88 in his study.

**Ethical Approval**

Ethical approval was obtained from Erciyes University Clinical Research Ethics Committee for this study (approval no: 2021/688, date: 20.10.2021). All volunteers who agreed to participate in the study completed an informed consent form.

**Statistical Analysis**

One-way analysis of variance includes the following data assumptions: i) data normality and ii) variance homogeneity. Therefore, histograms, qq plots and Shapiro-Wilk tests were used to assess data normality, while Levene's test was used to test variance homogeneity. In comparisons between matched groups, independent two-sample t-tests were applied for quantitative variables. Tukey and Tamhane tests were used for multiple comparisons. The relationship between quantitative variables was assessed by Pearson correlation analysis. Values between 0.80 and 1.00 represent very high correlation, values between 0.60 and 0.80 represent high correlation, values between 0.40 and 0.60 represent moderate correlation, values between 0.20 and 0.40 represent low correlation, and values between 0.00 and 0.20 represent negligible correlation. All analyses were performed using TURCOSA (Turcosa Analytics Ltd. Şti., Türkiye, www.turcosa.com.tr) and R 4.2.0 (www.r-project.org) software. A p-value below 5% was considered statistically significant.

## RESULTS

The mean ages in the patient and control groups were similar between groups and were 34.2±13.2 years in the TLE group, 37.1±10.4 years in the PNES group, and 36.3±10.2 years in the control group. Baseline demographic characteristics of the participants are shown in Table 1.

Negative self-attitude, somatic, cognitive, conceptual subscales, and BDI total score were higher in TLE patients compared to the control group and PNES patient group. Subjective anxiety, somatic symptom subscales, BAI total score, RTSQ total score and CDS subscales were higher in TLE and PNES patients compared to the control group (Table 2).

There was a moderate positive correlation between depression, anxiety, and ruminative thinking, a low positive correlation between depression and selected cognitive distortions, (mind reading, emotional reasoning, labeling, mental filtering, minimizing or excluding the positive), and a weak positive correlation between depression and overgeneralizing cognitive distortions. A moderate correlation was found between anxiety and ruminative thinking, a low positive correlation between anxiety and selected cognitive distortions (emotional reasoning, labeling, mental filtering, overgeneralization, and should statements). A moderate positive correlation was found between ruminative thinking and selected cognitive distortions (catastrophizing, emotional reasoning, labeling, and mental filtering), and a low positive correlation between ruminative thinking and selected cognitive distortions (mind reading, all-or-nothing thinking, overgeneralization, personalization, should statements, minimizing or excluding the positive).

In the PNES patient group, a high positive correlation was found between depression and anxiety, and a moderate positive correlation was found between ruminative thinking and selected cognitive distortions (catastrophizing, labeling, and should statements). A low positive correlation was found between depression and selected cognitive distortions (mind reading, all-or-nothing thinking, emotional reasoning, mental filtering, overgeneralization, personalization, and minimizing or excluding the positive). A moderate positive correlation was found between anxiety and ruminative thinking and selected cognitive distortions (catastrophizing, labeling), and a low positive correlation was found between anxiety and mind reading, all-or-nothing thinking, emotional reasoning, mental filtering, overgeneralization, personalization, should statements, and minimizing or excluding

**Table 1.** Basic demographic characteristics of participants

| Variables | n | % |
|---|---|---|
| **Age** | | |
| 18-25 | 84 | 28.0 |
| 26-33 | 53 | 17.7 |
| 34-41 | 72 | 24.0 |
| 42-49 | 51 | 17.0 |
| 50+ | 40 | 13.3 |
| **Gender** | | |
| Woman | 150 | 50.0 |
| Male | 150 | 50.0 |
| **Education level** | | |
| Primary school | 72 | 24.0 |
| Middle school | 59 | 19.7 |
| High school | 103 | 34.3 |
| University | 66 | 22.0 |
| **Working status** | | |
| It works | 138 | 46.0 |
| Doesn't work | 143 | 47.7 |
| Retired | 19 | 6.3 |
| **Marital status** | | |
| Married | 185 | 61.7 |
| Single | 115 | 38.3 |

the positive. A moderate statistically significant positive correlation was found between ruminant thinking and mind reading, emotional reasoning, and labeling.

A moderate positive correlation was found among depression, anxiety, ruminative thinking, and catastrophizing. A low level positive correlation was found between depression, and the cognitive distortions of mind reading, all-or-nothing thinking, mental filtering, overgeneralization, personalization, and minimizing or excluding the positive. A low-level low positive correlation was found between anxiety and the cognitive distortions of mind reading, catastrophizing, and personalization. A moderate level, significant, positive correlation was found between ruminative thinking and the cognitive distortions of mind reading, labeling, mental filtering, overgeneralization, should statements, and minimizing or excluding the positive. A weak positive correlation was found between ruminative thinking and other cognitive distortions. Correlation results and r values are shown in Table 3.

When evaluated according to gender, BDI total score and all subscale scores (p<0.001), BAI total score and all subscale scores (p<0.001), RTSQ score (p=0.005), emotional reasoning (p=0.001), labeling (p=0.030), and mental filtering (p=0.030) scores were significantly higher in women than in men. When evaluated according to educational status, differences were found in the scales. When examining employment status, it was found that BDI and subscales (p<0.001), BAI and subscales (p<0.001), RTSQ total score (p<0.001), and CDS mental reading subscale total score (p<0.001) were lower in unemployed individuals than in employed individuals. When marital status was examined, BDI (p=0.005) and negative self-attitude (p=0.003), somatic (p=0.048), cognitive (p=0.009), and conceptual (p=0.019) scores of married individuals were found to be lower than those of single individuals (Table 4).

## DISCUSSION

In our study, it was observed that the depression level of TLE patients was higher compared to PNES patients and the control group. However, anxiety, ruminative thinking, and cognitive distortions were found to be similar between the TLE and PNES groups, and significantly higher for both groups compared to healthy individuals.

In a study evaluating 30 TLE epilepsy patients and 30 healthy volunteers regarding mood disorders, major depression, and personality disorders, anxiety, depression, antisocial personality disorders, and OCD were found to be higher in patients than in healthy controls.[19] It is thought that the accompanying HSs

**Table 2.** Comparison results of group variable's sub-dimension and total scores of BDI, BAI, RTSQ and CDS scales

| Variables | Groups | | | p-value |
|---|---|---|---|---|
| | Patients with TLE (n=100) | Patients with PNES (n=100) | Control (n=100) | |
| **BDI** | | | | |
| Positive negative attitudes | 7.61±5.31[a] | 4.22±3.88[b] | 2.59±2.59[c] | <0.001 |
| Somatic | 3.33±2.39[a] | 1.69±1.62[b] | 1.16±1.29[c] | <0.001 |
| Cognitive | 9.12±6.21[a] | 4.49±4.18[b] | 2.58±2.56[c] | <0.001 |
| Conceptual | 3.31±2.51[a] | 1.49±1.65[b] | 0.88±1.28[c] | <0.001 |
| Total | 23.37±15.52[a] | 11.89±9.95[b] | 7.21±6.43[c] | <0.001 |
| **BAI** | | | | |
| Personal anxiety | 10.99±8.77[a] | 10.75±9.54[a] | 4.72±5.53[b] | <0.001 |
| Somatic symptom | 6.47±5.39[a] | 6.00±6.13[a] | 3.05±3.23[b] | <0.001 |
| Total | 17.46±13.46[a] | 16.75±15.3[a] | 7.77±8.36[b] | <0.001 |
| **RTSQ** | | | | |
| Total | 90.45±28.07[a] | 86.89±29.67[a] | 53.24±18.99[b] | <0.001 |
| **CDS** | | | | |
| Mind reading | 7.22±3.13[a] | 6.51±3.07[a] | 5.19±2.17[b] | <0.001 |
| Catastrophizing | 6.44±3.42[a] | 6.22±3.47[a] | 4.28±2.34[b] | <0.001 |
| All or nothing | 6.45±3.37[a] | 5.51±3.31[ab] | 4.96±2.61[b] | <0.001 |
| Conclusion from emotion | 5.99±3.49[a] | 5.97±3.28[a] | 4.40±2.17[b] | <0.001 |
| Labeling | 5.46±3.53[a] | 5.57±3.36[a] | 3.64±1.75[b] | <0.001 |
| Mental filtering | 6.42±3.64 months | 5.93±3.55[a] | 4.30±2.31[b] | <0.001 |
| Overgeneralization | 5.23±3.33[a] | 5.55±3.00[a] | 3.96±2.13[b] | <0.001 |
| Personalization | 6.01±3.32[a] | 5.76±2.85[a] | 3.97±1.72[b] | <0.001 |
| Difficulty | 6.16±3.22[a] | 5.81±3.16[a] | 4.55±2.19[b] | <0.001 |
| Don't underestimate the positive | 4.99±2.97[a] | 4.53±2.69[ab] | 3.91±2.25[b] | 0.016 |

Data are expressed as mean±standard deviation. Different lowercase letters ([a,b,c]) in the same row indicate a statistically significant difference among groups. One-way analysis of variance was used.
TLE: Temporal lobe epilepsy, PNES: Psychogenic non-epileptic seizures, BDI: Beck Depression Inventory, BAI: Beck Anxiety Inventory, RTSQ: Ruminative Thought Style Questionnaire, CDS: Cognitive Distortions Scale

**Table 3.** Correlation results between depression, anxiety, rumination and cognitive distortion states by groups

| Variables | TLE patients | PNES patients | | | Controls | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Depression | Anxiety | Rumination | Depression | Anxiety | Rumination | Depression | Anxiety | Rumination |
| **Depression** | 1 | | | 1 | | | 1 | | |
| **Anxiety** | 0.550** | 1 | | 0.747** | 1 | | 0.597** | 1 | |
| **Rumination** | 0.467** | 0.553** | 1 | 0.565** | 0.584** | 1 | 0.446** | 0.190 | 1 |
| **Cognitive distortions** | | | | | | | | | |
| Total mind reading | 0.278** | 0.225* | 0.385** | 0.366** | 0.334** | 0.400** | 0.397** | 0.262** | 0.419** |
| Total catastrophizing | 0.151 | 0.169 | 0.427** | 0.445** | 0.485** | 0.346** | 0.420** | 0.253* | 0.375** |
| Total all-or-nothing thinking | 0.077 | 0.242* | 0.279** | 0.277** | 0.220* | 0.334** | 0.366** | 0.114 | 0.374** |
| Total emotional reasoning | 0.349** | 0.302** | 0.456** | 0.318** | 0.299** | 0.439** | 0.250* | -0.031 | 0.316** |
| Total labeling | 0.294** | 0.284** | 0.490** | 0.463** | 0.454** | 0.407** | 0.233* | 0.085 | 0.466** |
| Total mental filtering | 0.304** | 0.297** | 0.431** | 0.334** | 0.259** | 0.317** | 0.336** | 0.137 | 0.466** |
| Total overgeneralization | 0.199* | 0.293** | 0.384** | 0.319** | 0.244* | 0.332** | 0.376** | 0.215* | 0.437** |
| Total personalization | 0.143 | 0.240* | 0.294** | 0.292** | 0.278** | 0.390** | 0.244* | 0.137 | 0.263** |
| Total should statement | 0.193 | 0.268** | 0.393** | 0.412** | 0.293** | 0.392** | 0.242 | 0.088 | 0.425** |
| Total minimizing or disqualifying the positive | 0.269** | 0.208* | 0.302** | 0.318** | 0.296** | 0.299** | 0.347** | 0.103 | 0.414** |

*p<0.05, **p<0.001
TLE: Temporal lobe epilepsy, PNES: Psychogenic non-epileptic seizures

**Table 4.** Presence of hippocampal sclerosis in patients with TLE

| | Hippocampal sclerosis | | p-value |
|---|---|---|---|
| **BDI** | **None (n=39)** | **Yes (n=61)** | |
| **Negative self attitude** | 2.36±2.21 | 10.97±3.75 | <0.001 |
| **Physical** | 0.92±0.90 | 4.87±1.65 | <0.001 |
| **Cognitive** | 2.41±2.56 | 13.41±3.38 | <0.001 |
| **Conceptual** | 0.82±1.30 | 4.90±1.64 | <0.001 |
| **Total BDI** | 6.51±5.37 | 34.15±8.73 | <0.001 |
| **BAI** | | | |
| **Subjective anxiety** | 6.33±5.92 | 13.97±9.04 | <0.001 |
| **Somatic symptom** | 4.31±4.55 | 7.85±5.46 | <0.001 |
| **Total BAI** | 10.64±10.17 | 21.82±13.56 | 0.001 |
| **RTSQ** | | | |
| **Total RTSQ** | 75.56±28.75 | 99.97±23.24 | <0.001 |
| **CDS** | | | |
| **Total mind reading** | 6.10±2.86 | 7.93±3.10 | 0.004 |
| **Total catastrophizing** | 5.74±3.48 | 6.89±3.32 | 0.103 |
| **Total all-or-nothing thinking** | 6.18±2.89 | 6.62±3.66 | 0.524 |
| **Total emotional reasoning** | 4.67±3.03 | 6.84±3.53 | 0.002 |
| **Total labeling** | 4.23±2.93 | 6.25±3.67 | 0.003 |
| **Total mental filter** | 5.26±3.07 | 7.16±3.80 | 0.010 |
| **Total overgeneralization** | 4.51±2.89 | 5.69±3.53 | 0.085 |
| **Total personalization** | 5.44±2.86 | 6.38±3.56 | 0.168 |
| **Total should statements** | 5.38±2.71 | 6.66±3.43 | 0.053 |
| **Total minimizing the positive** | 4.21±2.31 | 5.49±3.24 | 0.023 |

BDI: Beck Depression Inventory, BAI: Beck Anxiety Inventory, RTSQ: Ruminative Thought Style Questionnaire, CDS: Cognitive Distortions Scale

underlies the increased psychosocial impairment in TLE. In some studies, it has been theoretically suggested that hyperexcitability may have effects on the connection of hippocampal neurons with other limbic regions, even if the hippocampal volume is decreased or not.[20] We found there was a significant difference in terms of depression and anxiety, between the 61 people with HS and the 39 people without HS findings. This result suggests that the limbic system may be effective in depression and anxiety.The higher rate of depression in the TLE group compared to the PNES group in our study may be related to the limbic system involvement, and a higher susceptibility to depression associated with this type of epilepsy. No previous study in the literature has compared PNES with TLE using depression scales.

