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Original Article

# Protective Effects of Allantoin on Neural Cells of Hippocampal Region and Cognitive Function in a Mouse Model of Temporal Lobe Epilepsy

Mohsen Eslami Farsani[1], Ahmad Hatami Shahmir[2], Reihaneh Seyedebrahimi[1], Shima Ababzadeh[3], Azam Moslehi[4], Javad Tafaroji[5]

[1]Qom University of Medical Sciences Faculty of Medicine, Department of Anatomy, Qom, Iran

[2]Qom University of Medical Sciences Faculty of Medicine, Medical Student, Student Research Committee, Qom, Iran

[3]Qom University of Medical Sciences Faculty of Medicine, Department of Tissue Engineering and Applied Cell Sciences, Qom, Iran

[4]Qom University of Medical Sciences, Cellular and Molecular Research Center, Qom, Iran

[5]Qom University of Medical Sciences Faculty of Medicine, Hazrat-e-Masoumeh Hospital, Clinic of Pediatrics, Qom, Iran

Shima Ababzadeh PhD

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**Corresponding Author:** Shima Ababzadeh MD, E-mail: shimaababzadeh@gmail.com

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## Abstract

**Objective:** Excitotoxic damage results in cell death in several human neurodegenerative diseases. Epilepsy is one of the most common neurological disorders and it causes complications. To this end, we examined the protective role of allantoin (AL) in a model of excitotoxic neuronal death induced by intraperitoneal injection of kainic acid (KA) in mice.

**Methods:** Two-month-old C57 male mice (n=35) were divided into five groups: control (received 0.9% saline), AL (received 10 mg/kg of AL), KA (received a single dose of 10 mg/kg of KA), KA+AL10 and KA+AL15 groups (received a single dose of 10 mg/kg of KA then were treated with 10 mg/kg of AL or 15 mg/kg respectively). On the 14$^{th}$ day of the experiment, learning and memory were tested using a shuttle-box. The number of intact neurons and damaged neural cells in hippocampal CA1 and CA3 were assessed by Nissl staining and Flour-J B immunohistochemistry, respectively.

**Results:** The results showed that injection of KA decreased the latency time while administration of 10 mg/kg AL improved memory. In addition, there was a significant difference between KA and KA+AL10 mg/kg groups ($p<0.01$). The histological results revealed that the use of 10 mg/kg AL significantly increased the number of intact pyramidal cells in the hippocampal CA1 and CA3 regions compared with the KA group ($p<0.01$). Moreover, neurodegeneration of the hippocampal region was significantly decreased in the groups treated with AL compared with the KA group ($p<0.05$).

**Conclusion:** This study indicated that AL at a concentration of 10 mg/kg/day improved neurodegenerative complications following temporal lobe epilepsy.

**Keywords:** Neurotoxicity, kainic acid, allantoin, learning and memory, hippocampus

## INTRODUCTION

Excitotoxicity is one of the most important causes of neuronal cell death that occurs in many human neurodegenerative diseases such as Alzheimer's disease, multiple sclerosis, Parkinson's disease, epilepsy, and ischemia.[1]

Epilepsy is a neurological disorder that is determined by loss of consciousness and seizure.[2] Seizures result in neuronal death by overactivating glutamate receptors in the brain. 8Glutamate is activated as a chief excitatory neurotransmitter in the mammalian central nervous system (CNS), and it plays many roles in neural progress, synaptic plasticity, learning, and memory.[3] However, the high concentrations of this neurotransmitter and overactivation of its receptors interrupt calcium homeostasis in neural cells, so it can increase production of nitric oxide and free radicals.[4] In addition, high activation of glutamate excites some death signaling pathways through stimulation of metabotropic and ionotropic receptors, and it, finally, causes extensive neuronal complications.[5]

Kainic acid (KA)-induced model is one of the experimental models of epileptic status that KA is widely used in temporal lobe epilepsy (TLE). KA can induce neuronal injuries through the activation of ionotropic glutamate receptor.[6,7] Moreover, KA is a glutamate analog

that can act similar to patients with TLE.[8] Although the pyramidal neurons of the hippocampus region are damaged in TLE, GABAergic interneurons of the hippocampus and granule cells of the dentate gyrus are persistent to seizure.[9]

Despite the progress of many antiepileptic drugs, a number of patients do not respond to treatment. In addition, antiepileptic drugs have severe side effects.[10]

Allantoin (AL) (5-ureidohydantoin) is a heterocyclic derivative of purine that is found in many plants such as Melaleuca nodosa roots, comfrey, yam, sugar beet, and leguminous.[11,12] In addition, it is safe to stimulate new tissue development and has a positive effect on neuronal cell proliferation.[13] Moreover, anti-inflammatory, anti-hypertensive, anti-nociceptive, anti-ulcerogenic, and anti-asthmatic properties of AL have been AL.[14]

Therefore, we decided to assess the neuroprotective effects of AL on cell death and neurogenesis following KA-induced excitotoxicity damage in mice.

## METHODS

AL (Sigma Aldrich-05670, 25 g), KA (TOCRIS-0222, 10 mg), and cresyl violet acetate were purchased from Sigma. Fluoro-Jade B (FJB) (Millipore-AG310) was obtained from Abcam. In addition, phosphate-buffered saline, paraformaldehyde, xylazine, and ketamine were supplied by Invitrogen.

### Animals

Two-month-old C57 male mice (weight 20-25 g) were purchased from the Animals Care Center of Qom University of Medical Sciences. The animals were housed under stable conditions with a suitable temperature (22±1 °C) and a 12/12 h light/dark cycle. Mice had free access to water and food.[15]

All mice were randomly divided into five groups (n=7 for each group) including control group (receive 0.9% normal saline), AL group (injection of 10 mg/kg AL), KA group (injection a single dose of 10 mg/kg KA), treatment groups including injection a single dose of 10 mg/kg KA and treatment with 10 mg/kg (KA + AL10) or 15 mg/kg AL (KA + AL15). To induce the epilepsy model, mice received a single dose of 10 mg/kg KA intraperitoneally (IP) in which KA was dissolved in 0.9% normal saline. Seizures were evaluated and graded according to the Racine scale after administration of KA.[16,17] Seizures were evaluated and divided into 6 grades according to the Racine scale.[16] The mice were evaluated approximately 24 h after administration of KA for status epilepticus (SE). Only animals that reached the fourth stage of the Racine scale were selected for this study. Each seizure lasted greater than 1-2 min when mice were in the fourth stage and terminated abruptly following the stopping of abnormal movements. In addition, the animals were monitored for behavioral progression of seizure 5 h/day during the treatment period.

**MAIN POINTS**

- The injection of kainic acid decreased the latency time and induced a model of epilepsy in mice.
- The administration of allantoin (AL) at a concentration of 10 mg/kg improved neuronal degeneration in an epilepsy model.
- The use of 15 mg/kg AL has a low effect on neuronal injuries.

To treatment, two groups of mice were administered AL in concentrations of 10 or 15 mg/kg as IP on the next day of induction of epilepsy during 14 days. In addition, AL was solved in 0.9% normal saline. All procedures of this study were approved by the Ethics Committee of the Qom University of Medical Sciences (ethical no: IR.MUQ.REC. 1395.161, date: 14.03.2017).

### Shuttle-box Test (Passive Avoidance) for Learning and Memory

The shuttle-box test is used to evaluate CNS disorders in rodent models. This test was performed 14$^{th}$ days after the start of treatment for evaluation of the short and long memories based on previous studies.[18] The passive avoidance apparatus has two lighted and darkened compartments with 20×20×20 cm dimensions (Borj Sanat Company, Tehran, Iran). A guillotine door is located between the two compartments. The lighted compartment contained a 40 W bulb, whereas the darkened compartment was composed of 2 mm stainless steel rods spaced 1 cm apart. The avoidance test was performed in two trials: a training trial and a test trial 24 h later. Each animal was placed in the lighted compartment and could move freely to the dark compartment. When animals entered the dark compartment, an electric shock was received (0.5 mA, 1 s). One day after the training trial, a testing trial was performed in which the animals were again placed in the lighted compartment and the experiment was repeated. To evaluate memory and learning, the time taken by the animal to enter the dark chamber was recorded as the step-through latency.

### Histological Study of the Hippocampus Region by Nissl Staining

Evaluation of neurogenesis and survival of hippocampal cells was performed using Nissl staining.[19] The animals were anesthetized following intraperitoneal injection of xylazine (10 mg/kg) and ketamine (100 mg/kg). Perfusion was then performed using 4% paraformaldehyde in 0.1 mol/L phosphate buffer solution (pH: 7.4). Following tissue processing and embedding, coronal sections (4 µm thickness) were cut using a microtome rotary (LEICA RM 2235, Germany) and stained with Nissl (cresyl violet acetate: 0.01%). Sections were visualized under an optical microscope (Eclipse E200-LED, Tokyo, Japan). Then, the four sections of each sample at 400×magnification were selected to count pyramidal neurons and measure granular layer thickness in the CA1 and CA3 regions of the hippocampus. Finally, three fields in each section were evaluated using ImageJ analysis software.

### Evaluation of Degeneration of Neurons Using Fluoro-Jade B Staining

To detect neuronal degeneration, FJB staining was performed according to previously reported methods. First, the 4 µm sections were deparaffinize and dehydrated. The samples were immersed in descending alcohols and 1% sodium hydroxide solution. Then, they were stained with FJB (0.002%). Finally, the samples were examined using a fluorescence microscope with blue light and a FITC filter (450-490 nm).

### Statistical Analysis

The data were presented as mean±standard deviation and statistically analyzed using one-way analysis of variance and Tukey's post-hoc test using Statistical Package for the Social Sciences (SPSS) 26 software (SPSS Inc., Chicago, IL, USA). Statistical significance was determined at $p<0.05$.

## RESULTS

### Seizure Activity by Behavior Observation

The animal's behavior was assessed during the 24 h after KA administration according to Racine's standard classification. There was no seizure status in the control and AL groups, whereas spontaneous seizures with 4 and 5 stages were observed in 100% of the mice treated with KA.

The control and AL groups showed no signs of seizure behavior, whereas 98% of mice had several seizures with 4 and 5 classes based on the Racine scale during treatment. However, administration of AL at doses of 10 and 15 mg/kg significantly decreased the intensity of seizure compared with the AL group during treatment ($p<0.05$) (Table 1).

### Effect of Kainic Acid and Allantoin on Mouse Weight

The results showed that there was a significant increase in the final weight compared with the initial weight in the control group, while a decrease was observed in the final weight of mice in the KA group ($p\leq0.05$) (Table 2).

### Passive Avoidance in the Evaluation of Memory

There was a significant increase in latency time in the control group compared with the KA group ($p<0.01$), whereas there was no significant difference between the group treated with 15 mg/kg of AL and the KA group ($p\geq0.05$). Also, treatment with 10 mg/kg of AL resulted in an increase in latency time compared with the KA group ($p<0.01$) (Figure 1).

### Preservation of Neuronal Cells in the Seizure-induced Hippocampal Region by Allantoin Treatment

Nissl staining results indicated that KA decreased the number of neuronal cells in the CA1 region (Figure 2). The mean number of intact cells was significantly increased following injection of 10 mg/kg of AL compared with the KA group ($p<0.01$). There were no significant differences between the group treated with AL and the control group ($p\geq0.05$). In addition, treatment with 10 mg/kg of AL increased the thickness of the granular layer compared with the KA group ($p<0.01$), whereas there was no significant difference between mice receiving 15 mg/kg AL and the KA group ($p\geq0.05$).

Next, the histological results of the CA3 region are shown in Figure 3A. There was a significant reduction in the mean number of intact cells in the KA group compared with the other groups ($p<0.05$) (Figure 3B). Moreover, the mean of degenerated neurons significantly increased after induction of epilepsy in the KA group compared with other groups ($p<0.01$) (Figure 3C). However, administration of AL decreased the mean number of degenerated cells compared with the KA group ($p<0.05$). The average thickness of the granular layer of the CA3 region also significantly increased in mice treated with AL compared with the KA group ($p<0.05$) (Figure 3D).

### Allantoin Reduces Seizure-induced Hippocampal Neuronal Death

Degeneration of neurons was evaluated by FJB staining (Figure 4A). In the control and AL groups, no neurons were stained with FJB in hippocampal CA1. However, the number of degenerated neurons increased in the CA1 region in mice induced with KA. The number of FJB-positive cells (degenerated neurons) was rarely detected in the group treated with 10 mg/kg of AL, whereas there was more neuronal damage in the group treated with 15 mg/kg of

**Table 1.** Numbers and percentages of epileptic status in each group

| Groups | % of mice that reached the 4th stage in 24 h | Number of seizures in 24 h | % of mice that reached the 4th stage during treatment | Number of seizures during treatment |
|---|---|---|---|---|
| Control | 0 | 0 | 0 | 0 |
| AL | 0 | 0 | 0 | 0 |
| KA | 100 | 3.8±1.32 | 98.2 | 6.8±2.4 |
| KA+AL10 | 100 | 4±0.63 | 41.6* | 5.2±0.74* |
| KA+AL15 | 100 | 3.4±1.01 | 52.32* | 3.8±1.6* |

*P<0.05 compared with the KA group.
KA: Kainic acid, AL: Allantoin

**Table 2.** Comparison of average initial and final weight mice in different groups

| Groups | Initial weight | Final weight | p value |
|---|---|---|---|
| Control | 19.87±0.72 | 21.52±0.86 | p=0.042 |
| AL | 20.82±1.24 | 21.29±1.16 | p=0.3 |
| KA | 19.79±0.73 | 18.71±0.77 | p=0.002 |
| KA+AL10 | 21.95±0.94 | 21.62±0.39 | p=0.124 |
| KA+AL15 | 22.84±0.77 | 22.36±0.58 | p=0.7 |

KA: Kainic acid, AL: Allantoin

AL (Figure 4B). Also, there was a significant difference between the KA group and other groups ($p<0.01$), except for the group treated with 15 mg/kg AL ($p\geq0.05$).

## DISCUSSION

Epilepsy is a neurological disease with numerous unpredicted seizures. Due to extensive neuronal damage, continued SE can be life-threatening.[20]

KA acts similar to major excitatory neurotransmitters in the CNS and increases neuronal excitability[21]; thus, KA probably causes brain inflammation by increasing the expression levels of inflammatory cytokines and oxidative stress.[22] Additionally, administration of KA promotes the release of large amounts of neurotoxic substances, leading to the influx of $Ca2^{+}$ and $Na^{+}$ in the neurons in brain tissue.[23] Thus, administration of KA can induce SE, inducing neuronal death, especially in the hippocampal CA1 and CA3 regions.[24] In this study, KA induced a model of epileptic status in mice, and a significant decrease of memory and destruction of CA1 and CA3 regions was observed after injection of a single dose of KA.

Because regeneration of neuronal cells is extremely limited[25] and there is drug resistance during treatment for traumatic and degenerative brain injuries, the use of neuroprotective agents can prevent neuronal damage during the seizure process.[26] AL as a

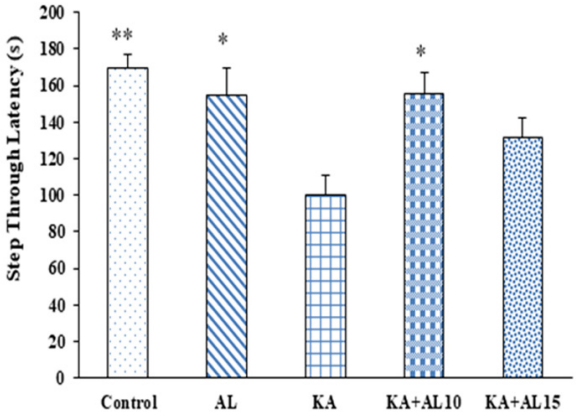


**Figure 1.** The comparison between the mean latency time to dark room in different groups (*p<0.05, **p<0.01 compared with KA group)
KA: Kainic acid, AL: Allantoin

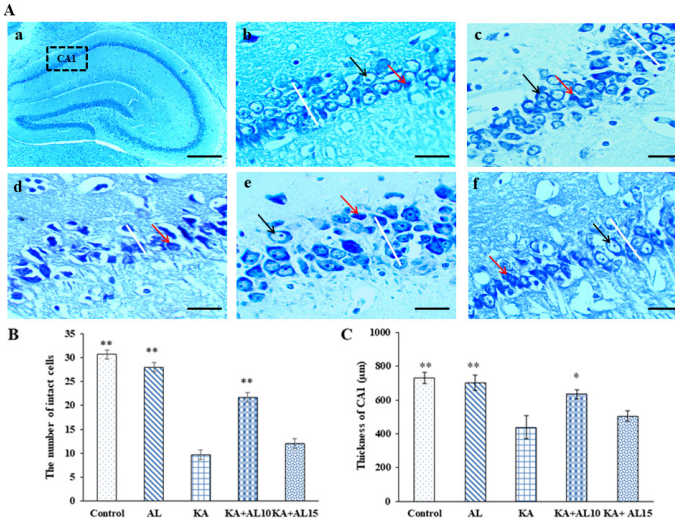


**Figure 2.** (A) Photomicrograph show CA1 area of hippocampus in control group with ×4 magnification; scale bar is 500 μm in Figure A. (a), control (b), AL (c), KA (d), KA+AL10 (e), KA+AL15 (f) groups with ×40 magnification; scale bar is 50 μm in Figures b-f. Intact neurons (black arrow), degenerated neurons (red arrow) and thickness of granular layer of CA1 (white line). (B) Mean of the number of intact granular cells of CA1 region of hippocampus in different groups. (C) The comparison of thickness of granular layer of CA1 among different groups (*p<0.05, **p<0.01 compared with KA group)
KA: Kainic acid, AL: Allantoin

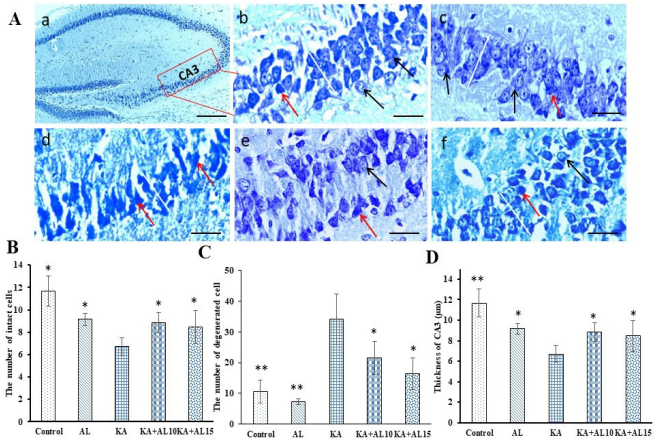


**Figure 3.** (A) Photomicrograph show CA3 area of hippocampus in control group with ×4 magnification; scale bar is 500 μm in Figure A. (a), control (b), AL (c), KA (d), KA+AL10 (e), KA+AL15 (f) groups with ×40 magnification; scale bar is 50 μm in Figures b-f. Intact neurons (black arrow), degenerated neurons (red arrow) and thickness of granular layer of CA3 (white line). (B) Mean of the number of intact cells of CA3 region of hippocampus in different groups. (C) Mean of the number of degenerated cells of CA3 region of hippocampus in different groups. (D) The comparison of thickness of granular layer of CA3 among different groups (*p<0.05, **p<0.01 compared with KA group)
KA: Kainic acid, AL: Allantoin

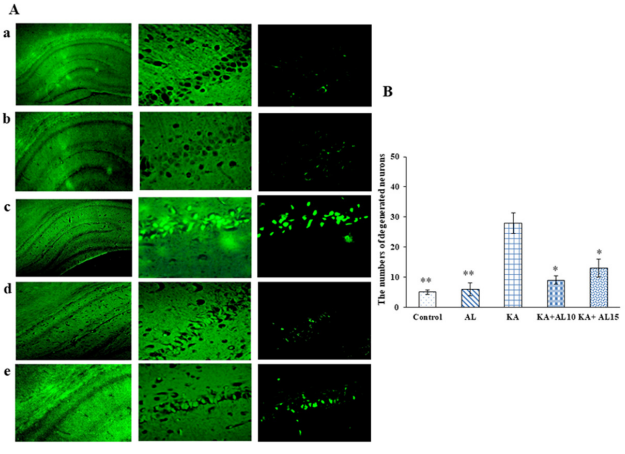


**Figure 4.** (A) Effect of AL on neurodegeneration in the CA1 area of hippocampus in different groups: control (a), AL (b), KA (c), KA+AL10 (d), KA+AL15 (e). The FJB positive cells exposed with green color. (B) The mean of the number of the degenerated neurons of CA1 region of hippocampus in different groups (*p<0.05, **p<0.01 compared with KA group)
KA: Kainic acid, AL: Allantoin

neuroprotective agent may recover faults of motor nerve conduction velocity and can defend against cisplatin-induced neuropathy.[27]

Many studies have indicated that the level of uric acid significantly increases in epilepsy patients.[28-30] Untreated epilepsy may chronically raise the level of uric acid in patients. In addition, it was proved that administration of KA can increase the level of uric acid in the brain in animal models for epilepsy.[28] Therefore, uric acid can be used as a biomarker in the prognosis and treatment of epilepsy. In fact, a reduction in uric acid levels can be valuable in suppressing clinical symptoms of epilepsy, such as seizure severity and frequency.[31] However, AL acts as a mediator in uric acid metabolism. It can pass through the blood-brain barrier and plays an essential role in the treatment of different neurodegenerative diseases.[32] Also, it may decrease the epileptic attacks through a decrease in uric acid levels.

