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Original Articles

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Original Article

Impact of Valproate and Levetiracetam Exposure on GAERS Behavior During Pregnancy

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Abstract

Objective: Valproate (VPA) and levetiracetam (LEV) are frequently prescribed for the management of idiopathic generalized seizures; however, their well-documented teratogenic effects raise concerns when administered to pregnant epileptic patients. This study aimed to assess the impact of VPA and LEV exposure during pregnancy on Genetic Absence Epilepsy Rats from Strasbourg (GAERS).

Methods: Female GAERS rats were categorized into three groups: saline-treated (n=6), VPA-treated (200 mg/kg, n=4), and LEV-treated (50 mg/kg, n=6). Intraperitoneal injections were initiated from mating start and continued until partition. Locomotor activity and anxiety-like behavior were evaluated using open-field and hole-board tests for the VPA-treated and VPA- and LEV-treated groups; respectively. These tests were conducted both before and during pregnancy.

Results: Across all groups, open-field testing demonstrated a tendency toward reduced locomotor activity parameters compared with pre-pregnancy, with VPA treatment showing significance ($p<0.05$). The hole-board test indicated a trend toward decreased rearing and hole exploration, coupled with increased freezing behavior in the saline- and VPA-treated groups. The LEV-treated group showed an elevation in freezing behavior and a decline in hole exploration.

Conclusion: Although minimal effects on anxiety-like behaviors were noted in anti-seizure drug-treated rats, subtle tendencies were evident in the hole-board test. VPA and LEV administration resulted in depressive parameters in the locomotor activity test. These findings emphasize the need for caution when prescribing and using VPA and the LEV during pregnancy in terms of maternal behavior and mood.

Keywords: GAERS, valproic acid, pregnancy, levetiracetam, maternal behavior

INTRODUCTION

Genetic Absence Epilepsy Rats from Strasbourg (GAERS) is a well-defined and validated animal model that has emerged as a valuable model for investigating the mechanisms underlying absence epilepsy.[1,2] With a genetic predisposition to absence seizures closely resembling those observed in humans, GAERS have provided researchers with a platform to decipher the intricate interplay between genetics, neural circuitry, and behavior, as well as sharing similar vital characteristics with human absence seizures and similar pharmacosensitivity to antiseizure drugs.[3]

Valproate (VPA) and levetiracetam (LEV), the two broad-spectrum antiseizure drugs with antiabsence effects and have high efficacy in managing seizures in epileptic patients,[4] although the effect of the latter has been discussed.[5] VPA is highly teratogenic, especially when administered during the first trimester of pregnancy, and is associated with significant congenital anomalies such as spina bifida, atrial septal defect, and cleft lip-palate. In addition, prenatal exposure to VPA has been linked to cognitive and developmental delays, and some studies suggest an increased risk of autism spectrum disorders in children.[6-11]

Compared with VPA, LEV has been considered to have a relatively safer profile in terms of teratogenic effect.[12-14] While some studies have suggested a slightly increased risk of certain congenital malformations, the overall risk appears to be lower than that associated with

VPA.[15] In particular, recent studies in humans have reported the LEV to be a safer alternative to VPA[16] or lamotrigine for teratogenicity.[17] However, data on the teratogenic effects of LEV are still evolving, and more research is needed to establish a clear understanding of its safety during pregnancy. Our team also showed congenital abnormalities in GAERS rats exposed to both VPA and the LEV in utero.[18] VPA and LEV have also shown ahigher risk of adverse psychobehavioral outcomes in the children of epileptic mothers, as well.[19]

Unlike offspring, there are only few studies addressing maternal behavior during pregnancy. Several studies have reported an increased risk of anxiety and depression in pregnant women taking VPA.[20] LEV might have a positive impact on anxiety-related behaviors measured by the elevated-plus maze test in a specific pathogen- free Sprague-Dawley rat model.[21] Other reports have shown individual anger-, aggression-, or depression-related behavioral outcomes with LEV monotherapy.[22] Recent reports in animals show that VPA induces cannibalistic behavior in mothers.[18,23] Conversely, another study showed that rats exposed to VPA during lactation exhibited extended pup nursing and increased active behaviors at specific postpartum days, whereas those exposed during pregnancy and lactation showed no significant impact on maternal care.[24]

In this study, we hypothesized that exposure to VPA and the LEV during pregnancy affects the behavior of pregnant rats. To investigate the potential impact of prenatal exposure to VPA/LEV on the behavior of pregnant GAERS, we injected pregnant GAERS with VPA or LEV and evaluated their locomotor and anxiety behaviors.

METHODS

Animals and Experimental Design

Female adult GAERS (n=22) were sourced from the breeding colony of the Department of Medical Pharmacology, Marmara University Faculty of Medicine. The animals were housed in a controlled environment at 21±3 °C with a 12-hour light/dark cycle (lights on at 8 am) and provided *ad libitum* access to food and water. Ethical clearance was obtained from the Marmara University Ethical Committee for Experimental Animals (protocol number: 108.2018.mar, date: 03.12.2018), in accordance with Directive 2010/63/EU of the European Parliament and Council.

GAERS were randomized into three groups: saline-treated (n=6), VPA-treated (n=8), and LEV-treated (n=8). Mating cages containing pairs of female rats from the same treatment group and a randomly selected male GAERS were established, with a total of three rats per cage. Twice-daily treatments of saline, VPA, and the LEV were initiated from the first day in the mating cage and continued until parturition.