In our study, while depression was higher in TLE, anxiety levels were similar to those in PNES. The results of the TLE group and the PNES group were each significantly higher than those of the control group. In the literature, it has been reported that anxiety is higher in patients with PNES than in those with epilepsy. Furthermore, anxiety is also higher in the epilepsy and PNES groups than in healthy controls.[21,22] However, as noted in studies of depression, epilepsy was treated generally in these studies, and TLE was not examined separately.

Depression, anxiety, and ruminative thinking scores were significantly higher in women than in men and higher in unemployed participants than in employed participants. When marital status was examined, depression scores of married individuals were found to be lower than those of single individuals. In general, women are more susceptible to depression and anxiety compared to men.[23] This difference, where females experience higher anxiety and depression levels than males, is even more pronounced in patients with chronic medical comorbidities such as epilepsy.[24] Also, studies showed that marital status and unemployment have a substantial effect on depression, anxiety, and well-being, a finding that is consistent with our study.[25]

In the study of Whitfield et al.[5] which included 26 patients with PNES and 29 patients with epileptic seizures, the levels of catastrophizing and recurrent negative thinking (rumination) were investigated in the two patient groups. As a result of the research, it was seen that the catastrophizing and rumination levels of the PNES patient group were higher than those of the epilepsy group.[5] In another study, rumination of past stressful events was reported at a higher rate in PNES than in epilepsy.[26] The results of these studies are different from ours. The differences between our study and the above studies are that our epilepsy group consisted of TLE, and the number of our patients was higher. We could not find any studies in the literature on rumination in individuals with TLE, and our findings on rumination in epilepsy patients indicate that temporal lobe pathology may play a role in the formation of rumination.

In a study conducted on cognitive distortions, it was observed that cognitive distortions were higher in epilepsy patients than in the control group.[27] Similar results were obtained in our study. It was found that both epilepsy and PNES patients had significantly higher cognitive distortion levels than healthy individuals. Another study showed that metacognitive beliefs, cognitive distortions, contribute to anxiety and depression even more than the perception of illness in epilepsy patients.[28] Hypothetically, we expected the PNES group to perform worse than the TLE and control groups in all scales. However, contrary to our expectations, the results showed that depression was higher in TLE patients, while TLE and PNES showed similar characteristics in other scales. With this study data we do not know the exact reason for psychiatric comorbidity in TLE patients. Psychiatric problems in TLE may be related to the presence of structural lesions in the brain, hippocampal volume changes, drug resistance, and side effects of antiepileptic drugs. We believe that multicenter, randomized controlled studies are needed.

The relationship between depression and anxiety was found to be significant in all three groups. The information in the literature also supports the current relationship between depression and anxiety. Again, significant relationships were found between depression and rumination in all three groups. There are many studies showing that as rumination increases, depression also increases. These data also support our findings.[29,30]

### Study Limitations

This study is limited to the participation of 300 volunteers between the ages of 18-65 who applied to the Neurology Polyclinic/Service of Erciyes University Faculty of Medicine Gevher Nesibe Hospital. The results of this study are limited to the data obtained from the personal information form, BDI, BAI, RTSQ, and CDS. The number and length of the scales in the study may have caused the volunteers to become bored and lose focus. Intelligence and attention tests were not administered to the volunteers because it was anticipated that the process would take too long and their compliance with the study process would decrease. The study is limited to 2021-2022. The data collection process of the study coincided with the period when the coronavirus disease-2019 pandemic occurred. This process may have also psychologically affected the volunteers who participated in the study. For this reason, the volunteers may have evaluated their anxiety and depression experiences at a higher level than normal.

## CONCLUSION

In conclusion, psychiatric comorbidity in TLE seems to be very important and reaches even more significant dimensions than in the PNES patient group. Neuropathological processes, psychosocial effects, and treatment-related factors that cause TLE may be responsible for this result. Therefore, in the approach to psychiatric comorbidity in TLE, examining and investigating the mentioned factors will enable us to understand different cause-effect relationships and plan effectively in the follow-up and treatment of patients.

### Ethics

**Ethics Committee Approval:** Ethical approval was obtained from Erciyes University Clinical Research Ethics Committee for this study (approval no: 2021/688, date: 20.10.2021).

**Informed Consent:** All volunteers who agreed to participate in the study completed an informed consent form.

### Footnotes

### Author Contributions

Surgical and Medical Practices: Y.B., F.F.E., D.K.G., Concept: Y.B., F.F.E., D.K.G., Design: Y.B., F.F.E., D.K.G., Data Collection or Processing: Y.B., F.F.E., D.K.G., Analysis or Interpretation: Y.B., F.F.E., D.K.G., Literature Search: Y.B., F.F.E., D.K.G., Writing: Y.B., F.F.E., D.K.G.

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# Assessing Neurologists' Knowledge and Experience with Neurostimulation Techniques for Epilepsy: A Cross-sectional Analysis in Saudi Arabia

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**Abstract**

**Objective:** This study aimed to evaluate neurologists' opinions on vagus nerve stimulation (VNS) therapy for managing all forms of epilepsy in Saudi Arabia.

**Methods:** This cross-sectional survey study was conducted across all five main regions of Saudi Arabia, using a structured questionnaire, and data were collected from a randomly selected sample of neurologists, with a final sample size of 229 participants. The study questionnaire was validated through a pilot study.

**Results:** A total of 112 Saudi neurologists were included in this study. Approximately 67.86% of neurologists reported the availability of VNS procedures at their practice, with 82.14% indicating patients undergo VNS implantation at epilepsy centers, and return for follow-up. Initial training in neurostimulation was rated excellent by 52.68%; but 10.71% reported it as poor. Clinical assessments were the most commonly used diagnostic tool (43.75%), and VNS was the primary technique for early epilepsy treatment (68.75%). VNS therapy was rated as highly effective in controlling seizures (68.75%), with significant benefits in reducing seizure frequency and improving quality of life (76.79%). Most neurologists (92.86%) encountered complications such as physical discomfort, mood changes, and device malfunctions.

**Conclusion:** This study highlighted that neurologists in Saudi Arabia generally recognize the effectiveness of VNS in managing drug-resistant epilepsy, though there is a need for improved training and wider availability of VNS devices. Addressing these gaps through enhanced educational programs and better access to VNS therapy could significantly improve patient outcomes and the overall management of epilepsy.

**Keywords:** Epilepsy, drug-resistant epilepsy, vagus nerve stimulation, neuromodulation therapy, Saudi Arabia

## INTRODUCTION

Epilepsy is a neurological disorder characterized by recurrent seizures and lasting brain changes, as defined by the International League Against Epilepsy.[1] Globally, around 1 to 2 percent of the population is affected by epilepsy.[2] The World Health Organization estimated in 2019 that nearly 50 million people worldwide have epilepsy.[3] In Saudi Arabia, the prevalence is approximately 3.96 cases per 1,000 persons [95% confidence interval (CI): 2.99-5.16].[4] Individuals with epilepsy face a higher risk of injuries related to seizures, as well as significant psychological effects, including anxiety, depression, and low self-esteem, which can lead to social isolation and fear of injuries.[5,6]

Anti-seizure medications (ASMs) are the primary treatment for epilepsy, but about 25% of patients do not achieve seizure freedom with these drugs. For a third of these patients, epilepsy remains uncontrolled or drug-resistant.[7] The rate of drug-resistant epilepsy is similar globally around 30-36.5%.[8] Early identification of these patients is critical for improving their management. Patients with drug-resistant epilepsy face a greater risk of complications and comorbidities. Patients with drug-resistant epilepsy are defined as those who continue to experience seizures despite appropriate trials of two or more adequately chosen and tolerated ASMs.[8] For these patients, if they are not candidates for resective epilepsy surgery, if they have failed epilepsy surgery, or if they have contraindications to epilepsy surgery, alternative treatment options include palliative therapies such as neurostimulation. Currently, three neurostimulation techniques vagus nerve stimulation (VNS), deep brain stimulation (DBS), and responsive neurostimulation (RNS) are approved for the management of drug-resistant epilepsy.[9-11] These therapies offer seizure reduction rather than curative outcomes, making them essential options for patients who are not suitable candidates for definitive surgical interventions.

VNS, approved in 1995, stimulates the vagus nerve, leading to a 50% or greater reduction in seizures for about half of the patients, with effectiveness potentially increasing over time.[12] The anterior nucleus of the thalamus-DBS, approved in 2014 (2010 in Europe), shows similar efficacy. RNS, also approved in 2014, targets brain activity patterns preceding seizures with the aim of preventing them and achieving similar results in seizure reduction to the VNS.[13]

While these neurostimulation therapies provide relief for some, they are generally considered palliative, with only a small percentage achieving long-term seizure independence.[14] Their use is particularly significant for patients who are not candidates for curative epilepsy surgery. Neurostimulation's primary benefit is manipulating the epileptic network by delivering stimuli to specific brain regions.[15] However, further theoretical studies are needed to understand the mechanisms of neurostimulation, and epilepsy networks.

Studies have explored neurostimulation techniques, with a retrospective study finding VNS therapy to be a safe and effective adjunct for both adult and pediatric patients. They showed promising results in reducing seizure frequency using VNS and DBS in patients unresponsive to medications.[13,16] Effective epilepsy control via neurostimulation could reduce the economic burden of epilepsy by decreasing hospitalizations and emergency visits, improving patients' quality of life (QoL).[17] This study aims to evaluate neurologists' opinions on VNS for managing drug-resistant epilepsy in Saudi Arabia, providing insights to enhance patient care and develop more efficient treatment approaches.

**MAIN POINTS**

- **Effectiveness of VNS:** The study found vagus nerve stimulation (VNS) highly effective in reducing seizure frequency and improving quality of life in patients with drug-resistant epilepsy.
- **Training Gaps Identified:** While most neurologists rated their initial VNS training as excellent or good, a notable 10.7% reported inadequate training, highlighting the need for improved educational programs.
- **Challenges in Accessibility:** One-third of participants reported limited access to VNS devices, underscoring disparities in availability across healthcare facilities in Saudi Arabia.
- **Complications Encountered:** Common complications of VNS therapy included physical discomfort, mood changes, and device malfunctions, emphasizing the need for better patient monitoring and support systems.
- **Recommendations for Improvement:** Neurologists suggested advancements in patient monitoring, less invasive procedures, and more effective stimulation techniques to optimize VNS therapy outcomes.

## METHODS

### Study Design, Area, and Setting

A cross-sectional survey study was used to evaluate the perceptions of neurologists regarding neurostimulation techniques in epilepsy treatment, their commonly utilized techniques, and their opinions on the safety of these procedures. This study was conducted in Saudi Arabia, covering all five main regions: Eastern, Central, Northern, Western, and Southern. These regions included various urban and rural settings, with neurologists working in different types of healthcare facilities, such as public hospitals, private hospitals, and specialized neurology clinics. Before starting data collection, ethical approval was obtained from the King Khalid University Research Ethics Committee (approval no: HAPO-06-B-001, date: 08.11.2023). Confidentiality and security of the data were ensured, with only the research team and principal investigator having access to the data for research purposes.

### Inclusion Criteria

The inclusion criteria for this study were certified neurologists currently practicing in Saudi Arabia across various healthcare facilities, including public and private hospitals, as well as specialized neurology clinics, with specific experience in neurostimulation techniques for epilepsy diagnosis and treatment. Exclusion criteria ruled out neurologists who were not currently practicing and those without experience in neurostimulation techniques.

### Sample Size

The sample size was calculated using Raosoft. According to the Ministry of Health Statistical Yearbook (2021), the population size of specialized neurologists and consultants was 560. With a confidence level of 95% and a 5% margin of error, the estimated sample size was 229 neurologist participants.

### Sampling Technique

Participants were selected through a random sampling technique. Saudi Arabia was divided into regions (Eastern, Central, Northern, Western, and Southern). Neurologists from each region were randomly selected from neurology clinics, ensuring an accurate representation of the entire population.

### Data Collection Methods and Tools

Data were collected using a structured questionnaire developed specifically for this study. The questionnaire was administered online and comprised a mix of multiple-choice questions, 3-point Likert scale questions, and open-ended questions. The questionnaire was divided into three parts: 1) demographic information (age, gender, region, hospital center, experience with neurostimulation techniques, initial training in neurostimulation techniques); 2) assessment of the efficacy and safety of neurostimulation techniques using a 3-point Likert scale; 3) data related to participants' perceived benefits, QoL, neurostimulation complications, and improvements.

A pilot study was conducted on a small group of neurologists to test the validity and reliability of the questionnaire. Necessary modifications were made based on the feedback received.

### Data Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS; IBM Corp., Version 25). Descriptive statistics were used to summarize the basic features of the dataset. Categorical data were represented as frequencies and percentages.

## RESULTS

The study included 112 neurologists (response rate 48%), with the majority (71.43%) aged between 30 and 45 years and 28.57% aged 45 or older. The gender distribution showed a higher percentage of male participants (59.82%) compared to females (40.18%). Regional representation was most significant from the Central Region (36.61%), followed by the Western Region (27.68%), the Eastern Region (19.64%), and both the Southern and Northern Regions (8.04% each). A significant proportion of participants (59.82%) were practicing neurologists at epilepsy centers. King Faisal Specialist Hospital and Research Centre had the highest representation (21.43%), followed by King Fahad Specialist Hospital (9.82%), King Fahad Medical City (8.04%), Prince Sultan Military Medical City (8.04%), Security Forces Hospital (8.04%), Prince Fahd bin Sultan Hospital (5.36%), National Guard (4.46%), and other hospitals (33.93%), as shown in Table 1.

In their current practice, 67.86% of neurologists reported that VNS procedures are available at their hospital or center, while 32.14% indicated that they refer patients elsewhere for the procedure. When patients are not at an epilepsy center, 82.14% of neurologists stated that these patients undergo VNS device implantation at an epilepsy center and then return to their clinic for follow-up and device adjustment, whereas 17.86% noted that patients schedule follow-up appointments there. Regarding their initial training in neurostimulation techniques, 52.68% of neurologists rated it as excellent, 36.61% as good, and 10.71% as poor (Table 2).

The study revealed that clinical assessments are the most commonly used diagnostic tool for detecting early signs of epilepsy, as reported by 43.75% of neurologists. Electroencephalography (EEG) was used by 18.75% of respondents, magnetic resonance imaging (MRI) by 16.07%, and computed tomography (CT) by 4.46%, while 16.96% indicated using all of these techniques. For early epilepsy diagnosis and treatment, VNS was the most commonly used technique, cited by 68.75% of neurologists, followed by RNS at 22.32%, with 8.93% indicating none of the above, or that the techniques were not available. Determining patient suitability for VNS therapy involved considering the frequency and severity of seizures (18.75%), conducting comprehensive neurological assessments (15.18%), collaborating with a multidisciplinary team (1.79%), and combining all of these methods (64.29%), as shown in Table 3.