A study showed that AL suppresses neuronal apoptosis by inhibiting the mitochondrial apoptotic pathway and decreasing the levels of oxidative stress and inflammatory cytokines. Therefore, it plays a high therapeutic role in brain injury.[33] AL has a high affinity to bind to the imidazoline receptors, and this property appears to prevent KA-induced seizures by preventing neuronal cell apoptosis.[34] In addition, another study showed that imidazoline agonists can be a valuable tool in the treatment of neurodegenerative disorders.[35]

This study showed that injection of 10 mg/kg AL improved memory and the thickness of hippocampus regions (CA1 and CA3), whereas the use of 15 mg/kg AL had a low effect on neuronal injuries. In addition, a study demonstrated the effect of different concentrations of AL on gastritis and determined that 12.5 mg/kg of AL provides better results on treatment.[36] Another study showed that intraperitoneal injection of AL may reduce Tau protein phosphorylation by activating the PI3K/Akt/GSK-3β signaling pathway in a rat model of Alzheimer disease. In addition, it was reported that administration of AL at 10 mg/kg concentration had a beneficial effect on improving memory impairment compared with other concentrations.[37] Therefore, the function of AL is probably dose-dependent.

Generally, 10 mg/kg AL presented better results compared with 15 mg/kg concentration, and this is a main issue that low dose has fewer side effects.

### Study Limitations

The aim of this study was to investigate the effects of AL on an epilepsy model in mice that accessed the memory and histopathology of the hippocampal region. However, due to lack of budget, the limitations of this study were the failure to investigate the many genes involved in epilepsy in real time and the inability to stain many protein markers in the tissue by immunohistochemistry.

## CONCLUSION

This study demonstrated that injection of KA can induce a model of TLE and that administration of AL at a specified dose had positive effects on memorial functions and the improvement of neurodegeneration in the hippocampal region following neuronal injury.

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### Ethics

**Ethic Committee Approval:** The ethical approval of the study was taken from the Qom University of Medical Sciences, Ethics Committee in Biomedical Research (decision no: IR.MUQ.REC.1395.161, 1395.161, date: 14.03.2017).

**Informed Consent:** Animal experiment.

### Authorship Contributions

Concept: M.E.F., S.A., Design: M.E.F., S.A., Data Collection or Processing: A.H.S., R.S., A.M., Analysis or Interpretation: A.H.S., R.S., A. M., Literature Search: A.M., S.A., J.T., Writing: M.E.F., R.S., S.A.

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

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Archives of Epilepsy

Original Article

# Status Epilepticus Type, Etiology, and Treatment: One-year Data

Didar Çolakoğlu[1], Humay İsmayilzade[1], Berk Büke[2], Kadriye Ağan[1], İpek Midi[1]

[1]Marmara University Faculty of Medicine, Department of Neurology, İstanbul, Turkey

[2]Marmara University, Faculty of Medicine and İstanbul University, İstanbul Faculty of Medicine, Department of Neurology, İstanbul, Turkey

İpek Midi MD

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**Corresponding Author:** İpek Midi MD, E-mail: ipekmidi@gmail.com

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**Abstract**

**Objective:** This study aimed to review the demographic characteristics, type, and etiology of status epilepticus (SE) cases followed in our hospital for a period of 1 year and to reveal the factors affecting the prognosis of the patients.

**Methods:** Patients diagnosed with SE among the patients who applied to the emergency department of our hospital within a 1-year period (August 2018 and August 2019) and who were consulted to us because of epileptic seizures or changes in consciousness and behavior while being followed up in the services or intensive care unit were retrospectively screened.

**Results:** A total of 51 patients, 28 female (54.9%) and 23 male (45.1%), were included in our study. Twenty-eight patients were under or equal to the age of 60, and 23 patients were over the age of 60. Twenty-one patients had convulsive SE, 18 patients had non-convulsive SE (NCSE), and 14 patients were transitioning from convulsive SE to NCSE. Causes of SE were; lack of anti-seizure drugs (ASD) in 9 patients, intracranial mass in 9 patients, infection in 8 patients, and cerebrovascular event in 6 patients. Refractory SE cases were mostly observed in patients who developed SE due to lack of ASD and infection. In addition to first-line treatment with benzodiazepines, intravenous (IV) phenytoin, levetiracetam, valproic acid, and oral topiramate and lacosamide treatments were used. It was observed that 26 patients who developed refractory SE were treated with IV midazolam, propofol, or thiopental infusion. It was observed that 2 patients died because of refractory seizures.

**Conclusion:** SE is an important condition that requires rapid treatment and can be fatal. In this cross-sectional study, the demographic characteristics and etiological causes of SE cases registered in our center were presented, and the characteristics of refractory SE cases were also mentioned.

**Keywords:** Status epilepticus, refractory status epilepticus, etiology, treatment

## INTRODUCTION

Status epilepticus (SE) is an epileptic emergency that has a time-dependent relationship with the risk of morbidity and mortality. It has different forms and a wide variety of etiologies. SE is practically divided into two main groups: convulsive and non-convulsive SE. The most widely accepted definition for convulsive SE (CSE) is either 5 minutes or more of continuous seizure activity or two or more separate seizures with no full recovery of consciousness between them.[1] A common definition of non-convulsive SE (NCSE) is electrographic seizure activity lasting more than 30 min in the absence of visible convulsions. The definition of SE proposed by the Neurocritical Care Society is defined as clinical and/or electrographic seizure activity of 5 min between seizures or recurrent seizure activity without improvement.[1] SE is one of the most important emergencies in neurology, and one out of every three patients is unresponsive to first-line treatment.[2] Refractory SE refers to clinical or electrographic seizures that persist after an adequate dose of initial benzodiazepine and an acceptable second-line therapy. In super-refractory SE, seizures continue to recur 24 h or more after the initiation of anesthetic therapy.[1,2]

The 2015 classification of the International League Against Epilepsy (ILAE) proposes a highly functional approach to subtypes by addressing 4 axes [semiology, etiology, electroencephalography (EEG) correlates, and age].[3]

It is important to initiate effective treatment without delay in SE patients. Benzodiazepines are effective agents used in first-line therapy. Phenytoin has been used as a second-line therapy for many years. In refractory SE cases, anesthetic agents are used.

In this study, we aimed to review the SE type, demographic characteristics, and etiologies of SE cases and treatment approaches, followed in our hospital in the emergency room, intensive care unit, neurology clinics, and other services within a 1-year period, and to indicate the prognosis of the patients.

## METHODS

Our study was planned as a single-center, cross-sectional study. Among the patients who were consulted to us because of epileptic seizures or changes in consciousness and behavior while being followed up in the emergency room, neurology service and other services, or intensive care unit within 1 years (between August 2018 and August 2019), the patients who were diagnosed with SE were included in the study retrospectively.

In terms of being more practical in our study, we divided SE into three groups: CSE, NCSE, and those transitioning from CSE to NCSE. EEG recordings of the patients were made, and EEG follow-ups were continued to evaluate whether there was a transition from CSE to NCSE.

To reveal the underlying etiology, a detailed anamnesis was taken from the patient's relatives or follow-up doctor. For the etiology, it was noted whether there was a history of anti-seizure drug (ASD) withdrawal, metabolic disorder, accompanying infection or stroke, intracranial mass, previous diagnosis of epilepsy or mesial temporal sclerosis (MTS), recent antibiotic use, and a history of exposure to hypoxia for a long time. To reveal the etiology, biochemical analyses, infectious panel, and autoimmune encephalitis panel were sent for the patients deemed necessary. Necessary imaging tests were performed for intracranial pathologies.

While IV diazepam was used as the first-line treatment in SE, IV levetiracetam, IV valproic acid, IV phenytoin, oral lacosamide, and topiramate were used as the second-line treatment protocol. In cases with refractory SE, midazolam, propofol, thiopental infusion, or a combination of these drugs were administered as general anesthetic agents in the intensive care unit. The death notification system (DNS) was used to determine the prospective life expectancy of the patients, and mortality rates were recorded.

### Statistical Analysis

In our current study, where 1-year data was discussed and 53 SE events of 51 patients were analyzed, the patients were categorized as CSE, NCSE and those who transitioning from CSE to NCSE. When each group was divided into subgroups such as demographic characteristics, etiology, and mortality, statistical analysis could not be performed due to the small number of patients included in these subheadings, and the current findings were summarized in tables and graphs.

## RESULTS

A total of 51 patients, 28 female (54.9%) and 23 male (45.1%), registered in our SE database between August 2018 and August 2019 were included in our study.

### MAIN POINTS

- Status epilepticus (SE) requires early intervention, has a high morbidity and mortality rate if treatment is delayed, and can be overlooked, especially in patients hospitalized in the intensive care unit.
- In our study, the most common causes of SE included withdrawal or missed dose of anti-seizure medication, intracanial mass, and infections.
- In addition, refractory SE was most frequently associated with the discontinuation or missed dose of anti-seizure medication.

**Demographic analysis:** The ages of the patients were between 19 and 89 years; the mean age was 55 years and the median value was 57 years. Twenty-eight patients were under or equal to the age of 60, and 23 were over the age of 60 years. A total of 53 SE data were available due to recurrence in 2 of 51 patients. Of these, 21 were patients with CSE, 18 with NCSE, and 14 with transition from CSE to NCSE. Seven patients had a previous diagnosis of epilepsy. While 4 of these patients had CSE, 3 had transitioned from CSE to NCSE (Table 1, Figure 1).

The mean age at CSE was 46.1 years, the mean age at NCSE was 64.3 years, and the mean age of those who transitioned from CSE to NCSE was 57.5 years (Table 1).

**Status epilepticus etiology:** The reason for developing SE in nine patients was the withdrawal of ASD. Of these, 3 were due to ASD missed by the patient, 3 were due to decreased oral intake, and 3 patients were due to cessation or reduction of ASD because of seizure-free follow-up. Of these patients, 6 had CSE, 2 had NCSE, and 1 had transitioned from CSE to NCSE (Figure 2).

Nine patients who developed SE due to intracranial mass were associated with postoperative complications. One patient developed SE due to a primary intracranial mass after radiotherapy

**Table 1.** Demographical data and etiology according to SE types

| | CSE | NCSE | CSE >>> NCSE |
|---|---|---|---|
| Gender (F/M) | 8/13 | 13/3 | 7/7 |
| Mean age | 46.1 | 64.3 | 57.3 |
| **Etiology** | | | |
| ASD | 6 | 2 | 1 |
| ICM | 5 | 3 | 1 |
| Infection | 2 | 5 | 1 |
| PDE | 4 | 3 | - |
| CVD | 1 | 3 | 2 |
| Metabolic disorder | 1 | 1 | 2 |
| Antibiotic usage | - | 4 | - |
| Idiopathic | 1 | 1 | 2 |
| MTS | - | 1 | - |
| Arrest | 1 | - | - |

SE: Status epilepticus, CSE: Convulsive status epilepticus, NCSE: Non-convulsive status epilepticus, ASD: Anti-seizure drug, ICM: Intracranial mass, PDE: Previous diagnosis of epilepsy, CVD: Cerebrovascular diseases, MTS: Mesial temporal sclerosis, F/M: Female/male

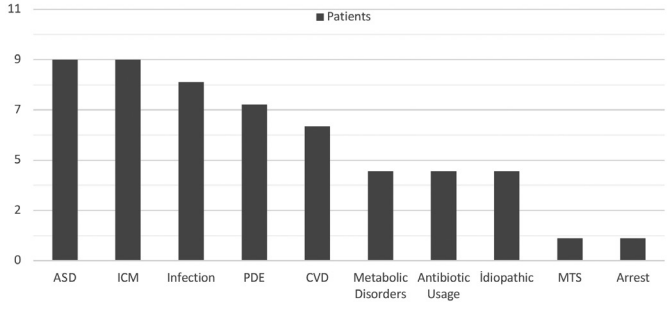


**Figure 1.** Frequencies of status epilepticus etiologies

ASD: Anti-seizure drug, ICM: Intracranial mass, PDE: Previous diagnosis of epilepsy, CVD: Cerebrovascular diseases, MTS: Mesial temporal sclerosis

and 2 patients developed SE due to intracranial metastasis. Of these patients, 5 had CSE, 1 had NCSE, and 3 were transitioning from CSE to NCSE (Figure 2).

Of the cases that developed SE due to infection, 2 were due to meningoencephalitis, 2 were due to aspiration pneumonia, and 4 were due to systemic infection. Of these, 2 were CSE, 4 were NCSE, and 2 were patients with transition from CSE to NCSE (Figure 2).

SE developed after cerebrovascular disease (CVD) in 6 patients and due to metabolic causes in 4 patients. Of the CVD patients, 1 had CSE, 3 had NCSE, and 2 had a transition from CSE to NCSE (Figure 2).

It was noted that antibiotic-associated SE developed in 4 patients three of whom were related to cefepime and 1 of them was related to linezolid. All 4 of these patients had NCSE (Figure 2).

Four patients presenting with SE for the first time were recorded. One patient developed MTS and one patient developed SE due to hypoxia after arrest. While the MTS patient was NCSE, the patient who developed post-arrest hypoxia was in myoclonic status (Figure 2).

Refractory SE cases (n=26) mostly occurred in SE due to ASD disruption and infection. Refractory SE was observed in more than 50% of SE cases with a known history of epilepsy and CVD (Table 2, Figure 3).

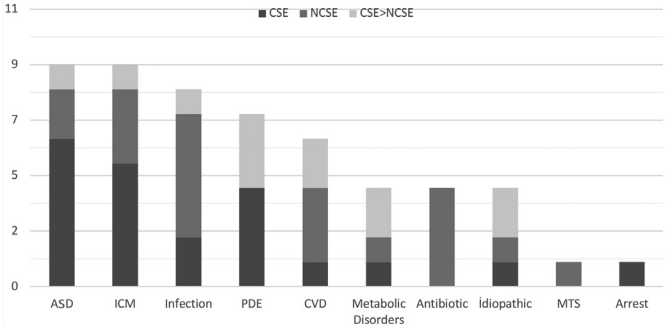


**Figure 2.** Status epilepticus types according to etiologies

ASD: Anti-seizure drug, ICM: Intracranial mass, PDE: Previous diagnosis of epilepsy, CVD: Cerebrovascular diseases, MTS: Mesial temporal sclerosis

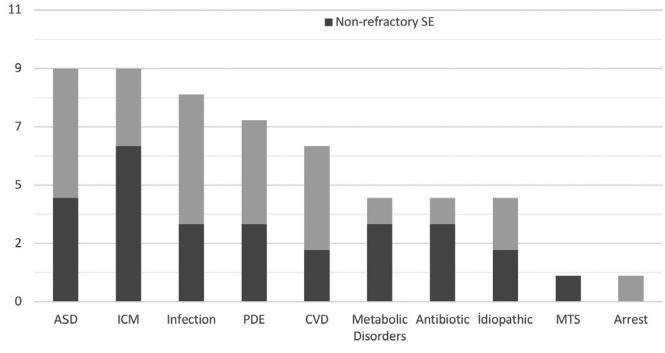


**Figure 3.** Refractory and non-refractory status epilepticus according to etiologies

ASD: Anti-seizure drug, ICM: Intracranial mass, PDE: Previous diagnosis of epilepsy, CVD: Cerebrovascular diseases, MTS: Mesial temporal sclerosis, SE: Status epilepticus

**Status epilepticus treatment:** In our study, first-line treatment (23 IV diazepam, 12 IM midazolam) was applied in 35 of 53 SE events. In 31 patients, second-line or third-line treatment was initiated. Agents frequently used in second-line treatment were levetiracetam (n=41), phenytoin (n=15) and valproic acid (n=10). Apart from these, high-dose oral topiramate or lacosamide treatment was applied (n=2). More than one second-line treatment agent was administered in 14 of the SEs that could not be stopped with a single agent. Second-line treatment was initiated in 18 patients with long SE duration at the time of admission, and success was achieved in 10 of them. In the remaining 8, third-line treatment was initiated. Twenty-six patients were evaluated with refractory SE, and midazolam was preferred as the primary anesthetic agent. Despite this, propofol and then thiopental infusion were administered to 2 cases whose seizures continued or electrophysiological seizure activity continued on EEG. It was learned from the DNS records that 18 of 51 patients were exitus (35.29%). Eleven were female patients.

## DISCUSSION

In our study, which included our one-year SE data, we found that there were more female patients and CSE was slightly higher than NCSE, and the most common etiologies were anti-seizure medication deficiency and infection. In another feature we obtained from our data, we found that CSE was more common in SE cases due to ASD deficiency and intracranial mass, whereas NCSE was more common in SE cases due to infection and antibiotic use. The mortality rate due to SE was approximately 35% in our study.

In our study, which analyzed 53 SE events of 51 patients, our finding of female superiority with a rate of 54.9% was similar to a study conducted in Italy and the study by Leitinger et al.[4,5] In our study, CSE was higher in males and NCSE was higher in females (Table 1). The incidence of SE has a bimodal distribution, increasing in the first year and in the elderly.[6] Alroughani reported that the mean age of 42 NCSE patients was 61.8 years, while

**Table 2.** Refractory and non-refractory SE frequencies according to variables

| | **Refractory SE n=26** | **Non-refractory SE n=27** |
|---|---|---|
| **Mean age** | 49.96 | 59.85 |
| **Gender** | | |
| F/M | 13/13 | 15/12 |
| **SE type** | | |
| CSE | 12 (46.15%) | 9 (33.33%) |
| NCSE | 7 (26.9%) | 11 (40.74%) |
| CSE >>> NCSE | 7 (26.9%) | 7 (25.92%) |
| **Etiology** | | |
| ASD discontinuation | 5 (19.23%) | 4 (14.81%) |
| ICM | 3 (11.53%) | 6 (22.22%) |
| Infection | 4 (15.38%) | 4 (14.81%) |
| PDE | 4 (15.38%) | 3 (11.11%) |
| CVD | 4 (15.38%) | 2 (7.4%) |
| Mortality | 2 | - |

SE: Status epilepticus, CSE: Convulsive status epilepticus, NCSE: Non-convulsive status epilepticus, ASD: Anti-seizure drug, ICM: Intracranial mass, PDE: Previous diagnosis of epilepsy, CVD: Cerebrovascular disease, F/M: Female/male

some studies showed a significant increase in the incidence of SE over the age of 50.[4,7] In our study, we found the mean age of SE to be 55 years, for CSE to be 46.4 years, and for NCSE to be 64.3 years. The mean age of NCSE patients was higher than that of other SE types (Table 1).

In our 53 SE records, we found our rate of CSE to be 39.6%, which was higher than that of NCSE (33.9%), and we found the most common etiology as anti-seizure medication discontinuation, while the second most common cause was intracranial mass. In NCSE cases, the most common etiologic event was infection, whereas the second cause was associated with antibiotic use. It has been reported in the literature that NCSE is observed in 25-50% of cases with SE.[7] Leitinger et al.[4] in their retrospective study of 221 first-episode SE cases reported, CSE as 65.6% and NCSE as 34.4%. In this study, the most common cause of SE was CVD (45.2%), followed by trauma (16.7%). In a study by Fountain[8], the most common cause of CSE in adults is a decrease in ASD levels and a history of central nervous system damage. Stroke, metabolic abnormalities, hypoxia, systemic infection, anoxia, trauma, overuse of drugs, central nervous system infections, and central nervous system bleeding are listed as acute causes of SE.[9] Among the chronic causes of SE are low serum levels of ASD, distant symptomatic causes such as tumor, stroke, and trauma, alcohol abuse, and idiopathic respectively.[9] Acute symptomatic causes for CSE are much more common, and the relationship between mortality and morbidity is higher.[9] In a study by Ozdilek et al.[10], SE attacks of 88 patients aged 16-50 years were analyzed, and the most common etiology of SE was found to be dose changes of anti-seizure medication at a rate of 31%. In the study conducted by Sünter et al.[11], in which 162 patients over 60 years of age who had an SE attack were evaluated, the most common cause of SE was found to be 37% of stroke, while the second most common cause was metabolic abnormalities at a rate of 18%.

Antibiotic groups, including penicillin, cephalosporin, carbapenem, and quinolones, have reported to cause seizures. Benzyl penicillin lowers the seizure threshold more than synthetic penicillins.[12] Among cephalosporins, cefazolin lowers the seizure threshold at a high rate, but SE has also been reported with ceftriaxone, cefotaxime, ceftazidime, and cefepime.[12] Imipenem is more convulsant than meropenem. Among quinolones, the convulsant effect of trovafloxacin is higher than that of levofloxacin, and SE has been reported with ciprofloxacin, ofloxacin, and gatifloxacin.[12] In our study, cefepime was found to be the most common among those who developed antibiotic-associated SE. NCSE has been reported, especially in patients with renal failure, after the use of ceftazidime, ceftriaxone, and cefepime.[13]

The incidence of refractory SE in patients with SE is between 23% and 43%.[2,9] In the study of Atmaca et al.[14], 59 SE cases were prospectively followed for 2 years, and the rate of refractory SE was found to be 25.4%. While retrospective studies reported the mortality rate of refractory SE between 16% and 23%, the mortality rate of refractory SE was 39% in a prospective study. The mortality rate of non-refractory SE was 11%.[14] SE developing with acute brain injury has an easier risk of transforming into refractory SE. If the etiology includes head trauma, brain infections such as encephalitis, brain tumors, and strokes, refractory SE may be more resistant to treatment. In our study, the rate of refractory SE was found to be 49.05%, and the most common etiology in patients who developed refractory SE was a decrease in the level of ASD, infections, and CVD. Ağan Yıldırım and Sünter.[2] analyzed the data of 290 patients with SE and found the rate of refractory SE to be 38%. In this study, when the etiology of refractory SE was examined, it was determined that acute causes predominated in 66.7%.[15] Sünter et al.[16] in a study of 38 patients who had SE due to an intracranial mass, 40% of the attacks were found to be refractory SE.

Benzodiazepines constitute the first-line treatment option for SE, although IV lorazepam is the first choice in international treatment algorithms. However, because it is not available in our country, treatment is started with IV diazepam. However, considering that its effect will decrease rapidly, treatment with longer-acting ASD should be continued. Phenytoin, fosphenytoin as well as IV valproic acid, levetiracetam, and phenobarbital are also among the options.[9,17] In a study by Kellinghaus et al.[18], first-line treatment success was reported as 21% in generalized CSE patients, 16% in non-generalized CSE patients, and second-line treatment success was reported as 46% for generalized CSE and 38% for non-generalized CSE. However, in this study, it was not overlooked that drug doses were used below the first-line doses recommended in the guidelines. In fact, benzodiazepines were not used as first-line therapy in 15% of patients.[18] In the literature, the success rate of first-line therapy is reported to be 55.5% for CSE and 14.9% for subtle SE.[19]

Considering the treatment response rates in our study, those who responded to second-line treatment were found to be 45.28%.

Midazolam, propofol, thiopental, and pentobarbital are the most commonly used anesthetic agents as third-line therapy in patients who develop refractory SE.[20,21] They act via the $GABA_A$ receptor. In a meta-analysis, the probability of having a seizure was 4% in patients treated with EEG suppression mostly provided by pentobarbital, compared with 53% in patients treated clinically and electrographically with midazolam or propofol. Here, while the probability of hypotension due to pentobarbital use was 76%, this rate was 29% in the other group.[21]

Midazolam (n=24) was the primary treatment in 26 patients with refractory SE, followed by propofol and then thiopental (n=2) treatment. Aggressive treatment should be considered in these patients because of the high risk of death, neuronal damage, and serious long-term morbidity.

Eighteen (35.29%) of 51 patients died in our study, 11 of them were female patients, and 2 of these patients were followed up with refractory SE. One of these two patients was being followed up with CSE and the other with NCSE, and the underlying causes in these patients were hypoxia after cardiopulmonary arrest and infection, respectively. It was determined that the remaining 16 patients in the follow-up with the DNS died because of other causes.

**Study Limitations**

The limitation of our study is that it was a study in which a certain percentage of patients were handled, covering a 1-year period, no data on SE durations were given, and the EEG characteristics of the patients could not be mentioned.

## CONCLUSION

SE is an important condition that requires rapid treatment and can be mortal. In this cross-sectional study, which included our one-year SE data, we found that there were more female patients and CSE was slightly higher than NCSE. We found that CSE were more common in SE cases due to ASD deficiency and intracranial mass, while NCSE was more common in SE cases due to infection and antibiotic use. The mortality rate due to SE was approximately 35% in our series.

### Ethics

**Ethics Committee Approval:** The Marmara University Faculty of Medicine Clinical Research Ethics Committee approved the study (number: 09.2023.182, date: 06.01.2023).

**Informed Consent:** The study was conducted in accordance with the ethical standards of the Declaration of Helsinki and informed consent was obtained from all patients.

### Authorship Contributions

Surgical and Medical Practices: D.Ç., H.İ., K.A., İ.M., Concept: K.A., İ.M., Design: K.A., İ.M., Data Collection or Processing: H.İ., B.B., Analysis or Interpretation: D.Ç., H.İ., B.B., Literature Search: D.Ç., Writing: D.Ç.

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

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# Demographic and Clinical Findings of Patients Monitored in a Newly Established Epilepsy Outpatient Clinic in the Çukurova Region: Experiences of a Tertiary Hospital in Turkey

Zeynep Selcan Şanlı[1], Hülya Binokay[2]

[1]University of Health Sciences Turkey, Adana Faculty of Medicine, Adana City Training and Research Hospital, Clinic of Neurology, Adana, Turkey

[2]Çukurova University Faculty of Medicine, Department of Biostatistics, Adana, Turkey

Zeynep Selcan Şanlı MD

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**Corresponding Author:** Zeynep Selcan Şanlı MD, E-mail: zeynepsanlimd@gmail.com

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## Abstract

**Objective:** The aim of this study was to investigate the demographic and clinical findings of patients monitored at the newly established Epilepsy Outpatient Clinic at the University of Health Sciences Turkey, Adana Medical Faculty, Adana City Training and Research Hospital.

**Methods:** A total of 315 patients who were monitored between July 2021 and October 2022 at the Neurology Clinic's Epilepsy Outpatient Clinic of the University of Health Sciences Turkey, Adana Medical Faculty, Adana City Training and Research Hospital were included in the study.

**Results:** Of the patients, 161 were male (51.1%) and 154 were female (48.9%). The average age of the patients was 33.9±13.98, and the average seizure frequency was 33.51±98.49 per year. The most frequently observed risk factors included a family history of epilepsy (31.3%), febrile convulsions (19.7%), and head trauma (18.4%). Neuroimaging findings were pathological in 47.6% of the patients, and electroencephalography findings were pathological in 65.8%. Focal onset seizures were observed in 45.1% of the patients, while generalized onset seizures were seen in 46.7%. Monotherapy was administered to 52.7% of the patients, and polytherapy was given to 41.6%. In epilepsy patients aged eighteen and above, pathological findings in neuroimaging were significantly higher ($p<0.001$).

**Conclusion:** Epidemiological studies provide invaluable information about the characteristics of an epilepsy clinic. However, there is still a notable scarcity of studies related to the regional epilepsy profile in our country. In this study, the clinical and demographic data of the patients were largely consistent with the literature. We believe that the regular monitoring of patients in comprehensive epilepsy clinics will enhance patient compliance and the success of treatment.

**Keywords:** Epilepsy, epidemiology, neuroimaging

## INTRODUCTION

Epilepsy is characterized by seizures that result from abnormal and excessive electrical discharges in cortical neurons and are not triggered by a definable event.[1] Epilepsy is one of the most common neurological disorders and affects individuals of all ages, races, social classes, and geographic regions. Community-based studies have reported that the prevalence of epilepsy is higher in developing countries than in developed countries.[2]

It is estimated that approximately 9% of the population may experience at least one seizure at some point in their lives. The decision to treat after the first seizure is determined by clinicians based on the risk of recurrent seizures, the potential impact of recurrent seizures, possible side effects of the treatment, and the patient's preference.[3,4] The goal in epilepsy treatment is to achieve seizure freedom with minimal side effects and maintain optimal quality of life. Unfortunately, under the busy general outpatient clinic conditions, sufficient time cannot be allocated to epileptic patients, and they cannot receive adequate treatment. It has been shown that establishing epilepsy outpatient clinics in hospitals enhances the regular monitoring of epilepsy patients, treatment success, seizure-free rates, patient compliance with treatment, and quality of life.[5,6]

In this study, the aim was to evaluate the demographic, etiological, clinical, and treatment characteristics of our epilepsy patients in the Çukurova region and to provide a basis for planning the general approach for use in applications.

## METHODS

The study included 315 patients who were monitored between July 2021 and October 2022 at the Epilepsy Outpatient Clinic of the University of Health Sciences Turkey, Adana Medical Faculty, Adana City Training and Research Hospital. Patients' age, gender, history characteristics, risk factors, age of first seizure, type of seizure, history of status epilepticus (SE), antiepileptic drug (AED), treatment received, drug resistance, whether treatment was changed, reason for change, the rate of benefit from drug change, electroencephalography (EEG), and cranial imaging examinations were recorded retrospectively by scanning file data.

### Statistical Analysis

Categorical measurements were summarized as number and percentage, while numerical measurements were expressed as mean and standard deviation (median and minimum-maximum where necessary). The chi-square test statistic was used for comparing categorical measurements between groups. For statistical analysis of the data, IBM Statistical Package for the Social Sciences statistics version 20.0 software was used. The statistical significance level was set at 0.05 for all tests.

## RESULTS

Of the 315 patients presenting to the epilepsy outpatient clinic, 161 were male (51.1%) and 154 were female (48.9%). The average age of the patients was 33.9±13.98; the age range varied between 17 and 82. One hundred and ninety patients (66.7%) reported being unemployed.

The age of first seizure ranged from 0 to 78 years; the average age of first seizure was 20.12±16.23. Seizure frequency varied from 0 seizures per year to 5 seizures per day. The average seizure frequency was 33.51±98.49 per year. Thirty-three patients (10.7%) had a history of SE. The most common risk factors were a family history of epilepsy (n=95), febrile convulsion (n=60), and head trauma (n=56) (Table 1).

In 45.1% (n=142) of patients, seizures began focally, and in 46.7% (n=147) they began generally. Twenty-eight patients were diagnosed as having psychogenic non-epileptic seizures (PNES) based on detailed history, EEG, and video EEG examinations (Table 2). Eleven patients had isolated PNES, whereas seventeen had PNES.

Thirty-seven patients did not have an EEG recorded at our hospital. Out of the 278 patients who had an electroencephalogram, 95 (34.2%) had a normal EEG. Ninety-four patients (33.8%) had focal and 69 (24.8%) had generalized epileptiform abnormalities. Fourteen patients (5%) showed slowing in the baseline activity, and six patients (2.2%) had non-specific EEG changes (Table 3).

### MAIN POINTS

- There is still a notable scarcity of studies related to the regional epilepsy profile in our country.
- The rate of abnormal neuroimaging findings was significantly higher in patients with a seizure onset age of >18.
- The incidence of status epilepticus in cases of drug-resistant epilepsy was found to be statistically significantly high.
- One-hundred ninety of our patients (66.7%) reported being unemployed.

Two hundred sixty-five patients had neuroimaging findings. Out of these, 152 (52.4%) were normal. Eight (3%) had mesial temporal sclerosis, 32 (12.1%) had encephalomalacia, five (1.9%) had cranial tumors, four (1.5%) had arachnoid cysts, seven (2.6%) had cerebral atrophy, eighteen (6.8%) had congenital malformations, and 39 (14.7%) had ischemic gliotic changes.

Eighteen patients (5.7%) were not receiving treatment, 166 patients (52.7%) were on monotherapy, and 131 patients (41.6%) were on polytherapy. Excluding the 18 patients not receiving treatment, 48 of the remaining 297 patients (16.1%) were diagnosed with drug-resistant epilepsy. Fifty-two patients (18.3%) were on antidepressants (Table 4).

Treatment was altered in 217 patients (71.6%). Of these 217 patients, 177 (81.6%) had seizures; five (2.3%) due to inappropriate medication, ten (4.6%) due to side effects, twenty-two (10.1%) due to being seizure-free, and three (1.4%) because they were in their reproductive years and were using sodium valproate. After the change in treatment, patients were re-evaluated. One hundred and fifty-nine patients (65.7%) were seizure-free, thirty-one (12.8%) had a reduction of more than 50%, forty-three (17.8%) had a reduction of less than 50%, three (1.2%) had a seizure when medication was reduced, and six (2.5%) saw no change in seizure frequency.

**Table 1.** Risk factors of patients

| Risk factor | Number |
|---|---|
| Family history of epilepsy | 95 |
| Febrile convulsion | 60 |
| Head trauma | 56 |
| Hypoxia | 35 |
| Intracranial operation | 18 |
| Brain tumor | 17 |
| Cerebrovascular accident | 10 |
| Central nervous system infection | 10 |
| Perinatal risk factor | 4 |
| Congenital disease | 1 |
| No risk factor detected | 9 |

**Table 2.** Clinical and electroencephalographic classification of epileptic seizures, (ILAE 2017)

| Seizure type | Number | % |
|---|---|---|
| Generalized onset | 147 | 46.7 |
| Focal onset | 142 | 45.1 |
| Unknown origin | 15 | 4.8 |
| Psychogenic seizure | 11 | 3.5 |

ILAE: International League Against Epilepsy

**Table 3.** EEG findings

| EEG findings | Number | % |
|---|---|---|
| Normal | 95 | 34.2 |
| Focal epileptiform abnormality | 94 | 33.8 |
| Generalized epileptiform abnormality | 69 | 24.8 |
| Slowing in the baseline activity | 14 | 5 |
| Non-specific EEG changes | 6 | 2.2 |

EEG: Electroencephalography

**Table 4.** Rates of antiepileptic drug usage

| Antiepileptic drug | Number | % |
|---|---|---|
| Levetiracetam | 206 | 70.5 |
| Sodium valproate | 83 | 28.4 |
| Carbamazepine | 83 | 28.4 |
| Lacosamide | 27 | 9.2 |
| Lamotrigine | 27 | 9.2 |
| Topiramate | 15 | 5.1 |
| Phenytoin | 9 | 3.1 |
| Oxcarbazepine | 5 | 1.7 |
| Clonazepam | 4 | 1.4 |
| Zonisamide | 4 | 1.4 |
| Pregabalin | 2 | 0.7 |
| Clobazam | 2 | 0.7 |
| Gabapentin | 1 | 0.3 |
| Ethosuximide | 1 | 0.3 |

## DISCUSSION

Epilepsy is the second most common neurological disease worldwide after cerebrovascular diseases, significantly impairing functionality, thus negatively affecting work productivity and the economy of nations.[7] Regular monitoring of such chronic and severe dependence-inducing diseases and documenting their epidemiological data will facilitate treatment strategies and prevention methods. In this study, we aimed to evaluate the demographic and clinical characteristics of patients in our newly established epilepsy outpatient clinic.