The outcomes of VNS therapy in epilepsy patients were rated by neurologists as excellent in controlling seizures by 68.75%, good by 29.46%, and poor by 1.79%. The typical duration of VNS treatment varied, with 24.11% indicating 6 months to 1 year, 7.14%

**Table 1.** Demographic characteristics

| Parameters | | n (%) |
|---|---|---|
| Age | 30-45 years | 80 (71.43%) |
| | 45 or older | 28 (28.57%) |
| General | Male | 67 (59.82%) |
| | Female | 45 (40.18%) |
| Region | Western Region | 31 (27.68%) |
| | Central Region | 41 (36.61%) |
| | Southern Region | 9 (8.04%) |
| | Eastern Region | 22 (19.64%) |
| | Northern Region | 9 (8.04%) |
| Are you a neurologist currently practicing at an epilepsy center? | Yes | 67 (59.82%) |
| | No | 45 (40.18%) |
| Please specify the name of your hospital and indicate whether it is a neuro clinic or monitoring epilepsy unit? | King Faisal Specialist Hospital | 24 (21.43%) |
| | King Fahad Specialist Hospital | 11 (9.82%) |
| | King Fahad Medical City | 9 (8.04%) |
| | Prince Sultan Military Medical City | 9 (8.04%) |
| | Security Forces Hospital | 9 (8.04%) |
| | Prince Fahad bin Sultan Hospital | 6 (5.36%) |
| | National Guard | 5 (4.46%) |
| | Others | 38 (33.93%) |

**Table 2.** Availability and implementation of VNS therapy

| Question | Responses | n (%) |
|---|---|---|
| At your current practice as a neurologist. Is VNS procedure available in your hospital/center? | Yes | 76 (67.86%) |
| | No, the referral is advised | 36 (32.14%) |
| If the patient is not at an epilepsy center, do they undergo VNS device implantation at the epilepsy center and then come back to your clinic for follow-up and device adjustment if necessary? | Yes | 92 (82.14%) |
| | No, the patient schedules a follow-up appointment at the epilepsy center | 20 (17.86%) |
| How would you rate your initial training in neurostimulation techniques? | Excellent | 59 (52.68%) |
| | Good | 41 (36.61%) |
| | Poor | 12 (10.71%) |

VNS: Vagus nerve stimulation

indicating 2 to 5 years, 25.89% indicating it varies depending on the patient's response, and 42.86% reporting indefinite duration. The effectiveness of VNS treatment was primarily monitored through periodic device programming and patient feedback (49.11%), followed by EEG monitoring and medication adjustments (31.25%), regular follow-up visits and seizure diaries (16.07%), and clinical observation and caregiver reports (3.57%). The potential benefits of VNS treatment included a reduction in seizure frequency and severity (1.79%), improved mood and QoL (13.39%), decreased use of anti-epileptic drugs (8.06%), and a combination of these benefits (76.79%) as shown in Table 4.

When assessing the QoL for patients who have undergone neurostimulation therapy for epilepsy, 64.29% of neurologists consider all factors, including patient-reported outcomes and satisfaction, impact on daily activities and social interactions, family support and involvement, and frequency of follow-up visits. Specifically, 16.07% prioritize patient-reported outcomes and satisfaction during clinic visits, 9.82% focus on the impact on daily activities and social interactions, 7.14% emphasize family support and involvement, and 2.68% consider the frequency of follow-up visits. Managing potential side effects or adverse events related to VNS therapy typically involves three strategies: medication changes or additions (9.82%), adjusting stimulation parameters or programming settings (7.14%), and collaborating with speech and language therapists (11.61%). The majority (71.43%) of practitioners employing all these strategies.

A significant majority of neurologists (92.86%) have encountered complications or observed adverse effects following neurostimulation procedures, with the most frequently reported issues being physical discomfort (58.93%), mood changes

**Table 3.** Diagnostic tools and techniques for epilepsy

| Question | Responses | n (%) |
|---|---|---|
| Which of the following techniques or diagnostic tools are most commonly used in the evaluation of epilepsy in your clinical practice? | EEG | 21 (18.75%) |
| | Clinical assessments | 49 (43.75%) |
| | MRI | 18 (16.07%) |
| | CT scan | 5 (4.46%) |
| | All of the above | 19 (16.96%) |
| Which neurostimulation technique do you most commonly use for the management of epilepsy in your patients? | VNS | 77 (68.75%) |
| | RNS | 25 (22.32%) |
| | None of the above or not available | 10 (8.93%) |
| How do you determine if a patient with epilepsy is a suitable candidate for VNS therapy? | Based on the frequency and severity of seizures | 21 (18.75%) |
| | By conducting a comprehensive neurological assessment | 17 (15.18%) |
| | Through collaboration with a multidisciplinary team | 2 (1.79%) |
| | All of the above | 72 (64.29%) |

EEG: Electroencephalography, MRI: Magnetic resonance imaging, CT: Computed tomography, VNS: Vagus nerve stimulation, RNS: Responsive neurostimulation

**Table 4.** Outcomes of VNS therapy

| Question | Responses | n (%) |
|---|---|---|
| On a scale of 1-3, how would you rate the effectiveness of neurostimulation in controlling seizures in epilepsy patients? | Excellent | 77 (68.75%) |
| | Good | 33 (29.46%) |
| | Poor | 2 (1.79%) |
| What is the typical duration of VNS treatment in epilepsy patients? | 6 months to 1 year | 27 (24.11%) |
| | 2 to 5 years | 8 (7.14%) |
| | It does vary depending on the patient's response | 29 (25.89%) |
| | Indefinite | 48 (42.86%) |
| How is the effectiveness of VNS treatment monitored in epilepsy patients? | It is through EEG monitoring and medication adjustments | 35 (31.25%) |
| | It is through regular follow-up visits and seizure diaries | 18 (16.07%) |
| | It is through clinical observation and caregiver reports | 4 (3.57%) |
| | It is through periodic device programming and patient feedback | 55 (49.11%) |
| What are the potential benefits of VNS treatment in epilepsy? | Reduction in seizure frequency and severity | 2 (1.79%) |
| | Improved mood and quality of life | 15 (13.39%) |
| | Decrease in the use of anti-epileptic drugs | 9 (8.06%) |
| | All of the above | 86 (76.79%) |

VNS: Vagus nerve stimulation, EEG: Electroencephalography

(41.07%), device malfunction (30.36%), hemorrhage (27.68%), infection (25.89%), and cognitive changes (25.00%) (Figure 1).

Regarding MRI scans, 46.43% noted that while complications can occur, precautions can be taken to conduct the scan safely whereas 24.11% reported that the device is entirely MRI-compatible, and 19.64% mentioned complications only if the MRI is of the head. Suggested improvements in neurostimulation techniques included better patient monitoring (51.79%), less invasive procedures (45.54%), better training programs (36.61%), and more effective stimulation techniques (32.14%). Specific patient characteristics or epilepsy types that tend to respond better to VNS treatment include patients with focal seizures (46.43%), a history of traumatic brain injury (13.39%), and drug-resistant epilepsy (10.71%), while 29.46% indicate all of the above (Table 5).

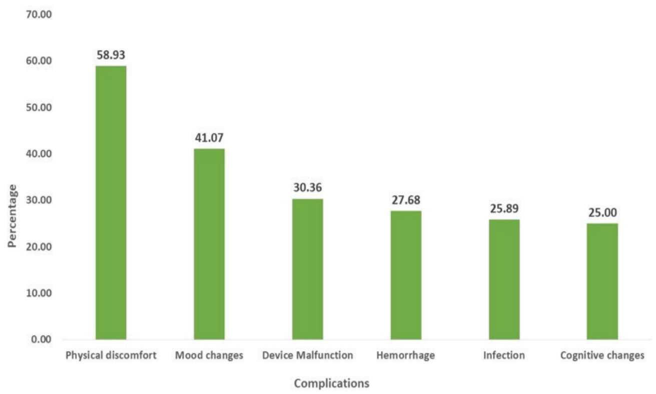


**Figure 1.** The most frequently reported complications encountered by the neurologists during implementation of VNS
VNS: Vagus nerve stimulation

## DISCUSSION

The findings of this study highlight the perceptions and experiences of neurologists in Saudi Arabia regarding the use of VNS therapy for epilepsy management. A substantial number of neurologists indicated that VNS procedures are available in their practice settings, demonstrating a favorable trend toward the adoption of this neurostimulation technique. Nevertheless, approximately 10% of participants reported inadequate training, highlighting the need for improvement in training materials and physician education programs to enhance understanding and proficiency in VNS procedures. In addition, about one-third of the participants reported that VNS devices are not available in their institutions or hospitals.

**Table 5.** QoL and management of adverse effects in VNS therapy

| Question | Responses | n (%) |
|---|---|---|
| Which of the following is an important factor to consider when assessing the QoL for patients who have undergone neurostimulation therapy for epilepsy, based on follow-up visits and family responses? | Patient-reported outcomes and satisfaction (QoL assessment in clinic visit) | 18 (16.07%) |
| | Impact on daily activities and social interactions | 11 (9.82%) |
| | Family support and involvement | 8 (7.14%) |
| | Frequency of follow-up visits | 3 (2.68%) |
| | All of the above | 72 (64.29%) |
| How do you manage potential side effects or adverse events related to VNS therapy in epilepsy patients? | Medication changes or additions | 11 (9.82%) |
| | Adjusting stimulation parameters or programming settings | 8 (7.14%) |
| | Collaborating with speech and language therapists | 13 (11.61%) |
| | All of the above | 80 (71.43%) |
| Have you encountered any complications during or observed any adverse effects after neurostimulation procedures? | Yes | 104 (92.86%) |
| | No | 8 (7.14%) |
| What improvements or advancements would you like to see in neurostimulation techniques? (Select all that apply) | Better patient monitoring | 58 (51.79%) |
| | Better training programs | 41 (36.61%) |
| | Less invasive procedures | 51 (45.54%) |
| | More effective stimulation techniques | 36 (32.14%) |
| Can the VNS device cause complications if a patient needs to undergo an MRI scan? | Yes, all MRI scans are contraindicated with a VNS device | 11 (9.82%) |
| | Yes, but precautions can be taken to conduct an MRI safely | 52 (46.43%) |
| | Yes, but only if the MRI is of the head | 22 (19.64%) |
| | No, the device is entirely MRI-compatible | 27 (24.11%) |
| Are there any specific patient characteristics or epilepsy types that tend to respond better to VNS treatment? | Patients with drug-resistant epilepsy | 12 (10.71%) |
| | Patients with a history of traumatic brain injury | 15 (13.39%) |
| | Patients with focal seizures | 52 (46.43%) |
| | All of the above | 33 (29.46%) |

VNS: Vagus nerve stimulation, QoL: Quality of life, MRI: Magnetic resonance imaging

The lack of VNS devices in certain healthcare settings highlights disparities in access to advanced neurostimulation therapies. While larger, specialized epilepsy centers may have the necessary resources and expertise to offer VNS, smaller hospitals or clinics may face limitations due to budget constraints, infrastructure, or training gaps.[18] As a result, patients in underserved areas may be deprived of this potentially beneficial treatment option.[19] Neurologists working in institutions without VNS devices face a challenging dilemma. When encountering patients who could benefit from VNS, healthcare providers must decide whether to refer them to external centers or explore alternative treatment modalities.[20] This decision-making process involves weighing the potential benefits of VNS against the logistical challenges of referral and follow-up. It also underscores the need for collaborative networks and clear referral pathways to ensure seamless patient care.

Clinical evaluations by neurologists play a crucial role in diagnosing epilepsy. These assessments consider seizure semiology, medical history, and physical examination. The substantial use of clinical assessments (43.75%) reflects their importance in identifying early signs of epilepsy.[21] EEG remains a cornerstone in diagnosing epilepsy. It records electrical activity in the brain and helps identify abnormal patterns associated with seizures.[22] The utilization of EEG (18.75%) needs to be increased to align with the international and regional recommendations.[23] MRI provides detailed structural images of the brain. It helps detect underlying lesions, such as tumors or vascular malformations, which may contribute to epilepsy. CT scans are less commonly used (4.46%) due to their lower sensitivity for detecting subtle brain abnormalities associated with epilepsy. However, they may be useful in emergency situations or when MRI is contraindicated.[24] Saudi neurologists reached a consensus recommending that, before VNS implantation, a comprehensive seizure evaluation must be documented, including baseline seizure type, severity, and frequency. Each patient must have at least one documented seizure and undergo a video-EEG recording for a minimum of 24 hours. Additionally, a brain MRI (at least 1.5 Tesla) should be performed to rule out potential resective epilepsy surgery with a CT scan as an alternative if MRI is contraindicated.[25]

Identifying suitable candidates for VNS involves assessing seizure frequency, severity, and response to previous treatments. Collaboration with a multidisciplinary team ensures comprehensive evaluation and optimal patient selection. A Saudi consensus showed that patients recommended for VNS therapy must meet specific criteria, including having symptomatic localized epilepsy with multiple or bilateral independent foci; cryptogenic or symptomatic generalized epilepsy with widespread epileptogenic abnormalities such as Lennox-Gastaut syndrome; a history of failed intracranial epilepsy surgery with no viable alternative surgical options; or refractory epilepsy that is not suitable for surgical intervention.[25]

The effectiveness of VNS in controlling seizures was rated highly, with a majority of neurologists acknowledging its benefits in reducing seizure frequency and improving the QoL for patients. These results align with existing literature that underscores the efficacy of VNS in managing drug-resistant epilepsy. A meta-analysis of 74 articles showed that following VNS therapy, seizure frequency decreased by an average of 45%, with a 36% reduction observed at 3 to 12 months post-surgery and a 51% reduction after more than one year of treatment. At the final follow-up, approximately 50% of patients experienced a 50% or greater reduction in seizures. VNS predicted a reduction of 50% or more in seizures with a main effects odds ratio of 1.83 (95% CI: 1.80-1.86).[26] A more recent systematic review and meta-analysis showed that high-frequency VNS was significantly more effective than the control, with a standardized mean difference of 0.82 (95% CI: 0.39-1.24, p<0.001). This significance persisted across subgroup analyses comparing low-frequency VNS as the control, different VNS modalities, and, after excluding studies with moderate-to-high risk of bias. Treatment response data from 8 studies involving 758 patients also favored high-frequency VNS over control, with a risk ratio of 1.57 (95% CI: 1.19-2.07, p<0.001). QoL outcomes were descriptively reported in 4 studies with 363 patients, and adverse events were documented in 11 studies comprising 875 patients.[27]

The study participants identified physical discomfort, mood changes, device malfunction, hemorrhage, infection, and cognitive changes as the most commonly encountered adverse events. In a cohort study conducted by Alshehri et al.[28] 67.4% of patients undergoing VNS therapy reported experiencing side effects. The serious adverse reactions identified included dysphagia (39.5%), dyspnoea (23.3%), aspiration pneumonia (9.3%), increased secretions (7%), snoring (7%), and an increase in seizure frequency (2.3%). Mild side effects encompassed cough (23.3%), hoarseness (18.6%), and also included vomiting and fatigue.[28] Toffa et al.[29] meta-analysis detailed additional side effects of VNS, such as postoperative infection, vocal cord paresis, cough, neck pain, hoarseness, dysphonia, and snoring. High-intensity stimulation often led to withdrawals and changes in voice, including hoarseness. At lower stimulation levels, side effects such as cough, dyspnea, pain, paresthesias, nausea, and headache were noted.[29] Furthermore, as an electrical device, the electrode used in VNS therapy may pose risks such as electrode breakage, disconnection, failure, and pacemaker malfunction. Surgical complications related to electrode insertion, including infection, hematoma, vocal cord palsy, and cable discomfort, should also be considered.[30]

The survey results reflect the evolving understanding of MRI compatibility with VNS devices. While a significant proportion of respondents (46.43%) acknowledged potential complications, they also recognized that safety precautions could mitigate these risks. This aligns with current guidelines, which state that MRI can be safely performed with VNS therapy systems, provided specific guidelines are followed.[31] 24.11% of respondents reported that the device was entirely MRI-compatible, reflecting advancements in VNS technology that have expanded MRI access. However, 19.64% of respondents mentioned complications only if the MRI the head, indicating a need for further clarification and education on this topic.

The survey responses highlight several areas for improvement in neurostimulation techniques. Better patient monitoring was the most commonly suggested improvement, aligning with recent literature emphasizing the importance of personalized strategies and dynamic closed-loop assessment of neural function.[32] Less invasive procedures were also highlighted, reflecting ongoing efforts to minimize patient discomfort and risk. Better training programs and more effective stimulation techniques were also suggested, underscoring the need for continuous innovation and education in the field of neurostimulation.[33]

The survey identified specific patient characteristics or epilepsy types that tend to respond better to VNS treatment. Patients with focal seizures were most commonly identified, consistent with literature indicating that VNS is particularly effective for patients with focal seizures.[34] A history of traumatic brain injury and drug-resistant epilepsy was also noted, reflecting the broad applicability of VNS therapy.[35] Interestingly, 29.46% of respondents indicated that all of the above characteristics could predict a better response to VNS, suggesting that a comprehensive patient assessment is crucial for optimizing VNS outcomes.

### Implications

The study's implications are significant for clinical practice and healthcare policy in Saudi Arabia. The high effectiveness rating of VNS therapy by neurologists suggests that it is a valuable tool in the management of drug-resistant epilepsy. Healthcare facilities should consider increasing the availability of VNS procedures and providing robust training programs for neurologists to enhance their competence in neurostimulation techniques. Furthermore, addressing the complications associated with VNS through comprehensive follow-up and patient support systems can improve patient outcomes and satisfaction. Policymakers should also consider integrating VNS therapy more broadly into national epilepsy management guidelines to ensure uniformity in treatment approaches.

### Future Directions

Future research should focus on exploring alternative mechanisms by which VNS might affect epilepsy beyond its current applications. Studies should investigate the potential of VNS in modulating neural networks and their impact on cognitive and psychological outcomes in epilepsy patients. Additionally, future studies should include subgroup analyses to identify specific patient characteristics that may influence the response to VNS therapy, such as age, gender, and epilepsy type. Sensitivity analyses are also crucial to assess the robustness of findings and to account for variations in study designs and patient populations. Long-term studies with larger sample sizes and diverse demographic representation are needed to establish the sustained efficacy and safety of VNS therapy in various clinical settings. This comprehensive approach will provide deeper insights into the optimization of neurostimulation techniques for epilepsy management.

### Study Limitations

This study has several limitations that need to be acknowledged. The sample size was relatively small, with only 112 neurologists participating, which may limit the generalizability of the findings. Additionally, the response rate was low at 48%, potentially introducing non-response bias and limiting the representativeness of the results. The descriptive nature of the study also restricts the ability to infer causality or explore more complex relationships between variables. Another limitation is the reliance on self-reported data, which may be subject to recall bias or social desirability bias. The assessment of neurostimulation effectiveness was based on the subjective opinions of participating neurologists, without using standardized clinical metrics such as seizure reduction rates. This reliance on subjective evaluation may have introduced variability in the reported effectiveness of neurostimulation techniques. Furthermore, the study was conducted within a specific geographic context Saudi Arabia potentially limiting the applicability of the findings to other regions with different healthcare systems and practices. Finally, variations in healthcare infrastructure and resources across the different regions included in the study may also influence the results, indicating the need for more nuanced analyses in future research.

## CONCLUSION

This study provided valuable insights into the knowledge, awareness, and perceptions of neurologists in Saudi Arabia regarding the use of neurostimulation techniques, particularly VNS, for epilepsy diagnosis and management. The findings indicate a significant level of awareness and implementation of VNS procedures, with most neurologists acknowledging its effectiveness in reducing seizure frequency and improving patient QoL. However, the study also identified gaps in training, with a portion of neurologists reporting inadequate initial training in neurostimulation techniques, highlighting the need for enhanced educational programs. Neurologists' views on the efficiency and safety of VNS were generally positive, aligning with existing literature on the benefits of this therapy for drug-resistant epilepsy. Factors influencing recommendations for VNS therapy included the frequency and severity of seizures, comprehensive neurological assessments, and multidisciplinary collaboration. The study also uncovered challenges such as limited availability of VNS devices in certain healthcare settings and the occurrence of adverse events like physical discomfort and device malfunctions.

Addressing these challenges requires targeted efforts to improve access to VNS therapy, provide robust training programs, and develop comprehensive patient support systems. Future research should explore alternative mechanisms of VNS, conduct subgroup analyses to identify specific patient characteristics influencing therapy response, and undertake long-term studies to establish the sustained efficacy and safety of VNS. By addressing these areas, healthcare providers can enhance the effectiveness and safety of neurostimulation techniques, ultimately improving patient outcomes in epilepsy management.

Finally, while VNS therapy is a promising intervention for drug-resistant epilepsy, further research and improvements in training, patient monitoring, and management of adverse effects are essential to maximize its benefits. By addressing these areas, healthcare providers can enhance the effectiveness and safety of VNS therapy, ultimately improving the QoL for epilepsy patients.

### Ethics

**Ethics Committee Approval:** Before starting data collection, ethical approval was obtained from the King Khalid University Research Ethics Committee (approval no: HAPO-06-B-001, date: 08.11.2023).

**Informed Consent:** Retrospective study.

### Footnotes

### Author Contributions

Concept: Z.A.Q., N.T., Design: Z.A.Q., N.T., Data Collection or Processing: N.N.A., A.A.A., K.M.O.A., Analysis or Interpretation: Z.A.Q., A.A.A., Literature Search: N.N.A., A.A.A., Writing: Z.A.Q., N.N.A., A.A.A., K.M.O.A., N.T.

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# Challenges in the Diagnosis of Patients Presenting with the "First Seizure"

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**Abstract**

**Objective:** Epileptic seizures are paroxysmal events resulting from abnormal neuronal activity. Diagnosing a first seizure presents a significant clinical challenge, particularly in patients without a previous similar history. This study aims to evaluate the clinical approach to first seizures, which are often posing diagnostic and therapeutic challenges.

**Methods:** This prospective study was conducted in a tertiary care hospital and included patients admitted to the emergency department and neurology outpatient clinic with suspected first seizures from January 2023 to March 2024. Patients were followed for at least one year. Data collected included age, gender, laboratory tests, cranial imaging, and electroencephalogram (EEG) results. Final diagnoses were classified as either "seizure" or "seizure mimics," with seizures further categorized into "unprovoked" and "acute symptomatic." The unprovoked category was divided into "true first seizure" and "recurrent seizure."

**Results:** A total of 210 patients were included in the study, with 152 diagnosed with seizures and 58 with seizure mimics. The mean age was 43.7 years. The male/female ratio was 55.3%/44.7%. In the "seizure" group, 119 patients (56.7%) had unprovoked and 33 (15.8%) had acute symptomatic seizures. In the unprovoked group, 106 patients (50.5%) were classified as having a true first seizure. Detailed history revealed that 13 patients (6.2%) had at least one similar seizure before. Seizure recurrence was observed in 27 patients (25.5%).

**Conclusion:** This study highlights the diagnostic challenges of first seizures. Accurate differentiation between epileptic seizures and mimics is crucial. Comprehensive history and EEG are essential for optimizing treatment, and initiating therapy in true seizure cases effectively reduces the risk of recurrence.

**Keywords:** First, seizure, recurrent, epileptic, treatment

## INTRODUCTION

Epileptic seizures are paroxysmal and episodic phenomena characterised by behavioural, somatosensory, motor, or visual signs and symptoms due to abnormal, excessive, or synchronized neuronal activity in the brain. The clinical situation in which patients present with seizure without a previous history of seizure is considered the first seizure.[1-3]

The evaluation of a suspected first seizure presents several diagnostic challenges, including determining the underlying etiology, assessing the risk of recurrence, determining the need for diagnostic electroencephalogram (EEG) or neuroimaging, determining whether to initiate anti-seizure medication (ASM), and managing patient and family concerns about social or emotional impact on lifestyle.[4]

A key concern is whether the event represents a true seizure associated with epileptogenic brain pathology or a "seizure mimic." This distinction is crucial, as it directly affects both seizure recurrence prognosis and the choice of treatment strategies.[3,5] A wide spectrum of differential diagnoses must be considered when evaluating a first seizure. These include psychogenic non-epileptic seizures (PNES), syncope, transient ischemic attacks (TIAs), migraine auras, paroxysmal movement disorders, transient global amnesia, sleep disorders, and panic attacks.[1,2]

Another critical aspect is differentiating between an acute symptomatic seizure and an unprovoked seizure, as their treatment and prognosis differ significantly. It is essential to distinguish between these conditions as early as possible. In addition to obtaining a detailed patient history and performing a thorough physical examination, healthcare providers use other diagnostic tools—such as laboratory tests, EEG, and neuroimaging—that play a crucial role. In cases of unprovoked seizures, evaluating the risk of recurrence and determining whether to initiate treatment is of utmost importance.

In this context, a structured approach should be implemented when assessing patients presenting with a suspected first seizure. This approach should include a thorough differential diagnosis, appropriate investigations, timely initiation of treatment when necessary, and continued follow-up with neurology specialists. In our study, we assessed patients admitted to our hospital with a suspicion of first seizure. The primary objective was to identify key clinical features critical for diagnosing an initial epileptic seizure, to determine criteria for initiating ASM, and to evaluate the effect of regular medication use on seizure recurrence.

## METHODS

The study was conducted in a tertiary care hospital. Patients who were prospectively admitted to the emergency department and neurology outpatient clinic with a suspected first seizure between January 2023 and March 2024 were included in the study. They were followed up for at least a year in the outpatient clinic. Patients who failed to attend follow-up visits were excluded from the study.

Clinical history was obtained through interviews with the patient, when possible, corroborated by family members or witnesses when available. Patient data, including age, gender, cranial imaging findings, and EEG results, were evaluated. Routine laboratory tests performed in the emergency department included complete blood count, glucose, urea, creatinine, liver enzymes, and electrolytes. Additionally, more detailed tests, such as vitamin B12 and thyroid function tests, were included if performed during follow-up. Cranial magnetic resonance imaging (MRI) and EEG results obtained either in the emergency department or during follow-up were analyzed.

EEG recordings were conducted while patients were awake for 30 minutes, and in some cases, prolonged recordings lasting up to two hours were performed including both sleep and wake periods. The routine EEG recordings were typically 20-30 minutes in duration, while extended recordings (up to two hours) were performed when clinically indicated when routine EEG was normal and the clinical diagnosis of epilepsy was strong, or in cases where sleep EEG was more informative, such as idiopathic generalized epilepsies. Scalp electrodes were placed according to the 10-20 international system. The time constant was set at 0.3 seconds, and the high-frequency filter was standardized at 70 Hz. Intermittent photic stimulation with flash frequencies ranging from 1 to 60 Hz was applied in all cases, followed by four minutes of hyperventilation. Eye-opening and eye-closure responses were noted in all recordings. EEG findings were classified as follows: normal, epileptiform discharges (focal, multifocal, generalized), and slowing (focal, generalized). EEG recordings were performed within the first 24 hours for patients who presented to the emergency department (84%), but for those who presented to the outpatient clinic, EEG recordings were performed later (within at most one month). All EEGs were interpreted by two neurologists with expertise in clinical neurophysiology.

The final diagnoses of the patients were determined as either “seizure” or “seizure mimics.” Seizures are further divided into “unprovoked seizures” and “acute symptomatic seizures.” Unprovoked seizures are further divided into “true first seizure” and “recurrent seizure.” The recurrent seizure group included patients who were admitted to the hospital for their first seizure but actually had a previous history based on a detailed medical history. The diagnosis of epilepsy was made based on the International League Against Epilepsy (ILAE) criteria.[6] The seizure semiology was evaluated according to the 2017 classification of the ILAE. In patients diagnosed with epilepsy, data on whether ASM was initiated and whether seizures recurred during follow-up were collected.

The study was approved by the Local Ethics Committee of the University of Health Sciences Türkiye, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital (approval no: 2023/04, date: 16.01.2023). Informed consent was obtained from all patients.

### Statistical Analysis

Statistical analysis was performed using SPSS version 26 (IBM Corp., Armonk, NY, USA). To compare categorical values, we used chi-square test. To compare quantitative data between two groups, we used t-test and Mann-Whitney U tests. A p-value of <0.05 was considered statistically significant.

## RESULTS

A total of 210 patients were admitted to our hospital with a suspected “first seizure.” The mean age of the patients was 43.7±19.5 years (18-86). The female to male ratio was 94/116 (44.7%/55.3%).

### Final Diagnoses of Patients with Admission “First Seizure”

Among the patients who presented with suspected first seizure, 152 were diagnosed with a seizure, while 58 were diagnosed as seizure mimics.