Various factors play a role in controlling epileptic seizures and resistance to treatment. At the forefront of these is the etiology of the seizure. In our study, based on the anamnesis information obtained from the patient and their relatives, records were taken of family history, head trauma, febrile convulsion, congenital diseases, perinatal risk factors, brain tumor, intracranial operation, and history of cerebrovascular disease. As in many chronic diseases, the most frequently detected risk factor in our epilepsy cases was determined to be a family history (31.3%). Compared with the literature, this high rate might be due to the higher incidence of consanguineous marriages in our region. Population-based epidemiological studies have found that the risk of seizures or epilepsy among first-degree relatives of epileptic patients is two to three times that of the general population.[8,9] The familial risk varies depending on the underlying etiology. This risk is seen more than twice as often in those with epilepsy of unknown cause, and in those with prenatal risk factors, it can increase almost fivefold. In a population-based study by Christensen et al.[10] involving more than 1.6 million people, it was reported that positive family history increased the risk of developing epilepsy more than tenfold following severe head trauma.

The risk of epilepsy varies between 2.4% in children with simple febrile seizures and 6% to 8% in children with complex febrile seizures. In one cohort study, it was found that children with febrile convulsions were five times more likely to develop subsequent unprovoked seizures compared to those without.[11] Several hypotheses gain significance regarding the increased risk of epilepsy development due to febrile seizures. The first is that acute hippocampal edema, which develops during febrile convulsion, increases the risk of epilepsy by leading to mesial temporal sclerosis. However, in two major longitudinal studies evaluating the outcomes of febrile seizures, the authors reported that a small number of children (approximately 7%) developed acute hippocampal edema, and none of them developed epilepsy.[12,13] Another potential mechanism is inflammation. Another potential mechanism is inflammation. Evidence suggests an increase in cytokines, particularly interleukin (IL)-1b, in the seizure onset zone during febrile seizures.[14] Cytokines interact with neurotoxic neurotransmitters, modulating brain damage and subsequently promoting leukocyte diapedesis across the blood-brain barrier, which is presumed critical for epileptogenesis. However, studies have yielded contradictory results regarding the role of these cytokines in the development of febrile seizures.[15-17] Recent research increasingly highlights the role of genetic factors.[11,18] In our patient group, 19.7% (n=60) had a history of febrile convulsions.

Seizures following traumatic brain injury are classified as acute (emerging within 24 hours), early (occurring within the first 7 days), and late (occurring after 7 days). Post-traumatic epilepsy is defined as the emergence of two or more unprovoked seizures more than seven days after the injury. In the minutes to hours following the injury, disruption of white matter tracts leads to neurotransmitter release, free radical formation, calcium-mediated damage, angiogenesis, mitochondrial dysfunction, and inflammatory responses. It's believed that these events, due to alterations in GABA and aspartic acid release, result in an imbalance between excitatory and inhibitory neurotransmitters, playing a role in the pathogenesis of epileptogenesis.[19,20] In our epilepsy outpatient clinic, 18.4% (n=56) of patients had a history of head trauma.

EEG is a vital neurophysiological method for supporting the diagnosis of epilepsy, classifying seizure types, selecting AED, and predicting prognosis.[21] An EEG taken on the first day after a seizure is crucial for detecting epileptiform findings. The probability of detecting a typical epileptiform anomaly in the first routine EEG is on average 50%. With repeated EEGs, well-applied activation methods, and, if possible, sleep recordings, this rate increases to 82-92%. Not every patient with epilepsy will display interictal epileptiform discharges, and epileptic activity can also be observed in healthy adults.[22] In our clinic, out of 278 patients with EEGs, 95 (34.2%) had normal EEGs. PNES was observed in 28 (8.9%) of our cases. Of those evaluated in the video EEG unit, 11 were diagnosed with PNES, and their medications were gradually discontinued.

Neuroimaging is employed primarily to determine the etiology of focal-onset epilepsy and demonstrate anatomical changes associated with seizure activity. Particularly in cases of drug-resistant epilepsy, magnetic resonance imaging (MRI) is imperative. Only 29% of patients with hippocampal sclerosis can be treated with AEDs, while the post-surgical seizure-free rate rises to around 70%.[23] Literature review indicates that MRI negativity rates reported in studies range between 17% and 55%.[24-26] In studies, it has been reported that the likelihood of detecting lesions significantly increases in patients subjected to 3T MRI.[27-29] Observed epileptogenic lesions vary depending on socio-economic level, age, and type of epilepsy.

In a prospective study conducted at a tertiary epilepsy center involving 738 patients, 3T MRI was performed on patients with drug-resistant epilepsy, and 262 (35.5%) were found to be normal. The most common imaging finding was mesial temporal sclerosis in 132 patients (17.9%), followed by encephalomalacia in 79 patients (10.7%).[30] In another prospective study, the most common lesion type identified in patients was encephalomalacia (49%), with other prevalent lesion types being tumors (15%), cavernomas (9%), and mesial temporal sclerosis (9%). Additionally, authors reported that in 55% of patients with epileptogenic lesions, the EEG was normal, and the frequency of epileptic lesions was highest (81%) in focal-onset epilepsies.[25] In our study, 152 (57.4%) of the patients had normal MRI findings, 39 (14.7%) had ischemic/gliotic lesions, 32 (12.1%) had encephalomalacia, and 8 (3%) had mesial temporal sclerosis. The higher MRI negativity rate in our clinic compared to the literature could be due to the absence of 3T MRI and the radiologist's experience. In accordance with literature, the rate of abnormal neuroimaging findings was significantly higher in patients with a seizure onset age >18 ($p<0.001$) (Figure 1), and the presence of an epileptogenic MRI lesion did not influence the chance of having an abnormal EEG. These findings are consistent with the higher prevalence of symptomatic epilepsies in adults. However, in contrast to the literature, our study did not find a high rate of epileptogenic lesions in focal-onset epilepsies ($p=0.065$). The reason for this discrepancy may be that, due to the retrospective nature of our study, seizure onset patterns could not be determined accurately and that not all patients were followed by the epilepsy protocol and 3 T MRI was performed.

The objective in epilepsy treatment is to achieve maximum seizure control with minimum side effects in patients. Monotherapy is considered the gold standard for this aim. Studies have found it superior to polytherapy, especially in terms of side effects, drug-drug interactions, patient compliance, and quality of life.[31,32] In approximately half of the patients, seizure control is achieved with the first prescribed AED, while it's reported that in 11% to 37% of the remaining patients, seizures are controlled with the second monotherapy agent.[33,35] In a multicenter study documenting AED prescription data between 2013-2018, 68.19% of the patients were on monotherapy, 31.81% were on polytherapy, and the most frequently prescribed AED was levetiracetam (LEV).[36] In an epidemiological study between 2009-2017, AED prescription rates for patients were documented by age and gender. Despite valproic acid (VPA) being the most frequently prescribed, the prescription rate for LEV has been reported to consistently increase throughout the study period regardless of age and gender. Furthermore, the authors highlighted a significant decline in VPA prescriptions in recent years, especially in women of reproductive age and in the elderly.[37] Of our patients, 166 (52.7%) were on monotherapy, while 131 (41.6%) were on polytherapy. In line with the literature, the most commonly prescribed AED was LEV (71.5%).

Drug-resistant epilepsy is defined as a situation where sustainable seizure control cannot be achieved despite the use of two AEDs, either as monotherapy or in combination, that are appropriate for the seizure type and tolerated by the patient.[38] The resistance rate in adult epilepsy patients ranges between 30% and 40%. In one review, strong risk factors for drug-resistant epilepsy were reported as abnormal EEG (both slow waves and epileptiform discharges), SE, symptomatic etiology, multiple seizure types, and febrile convulsions.[39] Of the patients we treated for epilepsy, 48 (16.6%) had drug-resistant epilepsy. This rate was significantly lower compared to the literature.[40-42] We think that this low rate may be related to the fact that we have few lesional epilepsy patients and that we can follow up patients regularly and frequently. Consistent with the literature, the incidence of SE in these cases was statistically significantly higher ($p<0.001$) (Figure 2). However, the rates of detected pathology on MRI ($p=0.233$) and observed abnormal EEG findings ($p=0.83$) in drug-resistant epilepsy cases were not significantly higher.

In our clinic, treatment was modified for 217 patients. After the treatment change, 159 (65.7%) of the re-evaluated patients were seizure-free, 31 had more than a 50% reduction, and 43 (17.8%) had less than a 50% reduction in seizure frequency. Seizure recurrence was observed in three patients during medication reduction.

Depressive disorders are the most common psychiatric comorbidity in people with epilepsy, affecting about one-third and having a

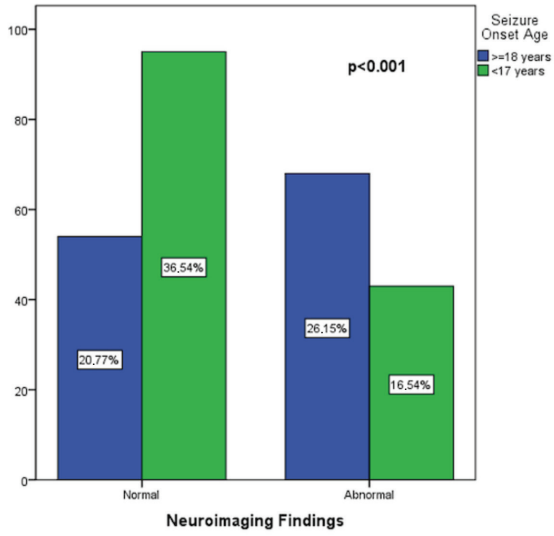


**Figure 1.** Relationship between seizure onset age and neuroimaging findings

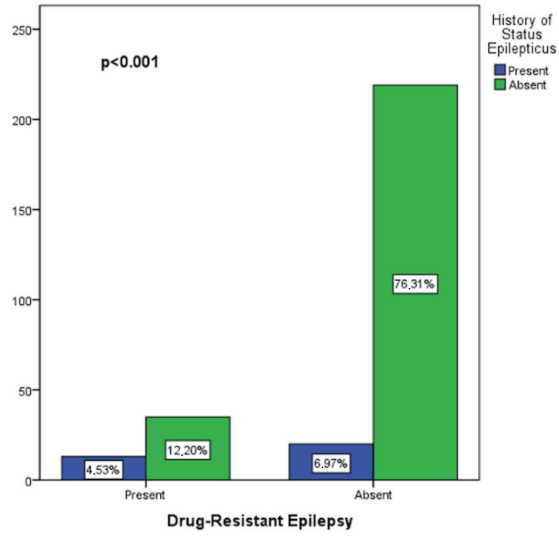


**Figure 2.** Association between refractory epilepsy and history of status epilepticus

significant adverse effect on quality of life. However, due to the fear that antidepressants might induce seizures, depression often remains untreated in people with epilepsy. In contrast, studies have shown that with antidepressant treatment, up to 97% of patients show improvement and it doesn't increase the frequency of seizures.[43] Of the patients followed up in our clinic, 52 (18.3%) were on antidepressant treatment.

Employment opportunities for individuals with epilepsy are unfortunately restricted in all countries around the world. In a case-control study conducted in Tanzania, researchers found a significantly lower rate of employment in people with epilepsy compared to the control group (33.3% vs 91.1%).[44] In a single-center cross-sectional study; even in an industrialized country like Hong Kong where unemployment is very low, the unemployment rate among epilepsy patients was found to be 33%, and this rate was reported to be quite high compared to the general population.[45] In a review published in Australia, authors reported that individuals with epilepsy are generally excluded from all employments requiring a uniform.[46] In our study, 190 patients (66.7%) reported being unemployed.

### Study Limitations

The limitations of this study are; due to data being sourced from patient files, there could be inaccuracies in determining the type of seizure onset; the absence of 3T MRI examinations and the rate of MRI negativity possibly being high due to radiologist experience compared to the literature.

## CONCLUSION

Our study provides valuable insights about epileptic patients in a tertiary hospital in Turkey and reflects a regional profile. In general, our findings were found to be consistent with the literature. We believe that evaluating sociodemographic and clinical features through community-based, multi-center comprehensive studies will potentially benefit the development of treatment strategies and achieve better outcomes.

### Ethics

**Ethics Committee Approval:** Ethical approval for this study was obtained from University of Health Sciences Turkey, Adana City Training and Research Hospital Clinical Research Ethics Committee (approval number: 128/2626, date: 08.06.2023).

**Informed Consent:** Retrospective study.

### Author Contributions

Surgical and Medical Practices: Z.S.Ş., Concept: Z.S.Ş., H.B., Design: Z.S.Ş., H.B., Data Collection or Processing: Z.S.Ş., H.B., Analysis or Interpretation: Z.S.Ş., H.B., Literature Search: Z.S.Ş., H.B., Writing: Z.S.Ş.

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

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# Limited Exposure to Social Isolation does not Affect the Spike Frequency and Amplitude of Penicillin-induced Epileptiform Activity in Adolescent Rats

Seval Müsüroğlu Keloğlan[1], Fatma Banu Aycık[2], Leyla Şahin[3], Fırat Aycık[2], Mustafa Ayyıldız[2], Erdal Agar[2]

[1]Adıyaman University Faculty of Medicine, Department of Physiology, Adıyaman, Turkey

[2]Ondokuz Mayıs University Faculty of Medicine, Department of Physiology, Samsun, Turkey

[3]Mersin University Faculty of Medicine, Department of Physiology, Mersin, Turkey

Seval Müsüroğlu Keloğlan PhD

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**Corresponding Author:** Seval Müsüroğlu Keloğlan PhD, E-mail: sevallkeloglan@hotmail.com

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## Abstract

**Objective:** It is known that the stress experienced during this period increases the risk of seizures. This study, it was investigated the effect of limited social isolation (SI) stress experienced in early life on penicillin-induced epileptiform activity.

**Methods:** Wistar Albino male rats (n=21) 28 days postpartum (PND21) were randomly divided into 3 groups (n=7); control group (C), SI group for 28 day (SI28), SI group for 14 days (SI14). SI stress was established by keeping rats in cages alone for 6 hours per day. Following the experimental protocol, rats were anesthetized with urethane (1.25 g/kg). The epileptiform activity was induced with Penicillin-G (500 IU, i.c.) and ECoG was recorded for 3 hours.

**Results:** SI stress was no effect on the spike frequency and amplitude of penicillin-induced epileptiform activity. There was no difference in penicillin-induced epileptiform activity whether the SI was 14 or 28 days.

**Conclusion:** SI stress per day for 6 hours was no effect on penicillin-induced epileptiform activity early in life. After the rats were exposed to SI stress for 6 hours a day, housing in a standard cage may have reduced or eliminated the effects of isolation providing social interaction. In order to better interpret this finding, we suggest that possible changes with different durations of SI should be investigated with further studies.

**Keywords:** Social isolation, stress, epilepsy, penicillin

## INTRODUCTION

Stress experienced early in life affects neuronal function and brain networks.[1] There are experimental animal models to investigate the effects of stress on humans.[2,3] Social isolation (SI) is one of the methods of creating social stress in animals.[4] SI stress after weaning has been reported to cause changes in different brain regions.[5]

The Coronavirus disease-2019 (COVID-19) pandemic has caused an unprecedented number of people to be affected by quarantine or isolation.[6] A strong association has been shown between SI and anxiety, depression in children and adolescents during the COVID-19 pandemic.[7] It is stated that children and adolescents are more likely to experience high rates of depression and anxiety after isolation.[8]

Epilepsy is a neurological disease closely related to stress and anxiety.[9,10] In studies in humans and animals, it has been shown that the risk of increased seizure susceptibility increases due to SI stress.[11,12] The current COVID-19 pandemic can influence the seizure frequency in adult people with epilepsy.[12] The impact of COVID-19 and quarantine isolation on the course of epilepsy and the incidence of new-onset seizures remains unclear.[13] For epilepsy, which most commonly begins in the first two decades of life, adolescence is a period of great change that takes place both in epilepsy itself and in many other areas.[14] Increasing knowledge about the interaction between early life stress, seizures, and epileptogenesis is thought to provide a basis for new treatment strategies for epilepsy.[15,16] However, although SI affects seizure development, its effect on the brain has not yet been clarified.[8,9]

It is important to investigate the effect of this isolation, which is mandatory exposure with the COVID-19 pandemic, especially childhood-onset epilepsy. Therefore, in this study, the effect of 6 hours of daily SI stress exposure on epileptiform activity was investigated in adolescent rats.

## METHODS

### Animals and Experimental Groups

This study was done at postnatal 21 days (PND21) old Wistar Albino male rat (n=21). The ethical approval of the study was taken from the Local Ethical Committee of Ondokuz Mayıs University (ethical no: 2018/25, date: 20.04.2018). All animals are purchased from, Ondokuz Mayıs University Laboratory Animal Center which has a 12-hours light/dark cycle at the ambient temperature of 21±1 ºC. The rats were acclimated one week before starting the experimental procedure. The rats were given free access to food and water. The experimental procedure started at PND28 and lasted 4 weeks (Figure 1). The rats were randomly divided into 3 groups (n=7); control group (C), SI group for 14 days, and SI group for 28 days.

### Social Isolation Procedure

SI involved removing the experimental animal from the home cage and placing it into an isolated cage with dimensions 25×42×15 cm. Every day rats were exposed to stress between 08:00-14:00 for 6 h in a separate cage. Rats were exposed to SI for 14 days or 28 days.[11,17,18] After completing their SI, rats spent the rest of the day in standard rat cages. During this period, the C group (per cage of 3-4 rats) spent their time in the standard cage.[19] These animals were exposed to the same environmental stimuli as group housed rats but were deprived of social contact.

### Electrocorticography Recordings

After the 28-day experimental procedure, on the PND57, the rats were anesthetized with urethane (1.25 g/kg, i.p.) and placed in the stereotaxic apparatus. Skin and subcutaneous tissue were removed from the skull. Two screw electrodes were placed on the left somatomotor cortex and a ground electrode was placed on the nasal sinus. Two bipolar Ag-AgCl ball electrodes were placed in the somatomotor cortex of the left hemisphere.[20]

ECoG activity was then monitored with an eight-channel recorder (PowerLab, 8/SP, AD Instruments, Castle Hill, NSW, Australia). Penicillin G (I.E. Ulagay, Turkey) 500 IU potassium was dissolved in normal saline, administered as a single dose and 2 µL was injected using a Hamilton microsyringe (type 701N; Aldrich, Milwaukee, WI, USA) into the 1 mm beneath the brain surface taking the bregma reference point. After 2 minutes of basal activity, penicillin was injected and epileptiform activity was recorded for 180 min. The frequencies and amplitudes of ECoG activity were analyzed offline.[20]

### Statistical Analysis

Statistical comparisons were made using Statistical Package for Social Sciences. In multiple comparisons, one-way analysis of variance was used after it was determined that the obtained data fit the normal distribution (Shapiro-Wilk test). Tukey Kramer post-hoc tests for multiple comparisons were performed. For all statistical tests, $p<0.05$ was considered statistically significant. The results are presented as the means±standard error of the mean.

## RESULTS

### Effect of Social Isolation on Penicillin-induced Epileptiform Activity

Approximately 30 min after the penicillin injection, epileptiform activity reached a constant level and this activity lasted for about 3h. The means of spike frequency and amplitude of penicillin-induced epileptiform activity in the control group were 78.13±8.13 spike/min and 1189.13±26.75 µV, respectively.

There was no found significant difference that the spike frequency and amplitude of penicillin-induced epileptiform activity in the SI28 and SI14 groups were compared to the C group ($p>0.05$) (Figure 2a and 2b). The means of the spike frequency and amplitude of epileptiform activity were 82.75±7.75 spike/min and 1011.31±81.50 µV in the 100 min after the injection of penicillin respectively in SI14. In SI28, the spike frequency and amplitude of epileptiform activity were 78.38±3.81 spike/min and 1095.62±83.37 µV, respectively, within 100 minutes after penicillin injection. In addition, there was seen a decrease in amplitude of epileptiform activity in the SI groups compared to the control group although it was not statistically significant (Figure 2b).

## DISCUSSION

In this study, we investigated the effect of SI on penicillin-induced epileptiform activity. According to our results, 6 hours a day of SI in early daily life did not change the frequency or amplitude of epileptiform activity. In addition, we did not detect any difference on epileptiform activity between 14 days of SI or 28 days of SI.

Studies in the literature show that SI induces stress and reduces seizure threshold.[21,22] In experimental animals, the daily SI period exposed during the experimental procedure can be as short as 1 hour, or it can be for the whole day, ie 24 hours.[23,24] Amiri et al.,[24]

**MAIN POINTS**

- It is known that the stress experienced during this period increases the risk of seizures.
- We are investigated the effect of limited social isolation stress experienced in early life on penicillin-induced epileptiform activity.
- Social isolation stress was no effect on the spike frequency and amplitude of epileptiform activity.

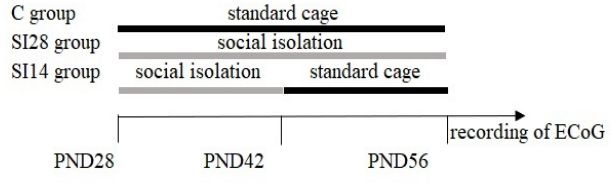


**Figure 1.** The schematic timeline of the experimental procedure
PND: Postnatal day, C: Control group, SI28: SI group for 28 days, SI14: SI group for 14 days

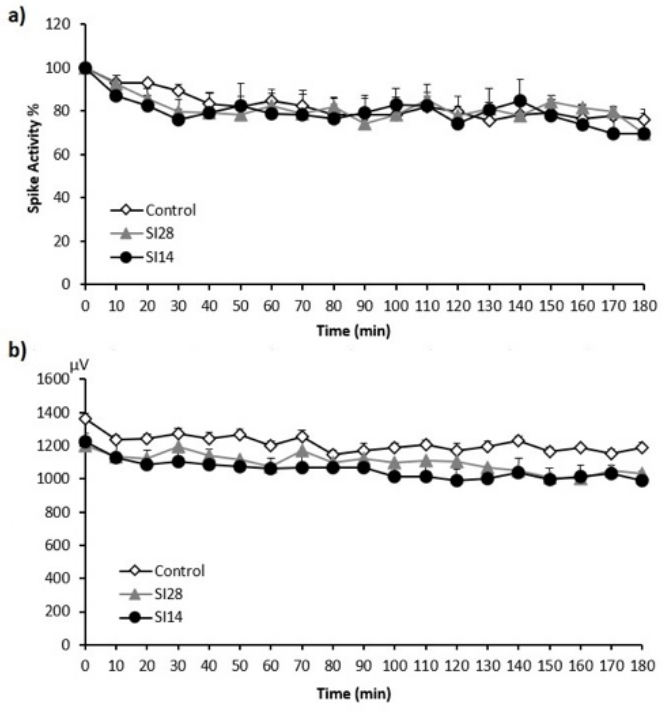


**Figure 2.** a) The spike frequency % of penicillin-induced epileptiform activity did not statistical significance change in between the groups. b) The mean of amplitude of penicillin-induced epileptiform activity did not statistical significance change in between groups ($p>0.05$). The results are presented as the means±standard error of the mean (SEM)
SI28: SI group for 28 days, SI14: SI group for 14 days

found that SI stress significantly decreased the seizure threshold in comparison with the social condition for PN21-PND50 in mice (all day SI). In our study, SI was applied for 6 hours a day, not all day. Furthermore, a previous study showed that applied stress during limited hours 180 or 15 minutes found that stress increased vulnerability to kindling.[25] However, in the study of Ali et al.,[25] stress was applied between PND 2nd and 14th days. In addition, Lai et al.[26] showed that the neonatal isolation (from PND day 2 (P2) to P9) plus status epilepticus induced rats had greater cognitive deficits and decreased seizure threshold. Lai et al.,[26] showed that applied stress to a much earlier period of life compared to our study. Therefore, we recommend that stress before PND 21 days has a more negative effect on epileptogenesis. This may be due to the partial or complete deprivation of maternal care of the offspring in the stress models applied before PND21.[1] Rau et al.,[27] showed that early life stress increases excitability but in their studies, the isolation was housed after PND21 until P101-P115. The SI applied in their study is longer than our study. Here, we think that affects our results especially the daily exposure time to SI and total duration of SI in the early stages of life.

In the present study, we showed that SI of rats for a limited time of 6 hours daily did not affect penicillin-induced epileptiform activity. Here, we suggest that the short duration of SI may have eliminated the possible negative effects of SI. In our study, rats spending the rest of the day in the normal cage after isolation, thus re-socializing, may have a curative effect on isolation. The previous study found that re-socialization can revert both long-term chronic SI stress induced anxiety and social memory impairment.[28] On the other hand, studies are showing the negative effect of SI on epilepsy. Another reason for the different results in our study may be that the epileptiform activity was directly evaluated, not the seizure susceptibility of the rats in our study.

Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter found in the cerebral cortex.[29] Enhancement of GABAergic inhibition is useful for the treatment of pathological conditions including epilepsy.[30] GABA has two major receptors; $GABA_A$ acts as a chlorine channel and a baclofen-sensitive metabotropic receptor $GABA_B$.[31] The convulsant properties of penicillin are associated with antagonism of inhibitions mediated by $GABA_A$ receptor within the mammalian central nervous system.[32] Studies are showing that SI is associated with epilepsy and that the GABAergic system plays a role in this relationship.[33,34] Early life stress causes prolonged neuronal hyperexcitability in some limbic regions with less effective inhibition by GABA.[35] Neurochemical, molecular, and electrophysiological evidences demonstrate that SI is associated with alteration in the structure and function of $GABA_A$ receptors.[36] Another study demonstrated that SI induced a decreased behavioral response to systemically administered GABA-mimetic drugs in mice.[37] In previous showed that long-term SI beginning PND28 and lasting 7 weeks increased seizure susceptibility to a $GABA_A$ antagonist picrotoxin in mice.[33] In our study, we did not see the effect of SI stress on penicillin-induced epileptiform activity, although penicillin is an agent that acts on GABA antagonism. This may be because penicillin is an acute seizure model and thus only 3 hours of epileptiform activity was recorded.

### Study Limitations

In addition, animal studies have limitations arising both from the problems associated with modeling neuropsychiatric disorders in the laboratory and from the disadvantages of animal models of epilepsy themselves.[38] For example, many epilepsy patients have a latency period of months or even years of no seizure activity after transient brain injury reported early in life.[39]

## CONCLUSION

According to our findings, SI applied for a limited time does not affect the frequency and amplitude of penicillin-induced epileptiform activity. The fact that the rats were in a normal cage after isolation may have prevented the effects of SI stress from appearing. In future studies, we suggest investigating the effect of exposure to SI stress at different durations on epileptiform activity.

### Ethics

**Informed Consent:** This study was done at postnatal 21 days (PND21) old Wistar Albino male rat (n=21).

**Ethics Committee Approval:** The ethical approval of the study was taken from the Local Ethical Committee of Ondokuz Mayıs University (ethical no: 2018/25, date: 20.04.2018)

### Authorship Contributions

Surgical and Medical Practices: F.B.A., F.A., Concept: S.M.K., Design: S.M.K., L.Ş. Data Collection or Processing: S.M.K., F.B.A., Analysis or Interpretation: S.M.K., F.B.A., L.Ş., M.A., E.A., Literature Search: S.M.K., L.Ş., M.A., E.A., Writing: S.M.K., F.B.A., L.Ş., F.A., M.A., E.A.

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# Puberty and Epilepsy Onset in Women

Galina Odintsova[1], Nina Dengina[2]

[1]Almazov Medical Research Center, Polenov Neurosurgical Research Institute, St. Petersburg, Russia

[2]Almazov National Medical Research Centre, Polenov Neurosurgical Institute, Epilepsy Research Laboratory, St. Petersburg, Russia

Galina Odintsova MD

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**Corresponding Author:** Galina Odintsova MD, E-mail: odintsova_gv@almazovcentre.ru

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**Abstract**

**Objective:** The significance of the onset of seizure based on the medical and social aspects of epilepsy. The aim of this study was to investigate the age of seizure onset based on the specific characteristics of each age of seizure onset in many epilepsy syndromes to make an appropriate diagnosis.

**Methods:** The age at epilepsy was retrospectively studied in 155 women aged between 16 and 45 years with a verified diagnosis of epilepsy. The epidemiological method revealed the age at epilepsy onset, and females were divided into three groups: pre-puberty (10-11 years old), puberty (10-18 years old), and post-puberty (18+ years old). A correlation study of the frequency of onset with the periods of formation and function of the female reproductive tract was conducted.

**Results:** A statistically significant quantitative predominance of females with epilepsy onset during puberty ($p<0.001$) was identified. Statistically valid was the prevalence of epilepsy onset in the combined age range of 12 to16 ($p<0.001$). A direct link between menarche and epilepsy onset was detected in the general cohort in 13% of females, which is among the risk factors for catamenial seizure onset.

**Conclusion:** Epilepsy onset in females of reproductive age dominates during childhood development. In more than half of the cases, the epilepsy onset occurs in the puberty period. Epilepsy onset most often occurs between the ages of 12 and 16. Seizure onset occurs at the ages of 12-16 years during menstrual bleeding and ovulatory cycle development due to the proconvulsive effects of estrogens.

**Keywords:** Epilepsy, seizure onset, female sex, puberty, hormones, estrogens

## INTRODUCTION

The topicality of the problem being researched results from the medical and social aspects of epilepsy onset. The significance of the age of seizure onset also results from the medical and social aspects of epilepsy.[1,2] The age of epilepsy onset is a determining factor in the development of the disease. A properly conducted differential diagnosis, timely diagnosis, and adequately selected antiepileptic treatment not only reduce social stigma but also determine the further course of the disease.[3] The opposite situation tends to progress to pharmacoresistant epilepsy. The age at onset is important in epileptology based on the specific characteristics of each age of the onset of many epilepsy syndromes, which helps to make the appropriate diagnostic testing.

Epilepsy onset is defined as the age at which the first unprovoked seizure occurs. However, the first unprovoked seizure and newly diagnosed epilepsy may not be synchronized (coincide with time of the onset). The accuracy of the determination of the age at epilepsy onset varies depending on the type of patient's seizures, as some types (e.g., absences, myoclonus) are often repeated for a long time before epilepsy is diagnosed. In recent years, the international league against epilepsy has formulated new definitions and classification systems of seizures and epilepsy that offer opportunities for the world community to communicate in a common language on many scientific and practical aspects of the disease.[4,5] This stems from the newly developed definitions of epilepsy in 2014. "Epilepsy is considered to be a disease of the brain defined by any of the following conditions: (1) at least two unprovoked (or reflex) seizures occurring >24 h apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures occurring over the next 10 years; and (3) diagnosis of an epilepsy syndrome.[4] It is expected that the percentage of patients meeting the criteria for newly diagnosed epilepsy after the first unprovoked seizure will be higher because the diagnosis can now be made after a single unprovoked attack with a high risk of recurrence." This further highlights the importance of onset issues. The incidence and prevalence of epilepsy change with age, dominating in childhood and at a young age.[6] Most epidemiological studies show a general trend toward an increase in prevalence among adolescents and young adults.[7] Epilepsy onset is observed mainly in childhood (about 75% of all cases).[8] Testing has proven that an immature brain has an increased predisposition to seizures and a greater susceptibility to them.

Two peaks of morbidity are distinguished in childhood: infancy and puberty. The age between 12 and 16 years begins immediately after the epilepsy onset and can reach up to 3 years according to the criterion of a poor prognosis.[9] Most studies emphasize that the prevalence of epilepsy in males is higher than that in females; however, the absolute difference in prevalence between genders is minimal. At the same time, the level of social activity and family functioning in females with epilepsy is lower than in men.[10,11] Side effects of antiepileptic drugs and the development of reproductive endocrine complications reduce demographic rates in females with epilepsy.[12] Therefore, it is important to clarify the gender characteristics of the onset of female epilepsy. It acquires a special significance in puberty. However, puberty is considered a homogeneous period, and the change in the hormonal background within the period and the time dependence of epilepsy onset on these changes are not considered. The study of factors affecting reproductive health is necessary to improve the early diagnosis and prevention of reproductive endocrine complications.

The objective of this study was to study the correlation between the age at epilepsy onset and hormonal regulation of the female reproductive cycle in female epilepsy.

## METHODS

This research paper is a follow-up study of a prospective observational non-randomized study on the side effects of antiepileptic drugs on the reproductive health of females with epilepsy.

### Study Cohorts

Five hundred females of reproductive age 16-45 years were selected randomly in the cohort study. Only females diagnosed with epilepsy based on a combination of clinical, electro-neurophysiological, and neuroimaging data were included in this study. The criterion for age-related selection was the exclusion of reproductive life cycle progression (up to the age of 16) and decline (after 45 years) of the reproductive life cycle in females. The method of retrospective epidemiological analysis was used. For 155 females, the age at epilepsy onset was ascertained by the method for recording and analyzing anamnestic data and medical records. In accordance with the age of epilepsy onset, patients were divided into 3 groups: the first group included females with epilepsy onset before puberty, the second group included females during puberty, and the third group included females after puberty. In the second phase of the study, females of the second group with the onset of epilepsy in puberty were divided into 4 subgroups according to the age at the onset of this disease: subgroup A:10-11 years old, subgroup B:12-14 years old, subgroup C:15-16 years old, and subgroup D:16-18 years old. A correlation analysis of the frequency of epilepsy onset and reproductive life function was conducted.

The Ethics Committee of Almazov National Medical Research Centre approved this study on 22.04.2022 under the number 2304-22. All patients signed a consent form.

### Statistical Analysis

The clinical evidence obtained in the research process was handled using the statistical 8.0 medical software system (StatSoft, Inc, USA). Quantitative comparison of parameters in the groups was accomplished using the Wilcoxon-Mann-Whitney test, Wald chi-squared test, median test, and ANOVA test.

## RESULTS

Based on the age at epilepsy onset and the World Health Organization classification of puberty age periods (1977), the females were distributed into three groups: 23 females of the first group had the onset in pre-adolescence (between the ages of 1 and 10), 92 females of the second group had the onset at adolescence (between the ages 11 and 18), 40 females of the third group had the onset at postadolescence (aged 18 or more). The average age did not correlate reliably when averaging with the first group, 25.1, the second group, 24.6, and the third group, 28.3 (p=0.006) (Table 1).

The duration of epilepsy was 18±1.15 years in the first group, 1.47±0.69 years in the second group, 4.85±0.63 years in the third group, which correlated reliably (p=0.0001). The distribution by epilepsy type was not significantly different between the groups. Generalized epilepsy was diagnosed in 35% of female sand focal epilepsy in 65% of females. The dominance of focal epilepsy with a predominance of the temporal lobe among females who received combining antiepileptic drugs was noted, which confirms the predominance of pharmacoresistant forms in the polytherapy group.

The quantitative predominance of epilepsy onset in puberty was identified in the second group, 92 females (59%) (p=0.05). The epilepsy onset in post-puberty was half as many as in the second group (40 females, 26%). The epilepsy onset in pre-puberty in this cohort was even less common, with 23 females (15%), owing in part to the patients with the highest disability rate with epilepsy onset in childhood and their poor social skills in the female reproductive cycles.

Thus, a statistically significant quantitative predominance of females in the second group with epilepsy onset in puberty between the ages 10 and 18 (p=0.001) was identified. In general, epilepsy

**Table 1.** Age profiles of groups

| Group | Valid (n) | Mean age | Error | Minimum age | Maximum age | Median age |
|---|---|---|---|---|---|---|
| 1 | 23 | 25.1 | 1.21 | 16 | 41 | 25 |
| 2 | 92 | 24.6 | 0.63 | 16 | 44 | 25 |
| 3 | 40 | 28.3 | 0.99 | 19 | 45 | 27.5 |

In the combined interval between the ages of 12 and 16 compared with groups between the ages of 10 and 11 as well as of 17 and 18, the differences are significant (p=0.001).

### MAIN POINTS

- Epilepsy onset predominates in childhood in females of reproductive age.
- Provoked seizures occur during puberty and are associated with sex steroid hormones.
- During puberty, epilepsy onset dominates in the combined age range of 12-16 years.
- During periods of the beginning of estradiol production and the development of the peak of estradiol, the proconvulsive effect of estrogen is most pronounced.
- The coincidence of epilepsy onset and menarche increases the risk of catamenial epilepsy and pharmacoresistant epilepsy development.

onset occurred in almost three-quarters of cases in childhood. Only about one-fourth of patients experienced epilepsy onset in post-puberty (Figure 1).