Within the seizure group, there were 119 patients with unprovoked seizures and 33 patients with acute symptomatic seizures. Upon further questioning of the patients’ history, it was found that 13 of 119 patients who presented with a first epileptic seizure had experienced at least one similar attack previously. These patients were classified as having recurrent seizures. After excluding patients with recurrent seizures, 106 (50.5%) patients were classified as having a true first seizure (Figure 1). The etiologies of these seizures are summarized in Table 1. Thus, a diagnosis of first epileptic seizure was confirmed in a total of 139 patients. As a result of this evaluation, the seizure type could be identified in 76 patients (54.7%). Among these, 59 patients (42.4%) had

### MAIN POINTS

- Differentiation between seizure and seizure mimicker during the “first seizure” presentation is critical for accurate diagnosis.
- Detailed anamnesis, additional investigations such as electroencephalogram/magnetic resonance imaging and a multidisciplinary approach are necessary to optimise the treatment process.
- The risk of recurrent seizures is higher in patients with status epilepticus.
- Early initiation of treatment was effective in reducing the risk of seizure recurrence.

generalized tonic-clonic seizures (GTCS), 11 (7.9%) had focal motor seizures, 3 (2.2%) had focal non-motor seizures, and 3 (2.2%) had focal onset seizures evolving into GTCS. However, since seizure type was primarily determined based on the anamnesis obtained from patients or their relatives, the onset pattern of seizures may not have been clearly identified in some cases. Therefore it should be considered that a portion of seizures recorded as GTCS may, in fact, originate as focal onset seizures that evolve into GTCS.

In the remaining 63 patients (45.3%), seizure semiology could not be definitively classified due to insufficient clinical data and was therefore categorized as "unknown."

There were 33 patients with acute symptomatic seizures. The most common cause was metabolic derangement, with hyperglycaemia being the leading type. Other identified causes included hyponatraemia, hypoglycaemia, hypocalcaemia, metabolic acidosis and metabolic alkalosis. The etiologies are summarized in Table 2.

**Table 1.** The etiologies of unprovoked true FSs

| The etiologies of unprovoked FSs | Patients with unprovoked FS (n=106) (n/%) |
|---|---|
| **Unknown etiology** | 46/43.4 |
| **Symptomatic focal epilepsy** | 41/38.7 |
| Poststroke | 10/9.4 |
| Gliotic lesions of unknown etiology | 9/8.5 |
| Posttraumatic | 6/5.7 |
| Tumor | 5/4.8 |
| Vascular malformation | 4/3.8 |
| Malformation of cortical development | 2/1.9 |
| Metastasis | 2/1.9 |
| Multiple sclerosis | 1/0.9 |
| Hipocampal sclerosis | 1/0.9 |
| Leukodystrophy | 1/0.9 |
| **Idiopathic generalized epilepsy** | 10/9.4 |
| **Dementia** | 7/6.6 |
| **Neurodevelopmental retardation** | 2/1.9 |

FS: First seizure

Fifty-eight of the patients were identified as seizure mimics, with their final diagnosis being syncope in 37, PNES in 18, migraine in one, vertigo in one, and TIA in one (Figure 1).

Demographic and clinical characteristics of patients in true first seizure, acute symptomatic seizure and seizure mimics group is summarized in Table 3.

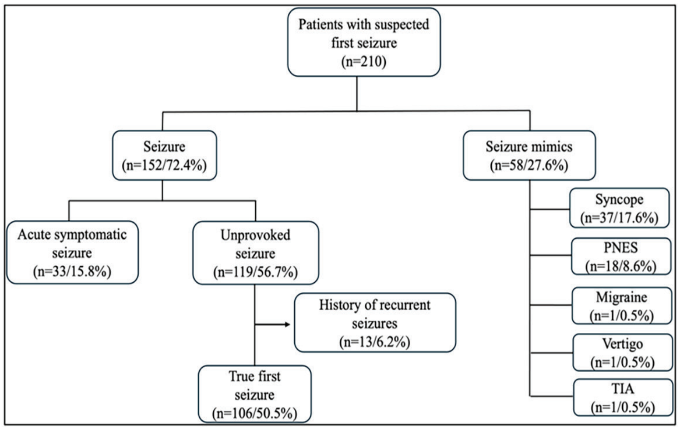


**Figure 1.** Final diagnoses of patients with admission "first seizure"
PNES: Psychogenic non-epileptic seizures, TIA: Transient ischemic attack

**Table 2.** The etiologies of acute symptomatic seizures

| Etiologies of acute symptomatic seizures | Patients with acute symptomatic seizures (n=33) (n/%) |
|---|---|
| **Metabolic derangements** | 14/42.4 |
| **Cerebrovascular disease** | 8/24.2 |
| Acute ischemic stroke | 3/9.1 |
| Cerebral venous thrombosis | 3/9.1 |
| Intracranial haemorrhage | 2/6 |
| **Drugs and alcohol and subtance abuse** | 8/24.2 |
| **Infection** | 2/6 |
| **Head trauma** | 1/3.1 |

**Table 3.** Demographic and clinical characteristics of the patients included in the true first seizure, e.g., acute symptomatic epileptic seizure group and seizure mimics group

| | True first seizure (n=106) (n/%) | Acute symptomatic seizure (n=33) (n/%) | Seizure mimics (n=58) (n/%) |
|---|---|---|---|
| **Age** | 44±20.2 | 55.3±19.4 | 38.7±15.8 |
| **Gender (F/M)*** | 40/66 (37.7/62.3) | 16/17 (48.5/51.5) | 32/26 (55.2/44.8) |
| **Family history of epilepsy** | 13/12.3 | 1/3 | 3/5.2 |
| **Aura** | 7/6.6 | None | None |
| **Abnormal EEG** | 39/40.2% | 6/25% | 2/4.9% |
| Focal epileptic | 9.3% | 4.2% | - |
| Generalised epileptic | 15.4% | 4.2% | - |
| Focal slowing | 7.3% | 8.4% | 4.9% |
| Generalised slowing | 8.2% | 8.4% | - |
| **Nocturnal** | 19/18 | None | None |
| **Status epilepticus** | 5/4.8 | None | None |
| **Recurrence** | 27/25.5 | None | 5/8.7 |
| **Patients underwent treatment with ASM** | 87/82.1 | 10/30.4 | 1/1.8 |

*F: Female, M: Male, EEG: Electroencephalogram, ASM: Anti-seizure medication

### EEG Findings

In the seizure mimics group, 41 patients (70.7%) underwent EEG for differential diagnosis. There were only two patients (4.9%) who had abnormal EEG findings in this group. One of these patients was diagnosed with syncope, and the EEG finding demonstrated frontal intermittent rhythmic delta activity. The other patient was diagnosed with PNES and the EEG findings demonstrated focal slowing in the left parietal area. EEGs of the remaining 39 patients were normal.

In the true first seizure group, 97 out of 106 patients (91.5%) underwent EEG for differential diagnosis. The EEG was not performed on 9 patients because they did not attend their scheduled EEG appointments. In this group, 39 (40.2%) patients had abnormal EEG; 24 (24.7%) demonstrated epileptiform abnormalities. Most of the patients with idiopathic generalized epilepsy (IGE) exhibited epileptic abnormalities on their EEGs. In the symptomatic focal epilepsy group, only 15.75% of EEGs showed epileptiform abnormalities.

In the acute symptomatic group, 24 patients (72.7%) underwent EEG for differential diagnosis. There were six patients (25%) with abnormal EEG in the acute symptomatic group (Table 3).

### Nocturnal Seizures

A total of 24 patients had a history of nocturnal seizures. All patients with nocturnal seizures were evaluated as having unprovoked seizures. Five of them did not have true first seizures when questioned in detail, but had recurrent seizures.

All patients with nocturnal seizures were started on ASM. Seizure recurrence occurred in four of them. Among the patients with seizure recurrence, two had a history of self-discontinuation of medication.

### Status Epilepticus

The first seizure episode was status epilepticus (SE) in five patients. The etiologies were atrophy/gliosis (n=3) and brain tumour (n=2). Drug treatment was initiated in all of them. Seizure recurrence was observed in 3 (60%) patients. One of the patients with seizure recurrence died in the intensive care unit.

### Cranial Imaging Findings

Cranial imaging was performed on all patients using MRI for etiological investigation. In the seizure mimics group, MRI was performed on 47 out of 58 individuals. Eleven of them had abnormalities. The abnormalities included gliotic lesions, ventricular asymmetry, a lipoma, arachnoid cysts, and atrophy. MRI was not conducted for eleven patients in this group because it was not deemed clinically necessary.

In the true first seizure group, cranial imaging of 101 patients was performed with MRI for etiological investigation. The MRI features are summarized in Table 1.

### Treatment

**Acute symptomatic group:** Drug treatment was started in 10 (30.4%) patients due to underlying etiologies that posed a high-risk for seizure recurrence. Levetiracetam was the drug of choice. Therefore, levetiracetam accounted for 100% of ASM usage in this group. Seven of them had cerebrovascular disease [ischemic; hemorrhagic; and cerebral venous thrombosis (CVT)]. One had an intracranial infection. The remaining two patients had metabolic disorders such as hyponatremia and hyperglycemia; since atrophy and white matter chronic ischemic gliotic changes were seen in their cranial MRIs, they were considered high-risk and were started on antiseizure medication. None of them had seizure recurrence during follow-up.

Drug treatment of one patient with acute stroke was discontinued after one year, and no seizure recurrence was observed during a drug-free one-year follow-up. All patients with haemorrhage, infection, and CVT continued their medication, and no seizure recurrence was observed during follow-up.

**True first seizure:** Eighty-seven (82.1%) patients were started on ASM. In this group, levetiracetam was the most commonly prescribed antiepileptic drug, administered to 73 patients (83.9%). Carbamazepine and lamotrigine were each prescribed to 4 patients (4.6%), and valproate to 6 patients (6.9%). All 18 patients who had their first seizure but were not started on medication were in the etiology undetermined group.

**Table 4.** Comparision of clinical features of recurrent and non-recurrent true first seizure patients

| Unprovoked seizure group (n=106) | Recurrent (n=27) (n/%) | Non-recurrent (n=79) (n/%) | p-value |
|---|---|---|---|
| **Presence of epileptic abnormality on EEG** | 11/40.8 | 31/39.3 | 0.89 |
| **Patient without ASM** | 3/11.1 | 16/20.3 | 0.23 |
| **Interruption in drug therapy** | 7/26 | - | <0.001 |
| **Etiology** | | | |
| Unknown etiology | 13/48.2 | 33/41.8 | 0.56 |
| Symptomatic focal epilepsy | 9/33.4 | 32/40.5 | 0.51 |
| IGE | 5/18.5 | 5/6.4 | 0.53 |
| **MRI abnormality** | 10/37.1 | 57/72.1 | 0.001 |
| **Nocturnal** | 5/18.5 | 14/17.7 | 0.92 |
| **Family history** | 2/7.5 | 11/14 | 0.51 |
| **Status epilepticus** | 3/11.1 | 2/2.5 | 0.69 |

MRI: Magnetic resonance imaging, ASM: Anti-seizure medication, EEG: Electroencephalogram, IGE: Idiopathic generalised epilepsy

**Seizure mimics group:** No medication was started. Only one patient was started on medication temporarily in the emergency department because of the difficulty distinguishing between seizure and seizure mimic semiologically at his first emergency visit while awaiting further diagnostic clarification. However, after a normal EEG and detailed clinical evaluation, the medication was stopped within the first week.

**Seizure Recurrence**

**Acute symptomatic group:** Seizure recurrence was not observed in the acute symptomatic seizure group.

**Seizure mimics group:** Four patients with PNES and one patient with syncope had recurrence of the attack.

**True first seizure:** Twenty-seven (25.5%) patients had seizure recurrence. When we look at the etiologies of the patients with recurrence, 13 of these patients had an unknown etiology (three of them were not on ASM; four patients had a history of medication failure, and one patient had a history of sleep deprivation and alcohol intake).

Five patients with recurrence of seizures have been diagnosed with IGE. Seizures were controlled with drug dose adjustment. The remaining 9 patients had symptomatic focal epilepsy. Three of them had issues with drug compliance.

The highest recurrence rate was in IGE (50%). The percentage was lower in the etiology undetermined group (28.3%) and symptomatic focal epilepsies (21.9%). The clinical and EEG features of the recurrent and non-recurrent groups are summarized in Table 4.

## DISCUSSION

The primary aim of this study was to determine whether the seizures in patients presenting with a "first seizure" were true epileptic seizures or non-epileptic attacks and to analyze the etiology and prognosis of seizures in these patients.

In this study, approximately 52% (109/210) of the patients were correctly identified as experiencing a seizure (acute symptomatic or unprovoked). Detailed histories revealed that 13 patients in the unprovoked seizure group had a history of similar seizures. Consequently, approximately 6.2% of patients initially suspected of having a first seizure were reclassified as having recurrent seizures. Similar to our findings, in the study conducted by Jackson et al.[3] 83% of the patients presenting with suspicion of a first seizure were diagnosed with a first seizure, but 39% of these patients had a history of previous seizures. Although this rate was lower in our study, it still underscores the importance of considering the possibility that patients presenting with a first seizure may have had prior seizures. These findings emphasize the necessity of obtaining a detailed medical history for accurate diagnosis. This step is crucial not only for identifying possible previous seizures but also for ruling out non-epileptic seizures.[7]

Non-epileptic attacks or seizure mimics represent significant diagnostic challenges in clinical practice. In our study, approximately 27.6% of patients were identified as having seizure mimics. The data indicate that while the majority of patients presenting with seizures experience true epileptic events, non-epileptic causes account for a significant proportion. Jackson et al.[3] reported that 17% of patients presented with seizure mimics, with syncope and PNES being the most common causes. In line with the literature, the most frequently observed conditions in our study were syncope (17.6%) and PNES (8.6%).[8,9]

Another important aspect of the initial seizure assessment is the identification of acute symptomatic seizures, which represent a critical differential diagnosis. In our study, we identified acute symptomatic seizures in 15.8% of all analyzed cases, with metabolic derangements being the most common cause (42.4%). Similar rates have previously been reported in the literature.[3,10] In the study conducted by Fields et al.[11] metabolic derangements were identified as the leading cause of new-onset seizures in hospitalized patients, accounting for 25% of cases. The annual incidence of acute symptomatic seizures is estimated to range from 29 to 39 per 100,000 individuals, with the most common etiologies including traumatic brain injury, cerebrovascular diseases, substance withdrawal, and metabolic disorders.[12] The distinction between acute symptomatic seizures and unprovoked seizures significantly impacts both diagnosis and treatment strategies.