The maturation of the female reproductive system goes through several stages. The development of the hypothalamic-pituitary-ovarian system is a long and complex process. It is in the group with the onset in puberty. In accordance with the classification of this period, an additional clarification of the age of disease onset was carried out in the group of females with epilepsy onset in puberty. The age of disease onset was specified according to the classification of this period. Additionally, females were allocated into 4 subgroups: subgroup A:10-11-year-old females (pre-puberty sub period), subgroup B:12-14-year-old females (beginning of menarche), subgroup C:15-16-year-old females (establishment of a stable ovulatory cycle), subgroup D:16-18-year-old females (sub period of social maturation).[13] Additionally, females were allocated into 4 subgroups: subgroup A:10-11-year-old females (precocious puberty sub period), subgroup B:12-14-year-old females (the first experience of menstrual bleeding), subgroup C:15-16-year-old females (stabilization of ovarian cycle), subgroup D:16-18-year-old females (sub period of social maturation).[13] The study of the onset rate in subgroups of puberty, relevant to the four main periods of maturation of the hypothalamic-pituitary-ovarian system, showed the following frequency distribution. In first place, the onset rate in the second subgroup was 35 females (38%), the onset rate in the third subgroup was second at 24 females (26%), the onset rate in the first subgroup was third at 18 females (20%), and the onset rate in the fourth subgroup was fourth with 15 females (16%). Seizures onset at the age of 12-14 was more often observed statistically significantly than at the age of 10-11 (p=0.01) and 15-16 years (p=0.05). The prevalence of epilepsy onset was statistically significant in the 12-16 combined age range (p=0.001). Thus, the findings showed that hormonal changes that characterize the onset of the menstrual cycle and the formation of ovulatory cycles often trigger epilepsy onset (Figure 2).

The most significant and sensitive period of puberty is menarche, or the first menstrual cycle. In the cohort, the median age of menarche was 13 years, ranging between the ages of 12 and 14. No significant differences in groups reliably varied (p=0.49). There is a direct correlation between epilepsy onset and menarche in the general cohort: it was identified in 13% of females, which refers to risk factors for the formation of catamenial epilepsy. The total catamenial epilepsy in the study group was 32%. This type of epilepsy is typical of females only. Catamenial epilepsy, also known as menstrual seizures, refers to the gender characteristics of female epilepsy. It is a type of gender-based seizure in which seizure onset is closely associated with the menstrual cycle and its specific phases. Sex hormones not only determine epilepsy onset but also affect the frequency of seizures. Sex hormone concentration changes at various stages of the menstrual cycle, thus affecting the course of epilepsy.[14] The dominance of catamenial forms in females with epilepsy during puberty results from the catamenial pattern that emerges when menarche begins.

The disease onset during pregnancy and childbirth was observed in 4 females (3%), with one in a 16-year-old female. Thus, the correlation between epilepsy onset and menarche and changes in the hormonal background during pregnancy and delivery also indicates gender-related profiles of female epilepsy. Thus, the relationship between epilepsy onset and menarche and changes in the hormonal background during pregnancy and delivery reveal the gender traits of female epilepsy.

## DISCUSSION

This research has confirmed the importance of puberty in the onset of epilepsy. The redefined epilepsy on one hand allows the detection of epilepsy earlier and the initiation of treatment, on the other hand, improves the accuracy of diagnostic. Approximately 8-10% of the population experience seizures over the course of their lifetime, but only 2-3% of them further develop epilepsy.[15] In the current circumstances, even the first seizure can be considered by doctors as epilepsy under the new definition: “one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years”.[6] This increases the importance of studying epilepsy onset and conducting epidemiological studies. The main tasks of the epidemiology of non-communicable diseases are: risk group identification, risk of disease to change with time, and identification of risk factors to minimize their subsequent effects.[16] In particular, in cases of female epilepsy, the issues of time and risk factors for disease onset and cause-and-effect relationships in the development of reproductive endocrine complications during polytherapy with antiepileptic drugs are important.[17]

Research directions in epilepsy onset are diverse and multidirectional. The dynamics of health-related quality of life in children who have just been diagnosed with epilepsy are being studied through cognitive, emotional, physical, and functional

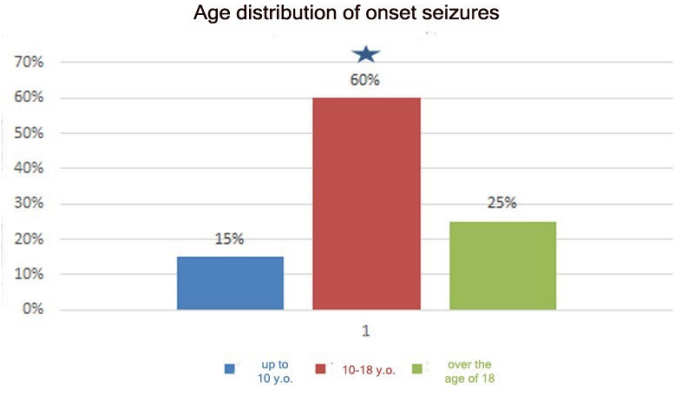


**Figure 1.** Age at seizure onset

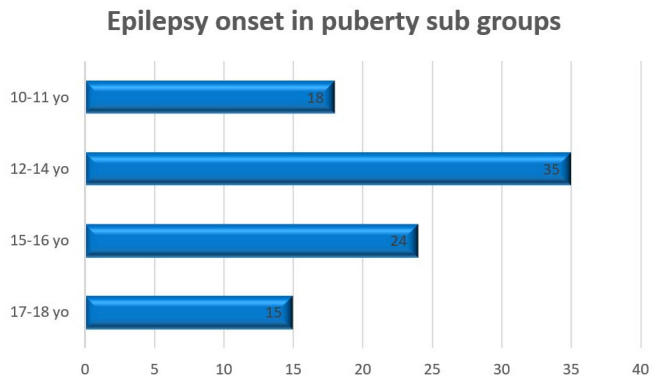


**Figure 2.** Epilepsy onset in puberty subgroups

status assessment.[18,19] A feature of the new classification of epilepsy is the addition of comorbid pathology to the classification structure. According to Kanner, psychiatric comorbidities should be recognized at the time of the initial evaluation of every person with epilepsy, and their treatment needs to be incorporated within the overall therapeutic plan.[20] It remains a huge challenge to make a differential diagnosis of a first-time seizure. Thus, the issues of epilepsy onset are topical and critical with a multi-directional range of research in this area and the prevalent issue of differential diagnosis of the etiology of a first-time seizure. In this regard, the gender features of seizure onset in female epilepsy patients are of particular importance, especially during puberty. The physiological instability of puberty and cycle hormonal imbalance often causes the collapse of mechanisms of antiepileptic protection and disease onset.[7,13]

Reproductive medicine is distinguished based on several anatomical and physiological characteristics of several stages in life: childhood, stages of puberty and sexual maturity, menopause transition, and postmenopausal period (advancing age, senility). The study included females of reproductive age, covering the stages of puberty and sexual maturity. Puberty is the time of hormonal storms that constitute the basis for the rapid development of all major disorders. Gynecologists call adolescence "crystal" in girls. Girls begin puberty at the ages of 10-11. The physiological course of puberty is important for physical and mental development. The period of 16-18 years completes puberty and enters adulthood. It is a flourishing of the functions of female reproductive organs. By the age of 16, in girls with normal sexual development, a stable ovulatory cycle is formed. By this age, delayed sexual development is identified (the first menstrual bleeding doesn't occurs after 15 years). The stage of sexual maturity (after 18 years) is marked by a high level of all specific body functions toward procreation. Puberty is one of the most turbulent years for the female body. Puberty includes a series of stages in the development of the female body at which the maturation of the female reproductive system emerges. This process is accompanied by markers of neuroendocrine and physiological changes in the reproductive system. Most pronounced is during the development of secondary sexual characteristics, the ability to ovulate, menstruate, and achieve fertility. This age is accompanied by intensive hormonal readjustment with an increase in estrogen levels and pronounced proconvulsive activity. In this period, in addition to maturation of the female reproductive system, physical development of the female body is completed, the body builds up, and female-type body fat and fat-free mass (muscle tissue) is distributed.

Puberty and formation of the female body normally have been completed by approximately 17-18 years. Puberty is initiated with a sustained increase in the pulsatile release of gonadotropin-releasing hormone "GnRH" from the hypothalamus, which stimulates the production of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in the pituitary gland. Normally, menarche occurs at the age of 12-14 years. During this period, a stable circhoral (hourly) rhythm of GnRH secretion is established. In response to the rhythmic discharge of the releasing hormone, the release of LH and FSH increases. This process has been ongoing through the consistent inclusion of the links of the hypothalamic-pituitary-ovarian system.

There are several phases of puberty: preadolescence (ages 10 to 12) with an acyclic release of gonadotropins in the hypothalamus, which stimulates the production of LH and FSH hormones in the pituitary gland; the first phase of puberty (ages 12 to 14) with the formation of the rhythm of the release of gonadotropins and increased synthesis of estradiol in the ovaries; the second phase of puberty (ages 15 to 16) with a quantitative increase in ejection and the formation of a cyclic rhythm of gonadotropin release, creating the formation of a positive feedback mechanism. When a certain level of estradiol in the blood is reached, the release of LH and FSH and ovulation occur. The phase of social puberty is characterized by the end of restructuring of the hypothalamic structures that regulate the function of the reproductive system and the establishment of a constant rhythm of hormone secretion[14]. The functional heterogeneity of the phases was clearly confirmed by the data obtained in the second stage of the study. Sex hormones not only determine the onset of epilepsy but also determine the characteristics of female epilepsy. The prognosis of epilepsy in first-time diagnosis becomes evident within a few years after the treatment starts. This study showed that in 13% of epilepsy onset cases, the risk of pharmacoresistance therapy is evident. This risk is characterized by the coincidence of menarche and epilepsy onset. Menstrual or catamenial epilepsy is closely associated with seizures in certain phases of the menstrual cycle. The change in sex hormone concentration at different stages of the period influences disease development. According to the population study results, catamenial epilepsy is observed in 10-72% of cases. Patients with catamenial epilepsy more often accept pharmacoresistant forms, which should be considered in the disease prognosis and antiepileptic treatment prescription. Thus, adolescence is characterized as a risk period for epilepsy development compared with other periods of life. In the female population, it indicates an age-related risk group that is characterized by a higher incidence rate as compared to other age groups. These peculiarities impact disease prognosis, influence treatment plan choice, and indicate the necessity of preventive measures for pharmacosistance development.

### Study Limitations

This is an anamnestic study with a limited sample size.

## CONCLUSION

Epilepsy onset in females of reproductive age dominates in childhood. In more than half of the cases, epilepsy onset is observed at adolescence (ages 10 to 18). In subgroups of puberty, disease onset occurs more frequently between the ages of 12 and 16 during menarche and stabilization of the ovulatory peak, which is explained by the proconvulsive effect of estrogens.

### Ethics

**Ethics Committee Approval:** The Ethics Committee of Almazov National Medical Research Centre approved this study on 22.04.2022 under the number 2304-22.

**Informed Consent:** All patients signed a consent form.

### Authorship Contributions

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

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Original Article

# Relationship Between Medication Adherence and Prospective Memory in Individuals with Epilepsy

Ece Hilal[1], Yağmur Uluhan[1], Serkan Aksu[2], Semai Bek[1], Gülnihal Kutlu[1]

[1]Muğla Sıtkı Koçman University Faculty of Medicine, Department of Neurology, Muğla, Turkey

[2]Muğla Sıtkı Koçman University Faculty of Medicine, Department of Physiology, Muğla, Turkey

Ece Hilal MD

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**Corresponding Author:** Ece Hilal MD, E-mail: 191701713@posta.mu.edu.tr

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## Abstract

**Objective:** Epilepsy is a condition characterized by sudden, recurrent epileptic seizures that occur as a result of abnormal and excessive electrical discharge in cortical neurons and are not triggered by an identifiable event. To date, no study has examined prospective memory and medication adherence in patients with focal and generalized epilepsy. This study aimed to examine medication adherence and prospective memory functions in individuals diagnosed with focal and generalized epilepsy.

**Methods:** In this study, 51 patients diagnosed with focal and 51 with generalized epilepsy at Muğla Sıtkı Koçman University Faculty of Medicine Epilepsy and Sleep Center were included. In addition to the sociodemographic and clinical data forms, participants were administered the Modified Morisky Scale to evaluate medication adherence and the Prospective and Retrospective Memory Questionnaire to evaluate prospective memory function.

**Results:** No difference was found between patients diagnosed with focal epilepsy and those with generalized epilepsy in prospective memory functions and medication adherence. Near-significant correlations were found between medication adherence and memory function.

**Conclusion:** More comprehensive studies evaluating cognitive functions and other parameters related to medication adherence simultaneously are required to clarify the relationship between memory and medication adherence in epilepsy.

**Keywords:** Cognition, epilepsy, medication adherence, memory, neurophysiology

## INTRODUCTION

Epilepsy is a condition characterized by sudden, repetitive, epileptic seizures not triggered by an identifiable event and result from abnormal and excessive electrical discharges in cortical neurons.[1] In addition to seizures, many patients experience seizures or treatment-related cognitive and psychiatric problems. Response to treatment is highly variable. Although numerous treatment modalities are available to control recurrent seizures, including medications, diet, immunotherapy, surgery, and neuromodulation, a large proportion of patients continue to suffer the consequences of uncontrolled seizures, including psychosocial stigma and death.[2] Seizure control can be achieved with antiepileptic treatment in only 60-70% of epileptic patients.[3]

Few studies have directly examined medication adherence in individuals diagnosed with epilepsy. In a study, 27.3% of patients said that they used medication irregularly. The most frequently reported reason for irregular medication use was forgetfulness (48.2%). The cause of forgetfulness is thought to be impairment in at least one cognitive domain. One is prospective memory. Because using the appropriate dose of medication at certain times of the day is an intention formation and implementation activity, it is thought that medication adherence may be related to prospective memory.[4]

Prospective memory is the ability to remember to perform an action intended to be performed in the future and is a complex process that includes various phases and cognitive domains.[5] The relationship between prospective memory and medication adherence has been observed in various neurological diseases such as Huntington's disease (HD).[6] To our knowledge, no study has examined prospective memory and medication adherence in individuals diagnosed with focal and generalized epilepsy. This study aimed to evaluate medication adherence and prospective memory functions in individuals diagnosed with focal and generalized epilepsy.

## METHODS

### Participants

Fifty-one focal epilepsy and 51 generalized epilepsy patients who were followed at Muğla Sıtkı Koçman University Faculty of Medicine Epilepsy and Sleep Center were recruited in the study. Muğla Sıtkı Koçman University Local Ethics Committee approval was obtained (decision number: 90, dated: 12/25/2022). Written informed consent was obtained from all participants. In addition to the sociodemographic and clinical data forms, participants were administered the Modified Morisky Scale to evaluate medication adherence and the Prospective and Retrospective Memory Questionnaire to evaluate prospective memory function.

### Measures

### Prospective and Retrospective Memory Questionnaire

It was developed by Smith et al.[7] and Turkish validity and reliability studies were conducted by Cinan and Doğan.[8] The scale, which consists of eight questions for each part, evaluates prospective and retrospective memory functions separately in daily life.[8] Among the activities evaluated are activities planned to be done, words spoken, places visited, things watched on television, people to call and appointments.

### Modified Morisky Scale

The scale was initially developed as four questions and modified by adding two new items: collecting "yes" or "no" responses.[9] In the second and fifth questions, "yes" is added as one point, and in the others, "no" is added as one point. If the total score from Questions 1, 2, and 6 is 0 or 1, it indicates a low motivation level; >1 indicates a high motivation level. If the total score obtained from questions 3,4 and 5 is 0 or 1, it indicates a low level of knowledge, and if >1, it indicates a high level of knowledge. A validity and reliability study of the scale recommended for use in evaluating adherence to long-term medication use in chronic diseases in primary care was conducted.[8] The content of the scale includes situations such as whether the drug is taken or not, timing, motivation for use, expected benefits, and tracking of the time of supply of the drug.

### Statistical Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) 25.0 (IBM SPSS Statistics, Armonk, New York State, USA). The suitability of the data for normal distribution was evaluated using Shapiro-Wilk tests. It was observed that the variables did not comply with the normal distribution. Therefore, differences between groups were examined using the Mann-Whitney U test. Spearman correlation analyses were performed between the parameters.

**MAIN POINTS**

- Cognitive disorders, including memory deficits, are common in epilepsy.
- Focal and generalized epilepsy did not differ in prospective memory.
- No significant relationship between mediation adherence and prospective memory was observed.

## RESULTS

The sociodemographic data of the participants are shown in Table 1. The sample consisted of 43 male and 59 female participants. Half of the participants were in the generalized epilepsy group and the other half were in the focal epilepsy group. The mean age was 32.03 (±10.79) years and the mean disease duration was 14.06 (±10.31) years. There was no difference between the groups regarding gender and disease duration. Age was slightly higher in the focal epilepsy group (p=0.048).

The memory functions and medication adherence levels of the participants are shown in Table 2. In Mann-Whitney U tests, no differences were observed between the focal and generalized epilepsy groups in terms of Prospective Memory Questionnaire scores (p=0.928), Retrospective Memory Questionnaire scores (p=0.765), and Modified Morisky Scale scores (p=0.564). Spearman correlation tests revealed near-significant correlations between medication adherence and prospective (r=0.178; p=0.073) and retrospective (r=0.186; p=0.061) memory functions.

## DISCUSSION

Prospective memory is the part of episodic memory that involves the formation, maintenance, and execution of intentions about the future.[10] It has been defined as the cognitive ability that allows remembering to perform an activity in the future[11] or fulfilling postponed intentions[12] without a direct and explicit cue. It is a memory for actions to be performed in the future.[13] It means remembering to something we plan to do when the correct time comes and putting it into action. In prospective memory, the decision to perform the intended action is activated by the person himself; that is, he remembers it and performs the relevant behavior, without a clear external reminder, when the targeted event occurs or the specified time ends. For example, a person receives a phone call during an important task; then, he says he is not available at all at that time and he will call back when he is done. It is through prospective memory that a person remembers and fulfills his or her plan or intention when he or she is available to call.[14]

Although memory is a frequently examined subject of study in the field of psychology, studies mostly focus on retrospective memory, whereas prospective memory, that is, the ability to remember what a person will do, is scantily studied. However, memory complaints in people's daily lives largely arise from situations caused by prospective memory difficulties, and a good prospective memory skill is an important condition for living an effective life. Individuals who are admitted to neurology clinics with memory complaints complain of difficulties related to prospective memory deficits, such as forgetting to turn off the stove, forgetting to take the keys from the door after opening the door of their house, and forgetting an appointment they had made.[15]

The finding of near-significant correlations between medication adherence and memory functions in our study is partially compatible with other disease studies in the literature showing this relationship. HD is one of these diseases. Individuals with HD received much lower scores on performance-based prospective memory tests than those in the control group. Prospective memory dysfunction negatively affects the daily lives of individuals diagnosed with HD.[6] In line with the results shown in the HD study,

**Table 1.** Comparison of the demographic and clinical data of focal and generalized epilepsy groups

| | Focal epilepsy (n=51) | Generalized epilepsy (n=51) | Total (n=102) | p values |
|---|---|---|---|---|
| Age (years) | 30.00 (16.00) | 27.00 (15.00) | 28.00 (16.25) | **0.048** |
| Gender (male rate) | 47.10 | 37.30 | 42.30 | 0.211* |
| Disease duration (years) | 9.00 (15.00) | 12.00 (12.00) | 11.00 (12.50) | 0.604 |

Medians (interquartile ranges) and p values of the Mann-Whitney U tests are shown. Significant p values are in bold. *Chi-square test

**Table 2.** Comparison of memory functions and medication adherence between the focal and generalized epilepsy groups

| | Focal epilepsy (n=51) | Generalized epilepsy (n=51) | Total (n=102) | p values |
|---|---|---|---|---|
| Prospective memory (score) | 17.00 (9.00) | 17.00 (12.00) | 17.00 (10.00) | 0.928 |
| Retrospective memory (score) | 16.00 (8.00) | 17.00 (9.00) | 16.50 (8.25) | 0.765 |
| Medication adherence (score) | 2.00 (0.00) | 2.00 (2.00) | 2.00 (2.00) | 0.564 |

Medians (interquartile ranges) and p values of the Mann-Whitney U tests are shown

it was considered that the deficits of prospective memory caused the weakening of daily living activities. One of these activities is medication adherence.

Persistent cognitive deficits are observed in individuals diagnosed with epilepsy for many reasons, such as seizures and drug adverse effects. Many studies have shown that the most frequently and severely affected cognitive domain is memory[16] almost all types of memory are affected in epilepsy, such as semantic and autobiographical episodic memory, verbal and spatial working memory, and object location memory.[16] Moreover, executive function disorders are frequently observed in individuals diagnosed with epilepsy. Executive function and working memory deficits are closely related to prospective memory impairment.[17] However, prospective memory has not been examined in individuals previously diagnosed with epilepsy. Contrary to the hypothesis put forward in the current study, no difference was found between individuals diagnosed with focal and generalized epilepsy in terms of prospective memory functions and medication adherence. Similarly, in a study with a small sample, no difference was found in cognitive functions between focal and generalized epilepsies.[18] In addition, no significant relationship was found between prospective memory functions and medication adherence. This situation may depend on many factors such as epilepsy type, disease duration, and severity. In addition, although the assessment tool evaluated the effect of prospective memory on daily functionality, it did not examine sensitive changes related to prospective memory function. It was considered that these situations also contributed to the obtained results.

### Study Limitations

Limitations of the study include the fact that it was conducted on a relatively small sample, that a measurement tool that evaluates prospective memory more precisely was not used, and that tests examining other cognitive functions related to prospective memory, such as executive functions and working memory, were not evaluated.

## CONCLUSION

Focal and generalized epilepsy groups may not differ in terms of memory function and medication adherence. It was considered that this difference may be detected in examinations performed with more sensitive evaluation tools. To clarify the relationship between memory and medication adherence in epilepsy, more comprehensive studies are needed in which other cognitive functions and other parameters related to medication adherence are evaluated simultaneously.

### Ethics

**Ethics Committee Approval:** The Ethics Committee of Muğla Sıtkı Koçman University approved this cross-sectional study (decision no: 90, dated: 12/25/2022).

**Informed Consent:** Written informed consent forms were obtained from all patients.

### Authorship Contributions

Surgical and Medical Practices: E.H., Concept: G.K., Design: S.B., G.K., Data Collection or Processing: E.H., Y.U., S.B., G.K., Analysis or Interpretation: E.H., S.A., Literature Search: E.H., Y.U., S.A., Writing: E.H., S.B., G.K.

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# Seeing Clowns with a Ring 20 Chromosome

Haşim Gezegen[1], İrem İlgezdi Kaya[1], Tuğba Kalaycı[2], Nermin Görkem Şirin[1], Birsen Karaman[2,3], Nerses Bebek[1], Betül Baykan[1,4]

[1]İstanbul University, İstanbul Faculty of Medicine, Department of Neurology, İstanbul, Turkey
[2]İstanbul University, İstanbul Faculty of Medicine, Department of Medical Genetics, İstanbul, Turkey
[3]İstanbul University, Child Health Institute, Department of Pediatric Basic Sciences, İstanbul, Turkey
[4]EMAR Medical Center, İstanbul, Turkey

Haşim Gezegen MD

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**Corresponding Author:** Haşim Gezegen MD, E-mail: hasimgezegen@hotmail.com
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**Abstract**

Ring chromosome 20 syndrome is a rare genetic disorder characterized by non-convulsive status epilepticus (NCSE) attacks, leading to prolonged confusional states of varying intensity. It is often accompanied by electroencephalography (EEG) changes, such as long-lasting slow waves and occasional spikes, primarily over the frontal lobes, as well as focal seizures with visual hallucinations, cognitive impairment, and behavioral problems. Although clinical suspicion, typical EEG abnormalities, and network disorders revealed by functional neuroimaging method aid in diagnosis, karyotyping remains essential. Seizures are typically drug-resistant although some limited success has been reported with certain anti-seizure drugs. In this report, we present the case of a patient with previously frequent drug-resistant NCSE periods characterized by prolonged confusional states and frightening visual hallucinations. Treatment with lacosamide partially decreased the frequency of seizures. In addition, positron emission tomography/computed tomography (PET/CT) imaging revealed hypometabolism in the frontal and parietal regions of the brain. In patients with drug-resistant and early frightening hallucinations, consideration of the ring 20 chromosome anomaly is crucial. PET/CT imaging may demonstrate hypometabolism in the parietal and frontal lobes, potentially associated with the hallucinations and epileptogenesis of the syndrome. Lacosamide may be a viable option for reducing seizures in Ring chromosome 20 syndrome.

**Keywords:** Non-convulsive status epilepticus, visual hallucinations, drug-resistance, karyotyping, ring 20, lacosamide

## INTRODUCTION

Ring chromosomes (RCs) are rare genetic disorders caused by intrachromosomal fusion. Among RCs, the ring 20 chromosome [r(20)] has attracted special interest because of its distinct electroclinic features, first reported in 1972.[1] The r(20) syndrome is characterized by focal seizures accompanied by visual hallucinations, prolonged confusional states, and cognitive and behavioral problems, which typically begin in childhood. Non-convulsive status epilepticus (NCSE) attacks are frequently observed. The r(20) chromosome is usually found in a mosaic state, and its specific diagnosis is made by karyotyping. While conventional cranial magnetic resonance imaging (MRI) usually does not detect any structural pathology, functional neuroimaging methods such as single photon emission computed tomography (SPECT), positron emission tomography/computed tomography (PET/CT), and fMRI have shown dysfunction in specific brain areas. In this report, we present the case of a patient with r(20) syndrome who experienced NCSE and vivid visual hallucinations, along with neuroimaging results, to raise awareness about this rare disorder.[2]

## CASE PRESENTATIONS

A 19-year-old male patient was admitted with frequent seizures and attention problems. At the age of six, he started experiencing hypermotor seizures, followed by rare generalized tonic-clonic seizures. The frequency of seizures decreased with oxcarbazepine. Before the seizures, he described complex visual hallucinations, often featuring a scary clown. At the age of nine, he began experiencing periods of staring and decreased responsiveness, lasting up to 45 min and occurring 5-6 times a day.

Despite administering various anti-seizure drug treatments, including levetiracetam, zonisamide, lamotrigine, carbamazepine, valproate, topiramate, ethosuximide, and clobazam, at appropriate doses and durations, seizure control could not be achieved. At the time of admission, the patient was taking valproate 2000 mg/day and zonisamide 300 mg/day. Neurological examination revealed normal findings, except for decreased time orientation and mild cognitive retardation. The patient's medical history was unremarkable, but a distant relative on the paternal side had been diagnosed with late-onset epilepsy.

Routine laboratory tests and cranial MRI results were normal. Electroencephalography (EEG) showed diffuse slowing of background activity, sharply contoured theta activity in the anterior part of the hemispheres (Figure 1a), and generalized epileptiform abnormality interictally, along with atypical absence seizures accompanied by perioral myoclonia (Figure 1b). In addition, generalized 3-7 Hz fluctuating slow wave periods were prominent in the anterior regions, lasting 45-60 min, which were evaluated as NCSE (Figure 1c). A brain PET/CT scan revealed mild hypometabolism in the left prefrontal and bilateral parietal inferior regions (Figure 2).

Karyotype analysis from peripheral blood lymphocytes showed mos45, XY, 20/46,XY/46,XY,r(20)(p13q13.32)[4/35/51].ish r(20)(pterqter)(D20S210+/RH1656+). FISH analysis using subtelomere-specific probes for the p and q arms of chromosome 20 (Cytocell, Cambridge, UK) demonstrated the presence of both subtelomeres in r(20). A microarray study found no genomic imbalance. In 57% (51 of 90 metaphases) of cells, it was confirmed that one of the normal chromosomes of 20 was replaced by a r(20) with no genomic imbalance, establishing the diagnosis of mosaic r(20) chromosome (Figure 2). The absence of chromosome 20 in 4% of cells (4 of 90 metaphases) in the patient was considered a result of the unstable status of RCs and their tendency to be lost in dividing cells.[1] Parental karyotype analyses were performed to rule out mosaic-to-mosaic transmission, and normal results were obtained for the parents.

After initiating lacosamide treatment, the patient experienced a notable improvement in his condition. Focal seizures with visual hallucinations ceased, and the duration and frequency of NCSE decreased significantly, nearly by half. This positive outcome was achieved through the combination of lacosamide 300 mg/day, valproate 2000 mg/day, and zonisamide 300 mg/day. In addition, cognitive evaluation revealed an improvement in reaction time, indicating a positive impact on cognitive function.

## DISCUSSION

In this report, we present the case of a patient diagnosed with r(20) syndrome who exhibited drug-resistant NCSE and focal seizures with frightening visual hallucinations. However, with the introduction of lacosamide treatment, there was a significant reduction in both the frequency and intensity of these seizures. In addition, PET/CT imaging revealed hypometabolism in the frontal and parietal regions of the brain. These findings provide valuable insights into the potential therapeutic efficacy of lacosamide and the underlying neurobiological mechanisms associated with r(20) syndrome.

**MAIN POINTS**

- r(20) syndrome is characterized by non-convulsive status epilepticus attacks, long-lasting atypical absence seizures, and focal seizures with visual hallucinations.
- The specific diagnosis for r(20) chromosome is karyotyping.
- Electroencephalography and functional imaging studies suggest r(20) syndrome relates to frontal lobe network failure rather than a specific epileptogenic region.
- Lacosamide can be an alternative anti-seizure medication for non-convulsive status epilepticus related to the r(20) syndrome.

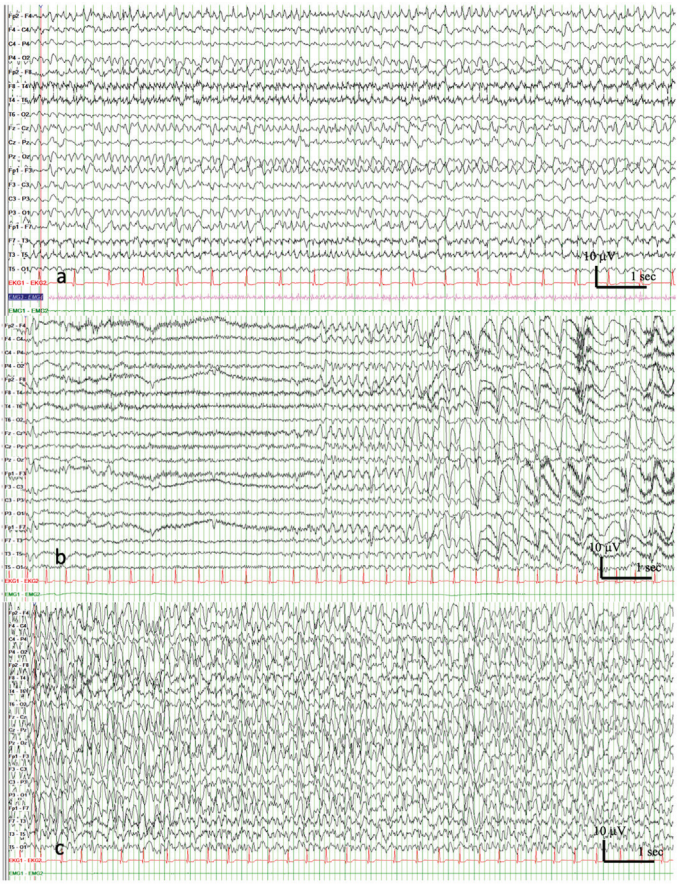


**Figure 1.** In electroencephalography (high pass filter 0.5 Hz, low pass filter 70 Hz, bipolar longitudinal montage). a) The sharply contoured theta activity prominent in the anterior part of the hemispheres interictally. b) Generalized 2.5 Hz spike and waves after evolution of 10-11 Hz fast rhythmic activity with the atypical absence seizure. c) Generalized 3-7 Hz fluctuating slow wave periods prominent in the anterior parts of the hemispheres, associated with the prolonged confusional state

### Epidemiological Characteristics of r(20)

RCs are estimated to be in between 30,000 and 60,000 live births annually.[3] To date, there have been 200 documented cases of ring 20 chromosomes in the literature. In r(20) syndrome, the typical age of seizure onset is seven years.[2] In this study, the r(20) rate was 57%, and seizures started at the age of six years.

### Seizure Types and Their Relationship to Mosaicism

In the literature, it has been observed that epilepsy in patients with ring chromosome 20 syndrome follows an age- and mosaicism-dependent course. The severity of cognitive impairment and the

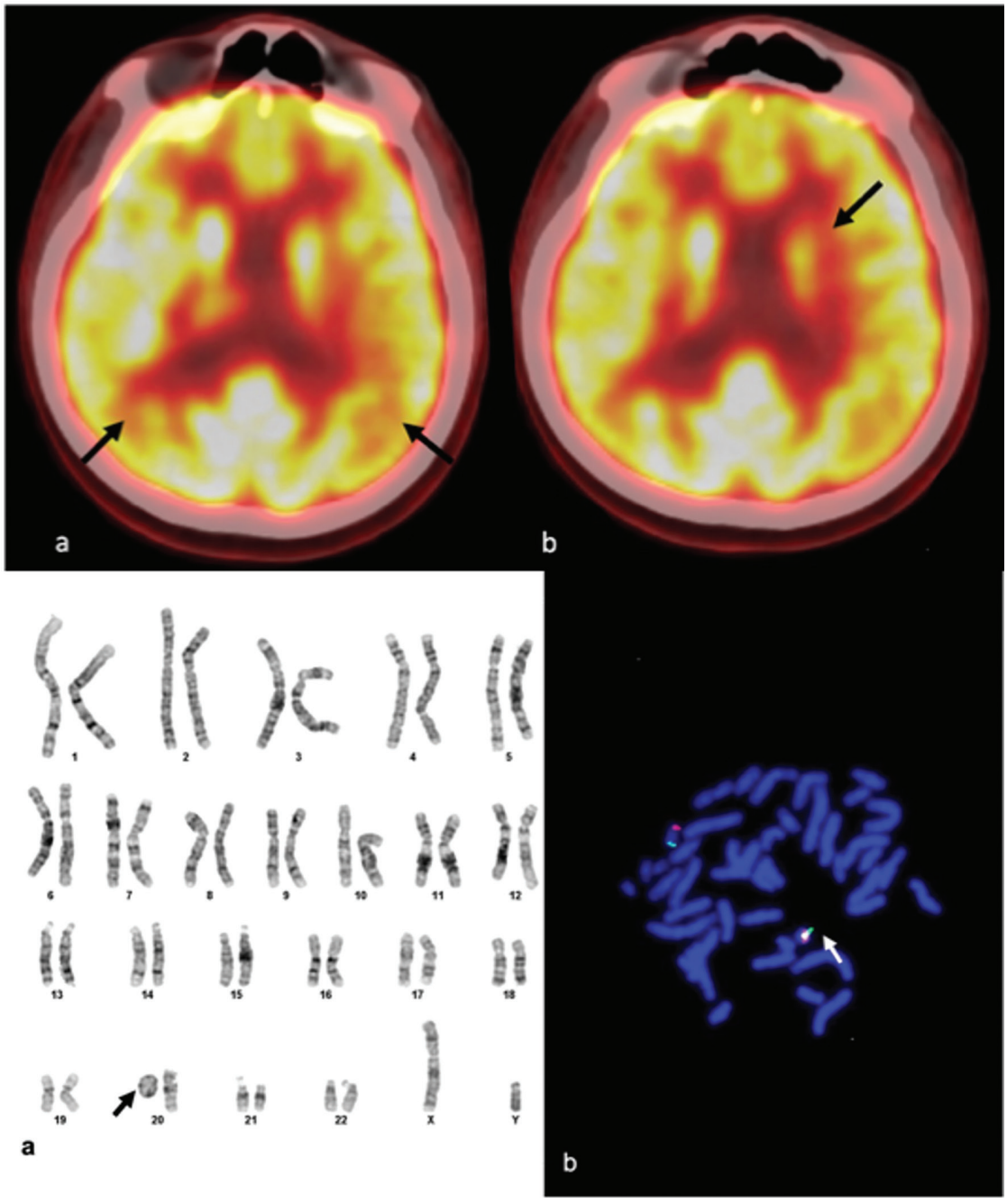


**Figure 2.** Upper image: a) Mild hypometabolism in the right and left parietal inferior, b) left prefrontal area in PET/CT examination (arrows).
Lower image: a) R(20) chromosome in karyotype analysis (black arrow) b) FISH image using a subtelomeric probe specific to the p and q arms of the 20$^{th}$ chromosome (white arrow)
PET/CT: Positron emission tomography/computed tomography

presence of r(20) mosaicism seem to be directly related, whereas they show an inverse correlation with the age of epilepsy onset. Non-mosaic patients tend to experience earlier seizures than mosaic patients.[2] In a study, the age at seizure onset was significantly lower in non-mosaic patients (median age of 2.1 years) than in mosaic patients (median age of 6.0 years). Furthermore, it was noted that males tend to develop epilepsy approximately 2 years earlier than females.[1,3]

When seizure onset occurs in childhood, patients often exhibit terrifying hallucinations along with focal motor seizures, which frequently occur during sleep. These prominent features can evolve into epileptic encephalopathy associated with NCSE. On the other hand, epilepsy onset during adolescence is often accompanied by a milder course without significant cognitive decline. Regrettably, less than 10% of patients achieve seizure freedom.[4] These findings demonstrate the complex and variable nature of ring chromosome 20 syndrome, with diverse clinical presentations and outcomes depending on patient age, mosaicism, and gender.