The etiology was identified in 56.6% of patients with unprovoked seizures, whereas it remained unknown in 43.4%. In these patients, MRI, as well as both initial and follow-up EEGs, were normal. Advanced investigations during long-term follow-up may aid in identifying the etiology in some of these cases. Not every lesion seen on MRI may be associated with epilepsy. For example, arachnoid cysts, which are detected incidentally in many patients, are not frequently associated with epilepsy. Stroke, traumatic gliotic lesions, tumors, vascular malformations including cavernoma and arteriovenous malformations, mesial temporal sclerosis, metastasis, malformations of cortical development, multiple sclerosis lesions, were considered to be associated with epilepsy.

While the presence of EEG abnormalities supports the diagnosis of epilepsy, a normal EEG does not rule it out. In a prospective study involving 300 older children and adults with a first seizure, 47% of cases were diagnosed based on clinical history and family medical history alone; however, the diagnostic accuracy increased to 77% when EEG data were included.[13] Accurate diagnosis of first seizures is essential for effective seizure management and selection of appropriate treatment options.[7] Therefore, detecting EEG abnormalities in patients with a first seizure can be valuable in the clinical diagnostic process. In our study, the rate of EEG abnormalities among patients with unprovoked seizures was found to be 40.2%. Similar rates have been reported previously in the literature.[14] Most of the patients with IGE exhibited epileptic abnormalities on their EEGs. In the symptomatic focal epilepsy group, 15.75% of EEGs showed epileptiform abnormalities. Consistent with our findings, studies have reported interictal epileptiform discharges (IEDs) in approximately 21-28% of patients with a first seizure.[3,15] Patients with generalized discharges on EEG and a first unprovoked generalized tonic-clonic seizure have a significantly increased risk of seizure recurrence without appropriate treatment.[16] In acute symptomatic conditions, such as those observed in our study, EEG findings are often normal, as these conditions are typically transient and may not be directly associated with epilepsy. Additionally, it is noteworthy that the rate of EEG abnormalities in healthy individuals without epilepsy ranges from 1% to 2%.[17] These findings may be influenced by factors such as medication use, but can also occur without any identifiable cause.

In addition to the increased frequency of EEG abnormalities in patients with unprovoked seizures, unprovoked seizures tend to be more nocturnal, family medical history is more common, SE is more common, and auras and recurrences are more common. All patients with aura and most patients with nocturnal seizures were confirmed to have true first seizures in our study.

In our study, all patients experiencing nocturnal seizures were classified within the epileptic group. Previous studies have also demonstrated that unprovoked seizures occurring for the first time during sleep carry a higher risk of recurrence, regardless of other risk factors. This risk should be taken into account when making treatment decisions.[18] However, in our study, no significant difference was observed in the rate of nocturnal seizures between the recurrent and non-recurrent groups. This finding may be attributed to the limited number of patients with nocturnal seizures in our cohort.

Determining whether to initiate treatment after a first epileptic seizure can be challenging. Studies indicate that the use of modern ASMs reduces the risk of recurrence by more than 50%, demonstrating a protective effect in the short term.[15] Factors associated with a high-risk of recurrence, as reported in the literature, include remote symptomatic etiologies such as cerebrovascular accidents, perinatal injuries, and central nervous system infections, as well as epileptiform activity on EEG, nocturnal seizures, and potentially epileptogenic lesions on neuroimaging.[4] However, in our study, when the groups with and without seizure recurrence were compared, no significant differences were observed regarding EEG abnormalities, family medical histories and the presence of nocturnal seizures. Seizure recurrence was significantly higher in patients whose first seizure presented as SE. In the literature, mortality was reported to be high (7.7%) in those whose first seizure was SE.[14] Etiologically, seizure recurrence was most frequent in the IGE group. However, although recurrence is common in patients with IGE, the response to treatment has been good after appropriate drug dosage adjustment.

Seizure recurrence was observed in 18.8% of the patients who had their first seizure, but were not started on medication. Current recommendations suggest initiating ASM in patients with newly diagnosed epilepsy. However, the decision to prescribe drugs in patients without a formal diagnosis of epilepsy should be based on individual risk factors for seizure recurrence and the potential complications of seizures. These factors should be carefully discussed with the patient.[19] A study demonstrated that ASM therapy in patients with a single tonic-clonic seizure significantly reduced the likelihood of seizure recurrence over a two-year period. Specifically, treatment reduced the risk of recurrence from approximately 60% to 20% in those with a single seizure. Similarly, research indicates that early treatment after an unprovoked first seizure can reduce the risk of recurrence by approximately 35% in the short term.[20,21]

The management of first seizure patients with an indeterminate etiology remains a subject of ongoing debate. For this group, it is crucial to assess the risk factors associated with seizure recurrence. Studies have identified several factors that increase the risk of recurrence, including abnormal MRI findings suggestive of epileptogenic lesions, nocturnal seizures, and the presence of IEDs on EEG. Conversely, factors such as age, gender, seizure type, and SE were not found to be associated with a higher risk of recurrence.[2,15,22]

However, some studies in teenagers have suggested that SE may be associated with an increased risk of recurrence. These risk factors can vary among individuals, underscoring the need for personalized treatment decisions.[23] It is also well established that patients with a first unprovoked seizure, even in the absence of structural abnormalities on neuroimaging and with normal EEG findings, still face a 20-30% risk of seizure recurrence in the early period.[24,25] The review conducted by Neligan et al.[26] revealed that the risk of seizure recurrence after a single unprovoked epileptic seizure progressively increases over time. The study provides specific estimates of recurrence risk: 27% at six months, 36% at one year, and 43% after two years. These findings highlight the importance of close monitoring, timely treatment, and comprehensive risk assessment in patients following a first unprovoked seizure event.[26]

In our study, pharmacological treatment was initiated in 10 (30.4%) of the patients who experienced acute symptomatic seizures. Even though acute symptomatic seizures do not meet the criteria for epilepsy, ASMs may need to be initiated in some cases. However, caution is necessary regarding the duration and continuity of this treatment. The etiology of an acute symptomatic seizure is important in deciding whether to initiate ASM. A study found that the 12-month cumulative risk of unprovoked seizure recurrence was 10.7% in patients with acute symptomatic seizures of structural etiology, while no unprovoked seizure recurrence was seen in patients with non-structural etiology. Specifically, the cumulative 12-month risk of unprovoked seizure recurrence was 6.4% for ischemic stroke, 12.2% for intracerebral hemorrhage, and 12.2% for acquired CVT.[27] Other studies have also reported that the risk of recurrence may be high in patients with acute symptomatic seizures with CVT.[28] Based on these findings, initiating ASM therapy is recommended for a certain period of time. In the absence of high-risk features, early discontinuation of ASM is advised to prevent overtreatment. However, further clinical guidelines or studies are needed to establish a specific treatment duration.

As a result, the decision to initiate treatment should be tailored to the individual patient, considering their medical history, risk factors, and overall condition following the first seizure. Physicians should carefully evaluate the potential risks and benefits of treatment, ensuring that decisions align with the specific needs and preferences of the patient.[29] In general, early treatment with modern ASMs may offer significant benefits and should be considered, particularly in cases where the risk of recurrence is high. However, the long-term implications of treatment should also be taken into account to avoid unnecessary medication in patients with a lower risk profile.

## CONCLUSION

Suspicion of a first seizure is a frequent reason for referral to emergency services and outpatient clinics. However, in our study, in line with the literature, it was observed that seizure mimics or recurrent seizures can actually be frequently confused with the first seizure. The distinction of acute symptomatic seizures, which constituted a significant portion of first seizures, is important in terms of treatment management.

In conclusion, our primary objective is to propose a fundamental framework for the evaluation and management of first seizures, emphasizing the importance of a systematic and multidisciplinary approach.

## Ethics

**Ethics Committee Approval:** The study was approved by the Local Ethics Committee of the University of Health Sciences Türkiye, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital (approval no: 2023/04, date: 16.01.2023).

**Informed Consent:** Informed consent was obtained from all patients.

## Footnotes

## Authorship Contributions

Surgical and Medical Practices: N.Ç., Ü.Z., P.B., Ö.E.Ç., Concept: E.K., N.Ç., Ş.Ş., Ö.E.Ç., Design: E.K., S.D., Data Collection or Processing: E.K., N.Ç., Ü.Z., P.B., S.D., Ş.Ş., Analysis or Interpretation: E.K., Ü.Z., P.B., Ş.Ş., Ö.E.Ç., Literature Search: E.K., S.D., Ö.E.Ç., Writing: E.K., Ö.E.Ç.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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# The Effect of Long-term Levetiracetam Use on Changes in ECG in Patients with Pediatric Epilepsy

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**Abstract**

**Objective:** Cardiovascular side-effects and arrhythmias can also be observed during levetiracetam use. The effects of levetiracetam on cardiac conduction and electrophysiology, and the probable effect mechanism are still unclear. The purpose of this study was to compare PR interval, QTc, QT interval, and QRS duration parameters on electrocardiography (ECG) performed before and on the second year of treatment, in patients diagnosed with epilepsy and started on levetiracetam monotherapy.

**Methods:** The files of 20 patients diagnosed with epilepsy who were started on levetiracetam therapy were examined in this study. Clinical findings, electroencephalography, cranial magnetic resonance imaging and ECG data of the cases before and at the twenty-fourth month of treatment were recorded.

**Results:** Twenty patients aged between five and 17 years (12.65±3.50) took part in the study. Comparison of the ECGs performed before the patients started treatment and in the second year of treatment revealed a pre-treatment mean QT value of 0.327±0.018 and a post-treatment value of 0.349±0.023. The increase was statistically significant (p=0.009). Comparison of pre- and post-treatment ECG parameters in terms of sex revealed that the pre-treatment PR interval was longer in males (p=0.031) and the QTc interval was longer in females (p=0.020).

**Conclusion:** Studies involving more cases are needed to examine the effects of long-term use of levetiracetam on the ECG.

**Keywords:** Seizure, levetiracetam, PR interval, QTc, QT interval, QRS duration, longtime

## INTRODUCTION

Epilepsy is one of the most common neurological diseases, with a worldwide prevalence of approximately 1%.[1] The objectives of treatment are to suppress seizures, reduce their frequency, and improve the patient's quality of life.[2] Antiseizure drugs (ASDs) are employed for that purpose.[3]

Various mechanisms are implicated in the pathogenesis of the disease, including ion channel dysfunction. Ion channels represent the basis of neurons electrophysiological excitability and communication, while functional disturbance is thought to be capable of triggering epileptic seizures by affecting the excitability of the brain.[4]

Heart rate and blood pressure abnormalities may sometimes be seen in addition to seizures in patients with epilepsy.[5,6] While studies have suggested that epilepsy alters the QT interval and corrected QT interval (QTc), levetiracetam has been reported to exhibit a protective effect in the pediatric population.[7-10]

Levetiracetam is a safe and relatively low-cost drug capable of being used in various types of epilepsy, and one that exhibits less interaction with other antiseizure agents.[11] Its principal side-effects are nasopharyngitis, somnolence, headache, dizziness, fatigue, asthenia, diarrhea, and constipation, although severe side-effects, including Stevens-Johnson syndrome, liver failure, hepatitis, pancreatitis, hematological disorders, aggression, and attempted suicide can also be seen.[12-15] Cardiovascular side-effects and arrhythmias can also occur during levetiracetam use.[10] In recent years, it has been reported that it is capable of altering the QT interval and even causing torsades de pointes. CredibleMeds added levetiracetam to the list of drugs involving a risk of potential QT prolongation and torsades de pointes on 11 September 2022.[16-19]

The effects of levetiracetam on cardiac conduction and electrophysiology and the probable effect mechanism are still unclear. The purpose of this study was to compare heart rate (beats/min), PR interval, QTc, QT interval, and QRS duration parameters at electrocardiography (ECG) performed before treatment and in the second year of treatment on patients diagnosed with epilepsy and started on levetiracetam monotherapy.

## METHODS

### Study Design

The records of 20 individuals diagnosed with epilepsy on the basis of International League Against Epilepsy criteria at the Balıkesir University Medical Faculty Pediatric Neurology Clinic, Türkiye, between August 1, 2019, and December 1, 2022, and started on levetiracetam therapy were investigated retrospectively. Patients with additional chronic diseases (including hypertension, diabetes mellitus, congenital or acquired heart disease, and chronic lung disease), with histories of the use of different drugs (such as macrolides, antipsychotics, antidepressants, antihistamines, or anti-arrhythmic drugs), who were not using levetiracetam regularly, or who were using polytherapy, were excluded.

Clinical findings and electroencephalography (EEG), cranial magnetic resonance imaging (MRI), and ECG data before and after two years of treatment were recorded for all cases.

Standard 12-lead ECGs were performed for all patients in the supine position, using a machine set at a paper speed of 25 mm/s and a calibration of 10 mm/mV. The recordings were obtained at rest and in a quiet environment. The duration of each ECG session was approximately 1-2 minutes. ECGs were manually interpreted by the same clinician to minimize interobserver variability. The following parameters were measured: heart rate, PR interval, QRS duration, QT interval, and QTc; with QTc values calculated using the Bazett formula. ECG parameters were evaluated according to gender and age groups. In the literature, age 12 has been identified as a critical threshold at which QTc interval alterations become more prominent in both male and female children. Based on these findings, age 12 was adopted in our study as a cut-off point to assess age-related effects on QTc changes.[20] Before starting the study, the necessary approval was obtained from the Clinical Research Ethics Committee of Balıkesir University Faculty of Medicine (approval no: 2022/145, date: 07.12.2022).

### Statistical Analysis

Statistical analyses were performed using SPSS version 23 (IBM Corp., Armonk, NY, USA). Descriptive parameters were analyzed in all patients and by sex. After testing for normality of data distribution, ECG parameters heart rate (beats/min), PR, QTc, QT, and QRS were measured in all patients and were compared before and after treatment using the Wilcoxon and Mann-Whitney U tests.

## RESULTS

Twenty patients aged between five and 17 years (mean age 12.65±3.50) took part in the study. The majority were girls, which constituted 11 individuals (55%). The great majority of patients had generalized type seizures (16, 80%), the majority showed EEG findings (15, 75%), and most had normal cranial MRI (16, 80%). Among the 20 patients, EEG findings were abnormal in 15 cases. Of these, 8 patients exhibited focal epileptiform discharges, while 7 had generalized epileptiform discharges. Cranial MRI was abnormal in 3 patients (e.g., arachnoid cyst, periventricular leukomalacia, cortical malformation) (Table 1).