Our patient experienced nocturnal seizures characterized by waking up, staring, and mild tonic stiffening of the face and

extremities at the age of 6 years. These seizure manifestations align with the description of nocturnal hypermotor seizures in the literature.[3] During some of these episodes, the patient experienced terrifying hallucinations. It is worth noting that the sudden onset of fear during seizures and horrifying hallucinations were reported as early clinical signs, and in up to 25% of cases, they were evaluated as auras before the onset of the actual seizures.[5] This highlights the importance of recognizing these symptoms as they may provide valuable insights for early diagnosis and management of the condition.

NCSE is characterized by unresponsiveness, staring, confusion, and may include oral or motor automatisms, a frightened expression, and focal motor symptoms. These episodes comprise prolonged confusional states of varying intensity.[6] Our patient also exhibited periods of staring and decreased responsiveness, lasting up to 45 min and occurring daily. Some of these prolonged confusional states were accompanied by perioral myocloni. When evaluated using ictal EEG, these episodes were identified as another clinical feature of prolonged NCSE, distinguishable from those observed in idiopathic generalized epilepsy syndrome with perioral myoclonia. This distinctive presentation highlights the importance of careful evaluation and differentiation to accurately diagnose and manage the patient's condition.

### EEG Findings

Interictal EEG typically shows slowed background activity and epileptic activity in the frontal lobes in r(20) syndrome. The focal epileptiform EEG findings observed since childhood in our patient indicated that visual hallucinations may be related to focal seizures. In our patient, we also observed interictal discharges with a frequency of 3-7 Hz in the anterior halves of the hemispheres, previously described as the "ring 20 rhythm".[6]

### Pathophysiology

It has been suggested that the "primary visual cortex", the region where visual information is primarily processed, is responsible for "elementary" visual hallucinations, whereas "complex" visual hallucinations result from the inappropriate interpretation of perceptions due to dysfunction in the "Dorsal Attention Network" (DAN). The DAN consists of neural networks within the frontal eye areas, the dorsolateral prefrontal and posterior parietal cortex, and certain areas of the striatum.[7] Additionally, limbic structures are also activated due to the strong emotional components of complex visual hallucinations, as seen in our patient expressing immense fear after seeing the clown images.[8]

Interictal and ictal SPECT and PET/CT studies associated with ring 20 chromosome patients' seizures revealed a reduction in bilateral frontotemporal cortical perfusion and metabolism. In individuals with r(20) syndrome, Vaudano et al.[6] found cortical correlations between the blood oxygen level-dependent signal at bilateral sensory-motor and temporoparietal cortices and slow-wave activity. The decline in default mode network and DAN activity was more significant with higher manifestation of this slow-wave activity.[5] Group-level data analysis of interictal fMRI studies demonstrated the involvement of a complex frontal network, including the prefrontal, opercular-insular, and bilateral temporoparietal cortex in these seizures.[9]

Data obtained from EEG and hemodynamic imaging studies support the idea that r(20) syndrome is related to frontal lobe-associated network failure rather than a specific localized frontal cortical epileptogenic region.

### Treatment

Although seizures in r(20) chromosome syndrome and NCSEs are typically drug resistant, some anti-seizure drugs such as valproate, lamotrigine, ezogabine, or their combinations have been reported to be beneficial in some individuals.[2] Lacosamide reduced the frequency of seizures by 50% in our patient, despite using many anti-seizure medications previously. Lacosamide treatment has been shown to reduce seizures, and this effect is attributed to the enhancement of the slow inactivation of voltage-gated sodium channels without affecting the fast component.[10,11]

## CONCLUSION

The presence of the ring 20 chromosome anomaly should be considered when encountering patients with frequent and drug-resistant NCSE and early frightening hallucinations, as observed in our patient. These hallucinations may be associated with hypometabolism in the parietal and frontal brain regions, as detected on PET/CT imaging. Although seizures in this rare genetic disorder are typically treatment-resistant, lacosamide could be considered as an option to reduce the frequency of seizures in these cases. This highlights the importance of early recognition and appropriate management for improved outcomes in patients with ring 20 chromosome syndrome.

### Ethics

**Informed Consent:** Written informed consent, including permission for publication, was obtained from the patient and his/her family.

### Authorship Contributions

Surgical and Medical Practices: İ.İ.K., N.G.Ş., B.K., N.B., Concept: H.G., N.G.Ş., N.B., B.B., Design: H.G., İ.İ.K., T.K., B.B., Data Collection or Processing: H.G., İ.İ.K., T.K., N.G.Ş., Analysis or Interpretation: H.G., B.K., Literature Search: H.G., İ.İ.K., Writing: H.G., İ.İ.K., T.K., B.K., B.B.

**Conflict of Interest:** No conflicts of interest were declared by the authors.

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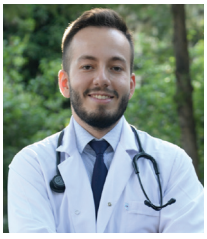
Archives of Epilepsy

Case Report

# A Case of LGI1 Encephalitis Presenting with NORSE

Gökberk Metin, Özden Kamışlı

Bursa City Hospital Department of Neurology, University of Health Sciences, Bursa, Turkey



Gökberk Metin MD

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**Corresponding Author:** Gökberk Metin MD, E-mail: gkbrk.mtn@hotmail.com

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**Abstract**

New-onset refractory status epilepticus (NORSE) is a rare, life-threatening clinical presentation in patients without a known history of epileptic seizures. Autoimmune encephalitis is the most common cause identified in adults; however, in up to 50% of cases, no cause can be found. We present a case of a previously healthy 26-year-old male admitted to the intensive care medicine with NORSE, whose condition improved with the initiation of immunotherapy. Later, he was diagnosed with anti-leucine-rich glioma-inactivated 1 (anti-LGI1) antibody encephalitis. Despite prompt initiation of immunotherapy, cognitive function deterioration and resistant seizures persisted. NORSE is a critical condition that requires urgent treatment. In patients with a negative initial work-up, a preliminary diagnosis of autoimmune encephalitis should be considered. It is critical to begin immunotherapy before the autoimmune encephalitis panel results, as early treatment improves outcomes and long-term prognosis.

**Keywords:** Antibody, autoimmune, encephalitis, leucine-rich glioma-inactivated 1, LGI1, neuroimmunology, neurology, norse, status epilepticus

## INTRODUCTION

New-onset refractory status epilepticus (NORSE) is a rare but life-threatening condition. NORSE is defined as refractory status epilepticus (SE) that occurs without a known history of epilepsy and without a structural, toxic, or metabolic cause.[1]

NORSE has been reported at all ages, although it is more common in healthy young adults.[2] Although its incidence is not fully known, it is believed to constitute approximately 20% of refractory SE cases.[3] In approximately half of adult NORSE cases, the underlying cause in the etiology has not been identified, and sporadic or paraneoplastic/autoimmune encephalitis constitutes most identified causes.[2,3] In addition, rarer infectious encephalitis, genetic disorders, and toxic causes have also been reported.[4] N-methyl-D-aspartate (NMDA) receptor antibodies and voltage-gated potassium channel (VGKC) antibodies have been detected most frequently among patients with autoimmune encephalitis.[2] In this article, we present the case of a patient without a history of seizure before, who applied to our hospital with NORSE and was diagnosed with leucine-rich glioma-inactivated 1 (LGI1) encephalitis and then followed up with refractory epilepsy.

## CASE PRESENTATIONS

A 26-year-old male patient with no pre-existing disease was admitted to the emergency department with a generalized tonic-clonic (GTC) seizure. Because he had a 4 GTC seizure on the same day that he did not regain consciousness, he was accepted as SE and admitted to the intensive care unit (ICU) of a different center. He had no known disease in his history; however, he had a history of upper respiratory tract infection a week ago. No smoking, alcohol, or substance use. No abnormality was found in routine blood tests, except for a slight elevated creatine kinase level. The biochemistry of the cerebrospinal fluid (CSF) of the patient was normal. No cells were observed by CSF microscopy. CSF brucella, ARB, herpes simplex virus, mycoplasma, Epstein-Barr virus, cytomegalovirus, toxoplasma, and rubella IgM tests were negative. Severe acute respiratory syndrome coronavirus 2 was also negative. When the seizures could not be controlled despite valproic acid and phenytoin loading, midazolam infusion was initiated. In addition, acyclovir was started with the preliminary diagnosis of viral encephalitis. In brain magnetic resonance imaging (MRI), T2 hyperintensity with edematous signal intensity was detected in both parahippocampal areas (predominantly in right temporal lobe); these lesions showed contrast enhancement in T1-post gadolinium MRI (Figure 1). The patient, whose seizures continued despite antiviral and anti-seizure treatments and anesthetic agents, was referred to our hospital for further examination and treatment. Immunotherapy was planned for the patient by considering possible autoimmune encephalitis. He was admitted to the ICU of our hospital, and an autoimmune encephalitis panel was sent. Pentothal infusion and intravenous immunoglobulin (IVIG) treatment at 2 g/kg for 5 days were administered. After the completion of IVIG treatment, seizures lasted, and the patient was extubate after 2 days. Generalized slow wave activity (5-6 Hz) was observed in the EEG (Figure 2). Anti-LGI1 antibody was positive because of the autoimmune encephalitis panel. He was taking levetiracetam 3000 mg/day and valproate 2000 mg/day as

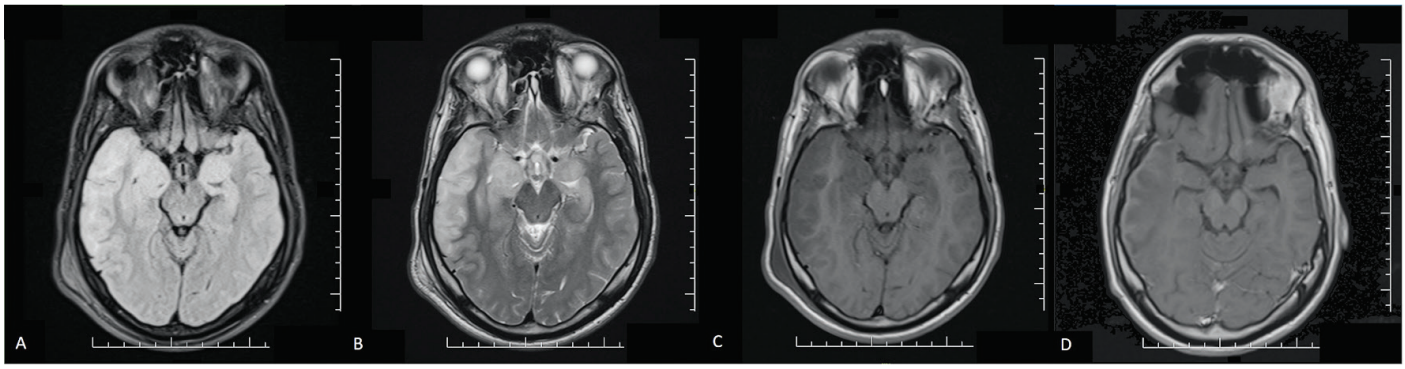


**Figure 1. A-D)** MRI findings of patient
MRI: Magnetic resonance imaging

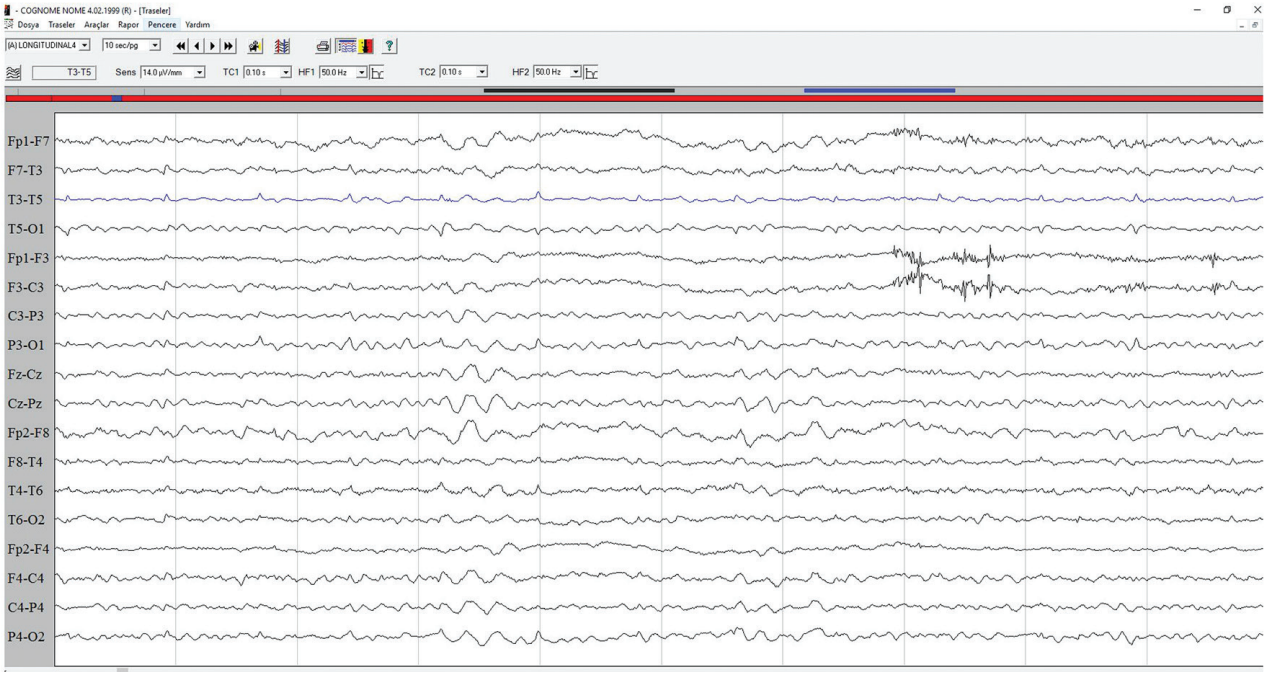


**Figure 2.** EEG of patient
EEG: Electroencephalography

anti-seizure medication. The patient had cognitive impairment and retrograde amnesia. The Montreal Cognitive Assessment (MoCA) test, which was conducted to evaluate cognitive functions, resulted as 18/30. The patient was also administered 1000 mg IV methylprednisolone treatment for 7 days and then continued with oral maintenance therapy. Malignancy screening was performed in terms of paraneoplastic etiology, and no malignancy was detected. The patient was discharged with a monthly single dose (0.4 g/kg) IVIG, oral steroids, and anti-seizure medications. The MoCA test, which was repeated at the 3-month follow-up, was found to be 27/30, but retrograde amnesia was ongoing. Because of the increase in the frequency of seizures and impaired cognition, rituximab treatment was initiated as second-line immunotherapy. Our patient is still being followed up with rituximab treatment, and his cognitive impairment and resistant seizures remain sequelae.

**MAIN POINTS**

- It's important to suspect an autoimmune aetiology in patients with refractory seizures and a negative initial work-up.
- Immune causes of seizures often respond to immunotherapy. However, they are usually resistant to antiseizure medication.
- Treatment shouldn't be delayed in patients with a suspected autoimmune cause, as early treatment can reduce disability.

## DISCUSSION

NORSE is a life-threatening clinical condition defined by a new onset of refractory SE without a known cause or pre-existing neurological disorder. After extensive work-up, if no cause is found to explain the NORSE clinic, cryptogenic NORSE is mentioned and the underlying cause is not found in approximately half of the cases.[1] In the remaining half, autoimmune or paraneoplastic encephalitis is the leading underlying cause. NMDA and VGKC receptor encephalitis (LGI1 and Contactin-associated protein-like 2) are the most common autoimmune encephalitis etiologies.[1,3]

Most patients with LGI1 present with limbic encephalitis. The clinic is characterized by subacute memory, behavioral changes,

and epileptic seizures.[5] The semiological features of seizures seen in LGI1 encephalitis are well defined. Fasciobracial dystonic seizures are typical for LGI1, and they are in the form of numerous (up to hundreds) involuntary contractions lasting 1-2 s per day on the arm and face.[5,6] Early notice of these seizures, early diagnosis, and early initiation of treatment are important in terms of long-term prognosis.[5,7] In our patient, no faciobrachial dystonic seizures were observed; all seizures were GTCS. The highest frequency of SE was reported in NMDA generalized tonic-clonic seizures. encephalitis (27%) in a study investigating the semiology of seizures in autoimmune encephalitis, and in the same study, it was found to be only 6% in LGI1 encephalitis.[8] However, to the best of our knowledge, LGI1 autoimmune encephalitis with NORSE has not been reported in the literature. Hyponatremia, which is frequently reported in cases of anti-LGI1 encephalitis, was not observed in our patient.

The most affected areas in NORSE are unilateral or bilateral limbic and/or neocortical regions, basal ganglia, and periinsular areas.[2] Therefore, when these areas are affected, encephalitis and autoimmune etiology should definitely be considered. In our patient, although it was more prominent on the right side, bilateral temporal lobes and limbic structures were affected, and the preliminary diagnosis was viral encephalitis.

NORSE treatment is an important and urgent condition; treatment of seizures within the first 48 h is the same as acute treatment of refractory SE, and there is a consensus on this issue.[9] There is no specific treatment for NORSE; anti-seizure medications, anesthetics, immunotherapy, and ketogenic diet combinations can be used[4,9], and cases with early or late vagus nerve stimulation implantation have also been reported in resistant cases.[10]

The most important difference in treatment from refractory SE is that corticosteroids, IVIG, and plasma exchange are performed in first-line immunotherapy in NORSE, and it should be started in the first 72 h after the onset of SE.[1,5] If infectious causes are excluded, it is recommended to start immediately in the first 48 h.[5,9] If seizures continue despite first-line immunotherapies, it is necessary to switch to second-line immunotherapies quickly within 1 week after the onset of SE. If infectious causes are excluded, rituximab treatment is also the most commonly used second-line immunotherapy.[5]

Even if the patient recovers in the long-term prognosis, severe memory defects and resistant seizures may remain sequelae.[10,11] Therefore, treatment in the early stage is essential. In our patient, treatment was started in the ICU for 15 days with the diagnosis of refractory SE; however, after immunotherapy, deterioration in cognitive functions and resistant seizures remained sequelae.

## CONCLUSION

In conclusion, autoimmune encephalitis should be considered admitted to the NORSE clinic in patients who present with NORSE, and considering the long-term results, it is important to start immunotherapy before the autoimmune encephalitis panel results. The importance of early treatment in terms of long-term effects should not be ignored.

### Ethics

**Informed Consent:** Written informed consent was obtained from the patient for the case report.

### Authorship Contributions

Surgical and Medical Practices: G.M., Ö.K., Concept: G.M., Design: G.M., Data Collection or Processing: G.M., Analysis or Interpretation: Ö.K., Literature Search: Ö.K., Writing: G.M., Ö.K.

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