Comparison of the ECGs performed before the patients started treatment and after 24 months revealed a pre-treatment mean QT value of 0.327±0.018 and a post-treatment QT value of 0.349±0.023. The pre-treatment heart rate was 97.8±11.77 (78-120) beats/min, and the post-treatment heart rate was 82.25±16.78 (59-125) beats/min. These differences were statistically significant (p=0.009 and p=0.003, respectively). Pre-treatment PR interval, QTc, and QRS values were 0.139±0.021, 0.404±0.019, and 0.080±0.000, respectively, compared to 0.130±0.022, 0.400±0.023, and 0.075±0.016 after treatment. The differences between these values were not statistically significant (Table 2).

Comparison of pre- and post-treatment ECG parameters in terms of sex revealed a longer pre-treatment PR interval in boys and a longer QTc in girls (p=0.031 and p=0.020, respectively). There was no significant sex difference in pre- and post-treatment QT or QRS values (Table 3).

In terms of age, differences in pre- and post-treatment ECG parameters of heart rate and QT interval were statistically significant in the under-12 group (p=0.012 and p=0.04, respectively) (Table 4). In the over-12 age group, the ECG parameters of PR and QRS did not differ significantly before and after treatment (p=0.038 and p=0.034, respectively) (Table 5).

No cardiac side effect was observed in any patient.

**MAIN POINTS**

- Heart rate and blood pressure abnormalities may sometimes be seen in addition to seizures in patients with epilepsy
- While studies have suggested that epilepsy alters the QT interval and QTc, levetiracetam has been reported to exhibit a protective effect in the pediatric population.
- Cardiovascular side-effects and arrhythmias can also occur during levetiracetam use. The effects of levetiracetam on cardiac conduction and electrophysiology and the probable effect mechanism are still unclear.

**Table 1.** Demographic and laboratory characteristics of patients using levetiracetam

| | |
|---|---|
| Age (years) | 12.65±3.50 |
| **Sex** | n, % |
| Male | 9 (45%) |
| Female | 11 (55%) |
| **Age group** | |
| <12 years | 8 (40) |
| >12 years | 12 (60) |
| **Seizure type** | n, % |
| Focal | 4 (20%) |
| Generalized | 16 (80%) |
| **Electroencephalogram** | n, % |
| Normal | 5 (25%) |
| Abnormal | 15 (75%) |
| - Focal epileptiform discharges | 8 (40%) |
| - Generalized epileptiform discharges | 7 (35%) |
| **Cranial magnetic resonance imaging** | n, % |
| Normal | 16 (80%) |
| Abnormal | 3 (15%) |
| - Arachnoid cyst, | 1 (5%) |
| - Periventricular leukomalacia, | 1 (5%) |
| - Cortical malformation | 1 (5%) |

**Table 2.** A comparison of ECG parameters before and after levetiracetam therapy

| | Pre-treatment mean±SD (min-max) | 24 months post-treatment mean±SD (min-max) | p-value |
|---|---|---|---|
| **Heart rate (beats/min)** | 97.8±11.77 (78-120) | 82.25±16.78 (59-125) | 0.003 |
| **PR interval (s)** | 0.139±0.021 (0.12-0.18) | 0.130±0.022 (0.10-0.20) | 0.084 |
| **QTc (s)** | 0.404±0.019 (0.36-0.45) | 0.400±0.023 (0.35-0.43) | 0.447 |
| **QT (s)** | 0.327±0.018 (0.32-0.38) | 0.349±0.023 (0.28-0.40) | 0.009 |
| **QRS (s)** | 0.080±0.000 (0.08) | 0.075±0.016 (0.06-0.10) | 0.166 |

s: Seconds, SD: Standard deviation, ECG: Electrocardiography

**Table 3.** A comparison of ECG parameters before and after levetiracetam therapy between the sexes

| | Pre-treatment mean±SD (min-max) | | | 24 months post-treatment mean±SD (min-max) | | |
|---|---|---|---|---|---|---|
| | **Female** | **Male** | **p-value (pre)** | **Female** | **Male** | **p-value (post)** |
| **Heart rate (beats/min)** | 98.09±12.82 (80-120) | 97.44±11.11 (78-110) | 0.882 | 91.09±14.24 (77-125) | 71.44±13.27 (59-97) | 0.06 |
| **PR interval (s)** | 0.129±0.016 (0.12-0.16) | 0.151±0.020 (0.12-0.18) | 0.031 | 0.129±0.026 (0.10-0.20) | 0.131±0.018 (0.12-0.16) | 0.656 |
| **QTc (s)** | 0.410±0.018 (0.39-0.45) | 0.396±0.019 (0.36-0.42) | 0.201 | 0.410±0.017 (0.37-0.43) | 0.387±0.024 (0.35-0.43) | 0.020 |
| **QT (s)** | 0.329±0.021 (0.32-0.38) | 0.324±0.013 (0.32-0.36) | 0.766 | 0.340±0.030 (0.28 -0.36) | 0.360±0.035 (0.28-0.40) | 0.175 |
| **QRS (s)** | 0.080±0.000 (0.08) | 0.080±0.000 (0.08) | 0.1 | 0.080±0.015 (0.06-0.10) | 0.069±0.015 (0.06-0.10) | 0.131 |

s: Seconds, SD: Standard deviation, ECG: Electrocardiography

**Table 4.** A comparison of ECG parameters before and 24 months after treatment in patients under 12 using levetiracetam

| | Pre-treatment mean±SD (min-max) | Post-treatment, 24 months mean±SD (min-max) | |
|---|---|---|---|
| | **<12 years** | **<12 years** | **p-value** |
| **Heart rate (beats/min)** | 98.25±8.32 (86-110) | 79±13.76 (59-100) | 0.012 |
| **PR interval (s)** | 0.145±0.0233 (0.12-0.18) | 0.14±0.028 (0.10-0.20) | 0.581 |
| **QTc (s)** | 0.408±0.024 (0.39-0.43) | 0.405±0.02 (0.37-0.43) | 0.546 |
| **QT (s)** | 0.327±0.021 (0.32-0.38) | 0.355±0.025 (0.32-0.40) | 0.040 |
| **QRS (s)** | 0.080±0.000 (0.08) | 0.083±0.016 (0.1) | 0.655 |

s: Seconds, SD: Standard deviation, ECG: Electrocardiography

**Table 5.** A comparison of ECG parameters before and 24 months after treatment in patients over 12 using levetiracetam

| | Pre-treatment mean±SD (min-max) | Post-treatment, 24 months mean±SD (min-max) | |
|---|---|---|---|
| | **>12 years** | **>12 years** | **p-value** |
| **Heart rate (beats/min)** | 97.5±13.97 (78-120) | 84.42±18.78 (59-125) | 0.05 |
| **PR interval (s)** | 0.135±0.019 (0.12-0.16) | 0.123±0.014 (0.10-0.20) | 0.038 |
| **QTc (s)** | 0.40±0.022 (0.36-0.45) | 0.395±0.025 (0.35-0.43) | 0.590 |
| **QT (s)** | 0.326±0.015 (0.32-0.36) | 0.345±0.037 (0.28-0.40) | 0.094 |
| **QRS (s)** | 0.080±0.000 (0.08) | 0.083±0.016 (0.1) | 0.034 |

s: Seconds, SD: Standard deviation, ECG: Electrocardiography

## DISCUSSION

The electrical stimulation of various regions of the brain may cause cardiac rate and rhythm abnormalities. The most common types of cardiac autonomic dysfunction associated with seizures are tachyarrhythmia, bradyarrhythmia, and ECG changes.[21] Some studies have shown an association between seizure disorders and QTc prolongation, but have reported no change in mean QTc interval regardless of the duration of the disease, its frequency, or type.[5,7,22] The mechanism involved in QTc interval prolongation is not yet fully understood.[23,24] In addition to seizures and autonomic dysfunction, studies have reported that changes in cardiac electrophysiology may also derive from pathophysiological factors, including the ion channels underlying the disease.[25,26] Similar underlying pathophysiological electrical mechanisms are present in cardiac arrhythmias and epilepsy. Electrical activity disturbance in different tissues plays a role in the pathogenesis of both diseases.[27] Ion channels are also known to be involved in their pathogenesis. In addition, in epileptic children diagnosed with idiopathic or cryptogenic seizure disorder, there is evidence of genetic mutations in ion channels.[28] Darbin et al.[29] found that the severity of convulsive seizures and seizure recurrence constitute determinants of disordered cardiac autonomic regulation and directly affect the duration of cardiac arrhythmia during the immediate postictal state.

The effect of ASDs on the heart can be unpredictable. While they can prevent sudden unexpected death in epilepsy (SUDEP) by improving seizure control, they can also potentially contribute to SUDEP if they are suddenly withdrawn or by exerting direct effects on cardiac control.[30] Although the mechanism involved in the cardiovascular effects emerging in association with levetiracetam use has not yet been fully established, the current focus is on potential mechanisms. The first of these involves the effect of the drug on autonomic nervous system functions. Barrueto et al.[31] reported that a number of findings associated with levetiracetam use involved autonomous functions. Page et al.[32] also attributed bradycardia and hypotension developing in association with levetiracetam use to increased muscarinic activity in the autonomic nervous system. The stimulation of M2 muscarinic receptors leads to bradycardia, and the activation of M3 muscarinic receptors can result in vasodilatation and hypotension.[32] The confirmation by Oliveira et al.[33] that levetiracetam exhibits agonist activity against M2 receptors supports this probable mechanism. Lukkarinen et al.[34] also reported improvement with levetiracetam in a patient with recurrent sinus arrest and asystole due to breath-holding spells and concluded that it may be of therapeutic importance in regulating disease-related autonomic system dysfunction. However, Yılmaz and Çiğdem[35] reported that levetiracetam had no significant effect on autonomic nervous system functions, either in monotherapy or in polytherapy. Another mechanism capable of causing changes in cardiac conduction is drug-related inhibition of the potassium ion channel flow. Levetiracetam is reported to inhibit the flow of potassium ions, which may lead to prolongation of the QT interval, as well as cardiac arrhythmia and sudden death.[36] PR and QTc prolongation observed by Krishnan and Krishnamurthy[17] in male patients receiving polytherapy and linked to levetiracetam, the pre-treatment PR (0.139±0.021) and QTc (0.404±0.019) values in the present study decreased after treatment (to 0.130±0.022 and 0.400±0.023, respectively), although the differences were not statistically significant. In addition, this decrease was present in all patients, including men.[17] In the study by Altun and Yasar,[24] the heart apex beat, QT, and QTc parameters of patients with epilepsy using levetiracetam differed significantly from the pre-treatment values. However, Hulhoven et al.[37] described the effect of levetiracetam on the QT interval as negligible. Siniscalchi et al.[38] also reported that levetiracetam had no effect on the PR interval in healthy individuals, but exhibited negative effects on QT/QTc. Phenobarbital has been shown to prolong the QTc interval more than levetiracetam in patients.[38] In the present study, a decrease in heart rate and prolongation of the QT interval were observed in the 24$^{th}$ month post-treatment compared to pre-treatment values. In terms of gender, the pre-treatment PR interval was longer in boys, while the post-treatment QTc was shorter. In the under-12 age group, a decrease in heart rate and prolongation of the QT interval were determined post-treatment, while in the over-12 age group, a decrease in heart rate, shortening of the PR interval, and prolongation of QRS were observed.

While some cases have exhibited no noteworthy side effects as a result of high-dose levetiracetam use, others have resulted in vomiting, loss of consciousness, decreased deep tendon reflexes and hypotonia, somnolence, altered consciousness, respiratory depression, and coma.[39,40] Since levetiracetam does not block sodium channels, it is regarded as a relatively safer ASD in terms of cardiotoxicity.[41] Indeed, studies have reported that overdoses cause no cardiovascular toxicity in children or adults, and no changes in ECG or blood pressure in healthy individuals.[40,42,43] Gurgul et al.[44] reported that levetiracetam exhibits protective features against neonatal hypoxic-ischemic injury-induced deteriorations in adulthood, in terms of ventricular contractility and ultrastructural and mitochondrial damage in the myocardium. In the most recent study on the subject, Cross et al.[10] compared cases using levetiracetam and oxcarbazepine in terms of cardiac effects (SUDEP and arrhythmia) and reported no relationship between levetiracetam and sudden cardiac death or ventricular arrhythmia.[44] However, some studies have shown that overdose with levetiracetam may affect cardiac electrophysiology and rhythm.[45] Page et al.[32] reported the development of cardiotoxicity in the form of bradycardia and hypotension, in a woman who was taking 60-80 g levetiracetam. Another study reported bidirectional ventricular extrasystoles with sinus bradycardia in a patient receiving high-dose levetiracetam for attempted suicide, and noted that the patient was normotensive at follow-ups.[45] No cardiac side effect associated with the use of levetiracetam at a normal dose range was observed in any of the patients in this study.

### Study Limitations

ECG findings change rapidly from birth through childhood, with age differences clearly related to increasing QRS voltages and a widening QRS complex. The only sex difference at this age is a slightly longer QRS duration in boys than in girls. In adulthood, sex differences in QRS voltage are greatest in the under-40 age group and tend to decrease with advancing age. QRS duration is longer in males than in females, but this difference is rarely utilized in terms of diagnostic criteria. The QTc interval is longer in females than in males.[46] Numerous factors which may prolong the QT interval should be checked whenever QTc prolongation is observed. These include drugs, electrolyte imbalances, hormonal influence, and comorbidities.[47] Due to the low sample size in the present study, ECG parameters could not be evaluated across different age groups by gender. In addition to its retrospective, single-center design, this study has several limitations. These include the relatively recent establishment of the pediatric neurology department at our hospital, the short study duration of two years, and the limited sample size, partly due to irregular follow-up by some patients. Furthermore, ECG evaluations were not conducted blinded, and the ECG parameters could not be assessed by a pediatric cardiologist due to the unavailability of one at our institution during the study period. Lastly, the absence of a control group further limits the generalizability of the findings.

## CONCLUSION

Levetiracetam is frequently prescribed by physicians due to its antiepileptic activity against various types of seizure, its efficacy, easy accessibility, and safety profile. The data from this study show that although the use of levetiracetam at therapeutic doses causes changes in ECG parameters depending on age group and sex, no levetiracetam-related cardiac side-effects were observed in any patients. Further prospective clinical studies involving more centers and cases are now needed in this area.

### Ethics

**Ethics Committee Approval:** Before starting the study, the necessary approval was obtained from the Clinical Research Ethics Committee of Balıkesir University Faculty of Medicine (approval no: 2022/145, date: 07.12.2022).

**Informed Consent:** Retrospective study.

### Footnotes

### Authorship Contributions

Concept: H.A., O.K., Design: H.A., O.K., Data Collection or Processing: H.A., Analysis or Interpretation: O.K., Literature Search: H.A., O.K., Writing: H.A., O.K.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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Case Report

# Lamotrigine-induced DRESS Syndrome in an Epileptic Patient: A Rare but Life-threatening Adverse Drug Reaction

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**Abstract**

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare, potentially life-threatening hypersensitivity reaction characterized by fever, skin rash, eosinophilia, and multiple organ involvement. Here we report an 18-year-old female patient with epilepsy who developed fever, widespread erythematous rash, facial edema, and elevated liver enzymes six weeks after the initiation of lamotrigine therapy. With a the registry of severe cutaneous adverse reaction score ≥6, a diagnosis of DRESS syndrome was established. Lamotrigine was discontinued, and oral corticosteroid therapy was initiated. Clinical improvement was observed by the third day, liver function tests normalized within 10 days, and cutaneous lesions gradually regressed. In patients receiving lamotrigine, the occurrence of fever and cutaneous rash should raise suspicion for DRESS syndrome in the differential diagnosis. Early diagnosis and treatment are critical for preventing systemic complications.

**Keywords:** DRESS syndrome, lamotrigine, epilepsy, adverse drug reaction, hypersensitivity

## INTRODUCTION

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a severe, idiosyncratic hypersensitivity reaction that typically presents with a delayed onset following exposure to certain pharmacologic agents. This syndrome frequently presents with non-specific prodromal symptoms such as malaise, pruritus, and high-grade fever ranging from 38 to 40 °C. The clinical presentation is characterized by prominent cutaneous manifestations, including morbilliform eruptions, widespread epidermal desquamation, facial edema involving preseptal and periorbital regions, often accompanied by erythroderma.[1] Furthermore, lymphadenopathy, hematologic abnormalities such as eosinophilia and atypical lymphocytosis, and internal organ involvement, particularly affecting the liver, lungs, and kidneys, might be observed.[1,2] This condition typically manifests within 2 to 8 weeks after drug exposure, with a reported mortality rate of up to 10%.[2]

The pathogenesis involves drug-specific T-cell activation, cytokine release, genetic predisposition, and reactivation of herpesvirus.[3] The incidence of DRESS varies depending on the causative drug, ranging from 1/1,000 to 1/10,000.[1] Lamotrigine (LTG), an aromatic antiseizure agent, is increasingly recognized as a potential cause of DRESS, especially when used concomitantly with valproic acid, which inhibits LTG metabolism and increases serum levels.[4] We present a case of LTG-induced DRESS in a young female patient with epilepsy, focusing on the clinical course, diagnostic process, and therapeutic management strategy.

## CASE PRESENTATION

An 18-year-old female patient with a known diagnosis of epilepsy presented to the emergency department with a one-month history of generalized rash accompanied by progressively worsening fever over the last ten days. Based on clinical suspicion of drug-induced hypersensitivity reaction, the patient was admitted to the dermatology department and subsequently referred to our neurology clinic for evaluation of potential antiseizure drug-associated adverse effects.

The patient had a one-year history of generalized onset tonic-clonic seizures, with a baseline frequency of approximately 10 episodes per month. Her antiseizure treatment consisted of levetiracetam (LEV) 1000 mg/day, initiated three months prior to evaluation. Due to persistent seizure activity, LTG was added six weeks before admission. Following this adjustment, her seizure frequency had decreased to three episodes per month.

Physical examination revealed right inguinal lymphadenopathy, generalized erythematous and desquamative rash, and preseptal and periorbital edema (Figure 1). Neurological examination was unremarkable, with no focal deficits, cognitive impairment, or signs of meningeal irritation. Ultrasonography demonstrated right inguinal and submandibular lymphadenopathies along with hepatomegaly (165 mm) and splenomegaly (139 mm).

Laboratory investigations showed hepatic involvement with elevated liver enzymes (aspartate aminotransferase 148 IU/L, alanine aminotransferase 165 IU/L, and gamma-glutamyl transferase 77 IU/L), along with markedly elevated lactate dehydrogenase (1017 IU/L). Hematological evaluation revealed peripheral eosinophilia (9.7%) and atypical lymphocytes on peripheral blood smear. Previous reports in skin biopsy have documented mild acanthosis, spongiosis, and intraepidermal vesicle formation accompanied by a dense perivascular inflammatory infiltrate in the dermis composed of lymphocytes, histiocytes, and occasional eosinophils. Additionally, intraepidermal spongiotic vesicles containing eosinophils with a concomitant perivascular lymphohistiocytic and eosinophilic infiltrate in the dermis have been described.[5] In our case, histopathological examination revealed irregular acanthosis; orthokeratotic hyperkeratosis; parakeratosis; exocytosis of neutrophils, leukocytes, and lymphocytes; and vasculopathic changes characterized by basal vacuolar degeneration.

The clinical and laboratory findings, with a the registry of severe cutaneous adverse reaction (RegiSCAR) score of ≥6, confirmed the diagnosis of DRESS (Table 1).[2]

LTG was discontinued, and LEV dose was increased to 3000 mg/day. Oral methylprednisolone therapy was initiated at 1 mg/kg/day. Clinical response was favorable, with resolution of fever by day three of treatment, and normalization of liver enzymes and eosinophil count by day ten. Cutaneous findings and edema gradually improved over two weeks (Figure 2).

After achieving clinical and biochemical stability, the patient was discharged with plans for outpatient continuation of methylprednisolone therapy and close follow-up in the neurology clinic.

Informed consent was obtained from the patient for publication of this case report and accompanying images, which were anonymized. Permission for publication was also granted by the attending dermatologist.

**MAIN POINTS**

- Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a rare but potentially life-threatening hypersensitivity reaction that may occur after lamotrigine initiation.
- Early clinical signs such as fever, facial edema, and widespread erythematous rash should raise suspicion for DRESS, especially in patients using aromatic antiseizure drugs.
- Prompt discontinuation of the culprit drug and initiation of systemic corticosteroids are essential for favorable outcomes.
- The registry of severe cutaneous adverse reaction scoring system is a helpful diagnostic tool in differentiating DRESS syndrome from other systemic conditions.

**DISCUSSION**

This case illustrates the presentation of LTG-induced DRESS syndrome and underscores the diagnostic and therapeutic challenges associated with aromatic antiseizure drug use. DRESS syndrome is a rare but potentially fatal severe adverse drug reaction that requires early recognition and management.

DRESS syndrome presents a diagnostic challenge due to its variable and delayed-onset clinical presentation. Internal organs, including the liver, lungs, and kidneys, and lymphatic system are among the most commonly affected, with hepatic involvement reported in approximately 65-70% of cases.[2] In the present case, transaminase elevation and hepatomegaly supported hepatic involvement. Lymphadenopathy and widespread maculopapular eruptions are among the diagnostic criteria and were clearly evident in this case. The clinical presentation fulfilled the diagnostic threshold for "definite DRESS" according to the RegiSCAR scoring system (score ≥6). Notably, the absence of neurological symptoms despite systemic inflammation highlights the selective organ involvement.

DRESS syndrome represents a discrete, clinically significant subgroup among SCARs, which also include Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis and acute generalized exanthematous pustulosis.[6] In the case described, a six-week latency period, striking peripheral eosinophilia, demonstrable internal organ involvement, and the absence of notable epidermal detachment collectively favored a diagnosis of DRESS over SJS.

The diagnosis of DRESS is often delayed due to non-specific manifestations, which can mimic other systemic conditions. Therefore, in patients presenting with fever, diffuse rash, and laboratory abnormalities, a thorough drug history is essential. The RegiSCAR scoring system remains a valuable tool for early diagnosis and clinical stratification.

The pathophysiology of DRESS syndrome is mediated by immune and genetic mechanisms. Activated T-cells and monocytes release cytokines such as interleukin-5 and interleukin-13, promoting eosinophilic inflammation and tissue infiltration. As a result, eosinophilia serves as both a pathogenic and diagnostic hallmark of the syndrome.[7] Viral reactivation, especially of herpesviruses, may exacerbate systemic inflammation and contribute to disease severity and recurrence.[8] Genetic predisposition has been associated with an increased susceptibility to DRESS induced by specific drugs. *HLA-A3101, HLA-B5801* and *HLA-B1502* alleles have been linked to the risk of hypersensitivity reactions with LTG, allopurinol, and carbamazepine, respectively.[9-11] These mechanisms collectively

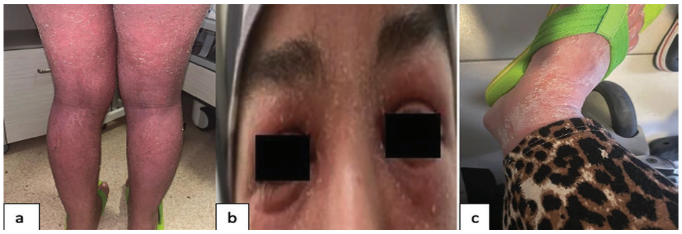


**Figure 1. a)** Diffuse erythematous and desquamative rash of the lower extremity. **b)** Pronounced preseptal and periorbital edema of the face (anonymized). **c)** Appearance of the rash on the ankles and feet

**Table 1.** RegiSCAR scoring system[2]

| Score | -1 | 0 | 1 | 2 |
|---|---|---|---|---|
| Fever >38 °C | No/Unknown | Yes | | |
| Enlarged lymph nodes | | No/Unknown | Yes | |
| Eosinophils | | No/Unknown | 0.7-1.499×10⁹/L | ≥1.5×10⁹/L |
| Eosinophils if WBC <4.0×10⁹/L | | | 10-19.9% | ≥20% |
| Atypical lymphocytes | | No/Unknown | Yes | |
| Extent of skin rash | | None | >50% of body surface area | |
| Skin rash suggestive of DRESS | No | Unknown | Yes | |
| Skin biopsy suggestive of DRESS | No | Yes/Unknown | | |
| Liver involvement (elevated LFTs, ALP, PT, or bilirubin) | | No/Unknown | Yes | |
| Renal involvement (e.g., nephritis, AKI) | | No/Unknown | Yes | |
| Muscle/heart involvement (e.g., myocarditis, pericarditis) | | No/Unknown | Yes | |
| Pancreatic involvement | n | No/Unknown | Yes | |
| Other organ involvement (thyroiditis, colitis, etc.) | | No/Unknown | Yes | |
| Resolution ≥15 days | No/Unknown | Yes | | |
| Investigation of alternative potential causes (ANA antibodies, blood cultures, hepatitis A/B/C serology, Chlamydia, Mycoplasma): if three or more of the above tests have been performed and all results are negative | | | Yes | |

RegiSCAR: The registry of severe cutaneous adverse reaction, WBC: White blood cell, DRESS: Drug reaction with eosinophilia and systemic symptoms, LFTs: Liver function tests, ALP: Alkaline phosphatase, PT: Prothrombin time, AKI: Acute kidney injury, ANA: Antinuclear antibody

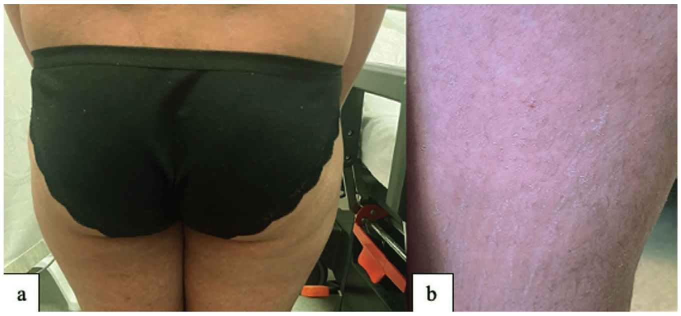


**Figure 2. a,b.** Marked regression of the cutaneous eruptions following initiation of systemic corticosteroid therapy

explain the multisystem involvement and variable clinical course observed in DRESS syndrome.

LTG is an aromatic antiseizure drug, which is metabolized via hepatic glucuronidation, a process inhibited by valproate, leading to increased LTG serum levels and heightened risk of adverse immune-mediated reactions.[4] In contrast, non-aromatic antiseizure drugs such as LEV have a safer immunologic profile. The patient's condition improved following LTG withdrawal and dose escalation of LEV. Early recognition remains challenging due to symptom overlap with infectious and autoimmune disorders, emphasizing the need for heightened clinical suspicion in patients developing rash and systemic symptoms during antiseizure treatment.

Systemic corticosteroids remain the first-line treatment for moderate to severe DRESS. A gradual tapering is recommended, as abrupt discontinuation may increase the risk of relapse. For steroid-refractory cases or patients with contraindications, second-line options include intravenous immunoglobulin, plasmapheresis, and immunosuppressive agents such as cyclosporine, cyclophosphamide, mycophenolate mofetil, or rituximab.[12] In our case, oral methylprednisolone therapy alone was sufficient to achieve remission.

Long-term follow-up is essential due to potential late-onset autoimmune sequelae, including thyroiditis, autoimmune hepatitis, and systemic lupus erythematosus, which may develop weeks to months after resolution of the acute phase. Therefore, periodic monitoring of thyroid and liver function is strongly recommended.[13]

## CONCLUSION

This case highlights the diagnostic and therapeutic challenges of LTG-induced DRESS syndrome in a patient with epilepsy. The favorable outcome was achieved through timely recognition, early withdrawal of the offending drug, appropriate corticosteroid therapy, and close clinical follow-up. Effective management of DRESS requires a multidisciplinary approach involving neurology, dermatology, infectious disease, and hepatology specialists.

Moreover, increased clinician awareness may improve early identification of high-risk individuals and reduce the incidence of severe drug hypersensitivity reactions. Future efforts should focus on improving pharmacogenetic screening and developing biomarkers to predict disease severity and optimize therapeutic approaches.

### Ethics

**Informed Consent:** Informed consent was obtained from the patient for publication of this case report and accompanying images, which were anonymized. Permission for publication was also granted by the attending dermatologist.

**Footnotes**

**Authorship Contributions**

Surgical and Medical Practices: E.D., A.A.G., Concept: E.D., A.A.G., Design: E.D., A.A.G., Data Collection or Processing: E.D., A.A.G., Analysis or Interpretation: E.D., A.A.G., Literature Search: E.D., A.A.G., Writing: E.D., A.A.G.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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The article titled *"Aydemir S, Torkamanian Afshar M, Sarı Torkamanian Afshar Ö, Taş Cengiz Z, Kiraz M, Baydar C, Yılmaz H. Evaluation of Toxoplasma gondii in the Etiology of Cryptogenic Epilepsy: A Case-control Study. Arch Epilepsy. 2024;30(2):39-42. doi: 10.4274/ArchEpilepsy.2023.23102"* published in the journal Archives of Epilepsy has been corrected due to an error inadvertently made by the author in the Financial Disclosure section.

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**(The corrected parts are given in bold)**

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