MAIN POINTS

- This study provides evidence for the effect of levetiracetam (LEV) and valproate (VPA) on altered maternal behavior during pregnancy.
- Increase in freezing behavior and a decrease in hole exploration was observed in Genetic Absence Epilepsy Rats from Strasbourg (GAERS) treated with LEV.
- Locomotor activity parameters were decreased in pregnant GAERS treated with VPA.

Drug Injections

Seizure-controlling doses of VPA (200 mg/kg) and LEV (50 mg/kg) were determined to provide effective control of seizures and were selected based on established efficacy.[1,25] VPA (Depakin, 400 mg/4 mL) or LEV (Keppra, 500 mg/5 mL) were dissolved in 2 mL or diluted with 5 mL of saline (0.9% NaCl) for dose adjustment. Final solutions of saline, VPA (200 mg/mL), or LEV (50 mg/mL) were injected intraperitoneally at a volume of 1 mL/kg body weight according to their respective groups twice daily (at 10 am and 4 pm) to their respective groups, starting from the first day of placement in mating cages and continuing until parturition.

Open Field Test for Locomotor Activity

In these experiments, VPA (200 mg/kg, n=5) treated groups before and after PA injections (7th day) were used, and the experiments were performed at the same daytime slot (09:00-11:00 am). The animals were placed in a 40 × 40 × 40 cm seized open area test apparatus (Locomotor Activity Cage ACT 508, Commat, Ankara, Turkey) with an animal exposure of 150 lux light. The system was equipped with infrared photocells and integrated Activity Metering Software II version 2.1, in which the location of the test animal was recorded with an accuracy of 100 ms. The total distance and stereotypic activity of rats were evaluated. All parameters were calculated automatically by the program. The activities of grooming, chewing, gnawing, sniffing, orofacial movements, vibrissae twitching, and head weaving were classified as stereotypic activities.

Hole-Board Test

The hole-board test was performed on female GAERS treated with saline (n=6), VPA (200 mg/kg, n=4) and the third with LEV (50 mg/kg, n=6). The test was performed before the injections, during pregnancy, and post-term. The hole-board apparatus employed an enclosed wooden board measuring 40 × 40 × 40 cm, featuring 16 equally spaced cylindrical holes with a diameter of 3.8 cm. Each trial spanned a duration of 5 min, starting with the placement of the subject at the center of the board. A video camera positioned above the apparatus mounted on a tripod recorded the trials. Subsequently, two observers analyzed the 5-minute footage of each subject. Parameters, including head dipping frequency, rearing instances, and freezing time were quantified.

In this context, 'head dipping behavior' referred to instances where the animal inserted its head into a hole to a depth such that the subject's eyes were level with or below the hole-board apparatus floor. The term 'freezing time' denoted periods when no movement of the body or head was observed. Rearing was noted when the rat elevated itself onto its hind legs, with the forepaws either supported or unsupported by the walls. A decrease in head dipping frequency and rearing instances, coupled with an increase in freezing time, were interpreted as indicators of reduced exploratory behavior linked to heightened anxiety levels.[26,27]

Statistical Analysis

All statistical analyzes were performed using GraphPad Prism version 8.00 (GraphPad Software, San Diego, USA). Statistical analysis of locomotor activity in the VPA-treated groups before and after injections. Unpaired t-tests were used to analyze stereotypic, ambulatory, vertical, and horizontal activities. To compare

rearing, hole exploring, and increase in freezing behavior between female GAERS treated with saline (n=6), VPA (200 mg/kg, n=4) and with LEV (50 mg/kg, n=6, before the injections, during the pregnancy and post-term two-way ANOVA design with 2 factors "time" and "treatment" followed by the Tukey's test, was used. For the comparison of the three treatment groups, with 2 factors "treatment" (3 levels: saline, VPA and LEV) and "Injections" (3 levels: before injection, during pregnancy and post-term) were applied. The data are represented as t(df)=t-value, p=p-value for t-tests and "F(DFn, DFd)=F value, p value" for two-way ANOVA with $p<0.05$ significant difference.

RESULTS

Effect of Acute Injection of VPA on the Locomotor Activity Parameters of Pregnant GAERS

The stereotypic, ambulatory, vertical, and horizontal activity of GAERS before and after injections of VPA were compared for a duration of 5 min. There were significant differences in the stereotypic, vertical, and horizontal activity parameters. For the stereotypic activity t(10)=4.46, p=0.001 (Figure 1A), for the vertical activity t(10)=8.39, $p<0.0001$ (Figure 1C), and for the horizontal activity is t(10)=4.59, p=0.001 (Figure 1D). Although there were no significant differences for the ambulatory activity, the p value was 0.057 and t(10)=2.15 (Figure 1B).

There were also significant differences in the resting behavior and total distance taken by pregnant GAERS. For the resting behavior t(10)=2.4, p=0.03 (Figure 1E) and for the total distance; t(10)=3.07, p=0.01 (Figure 1F).

Effect of Acute Injection of VPA and the LEV on the Rearing Behavior, Head Dipping Frequency, and Freezing Behavior of Pregnant GAERS

The rearing behavior of female GAERS treated with saline (n=6), VPA (200 mg/kg, n=4) and with LEV (50 mg/kg, n=6), before the injections, during pregnancy, and post-term were evaluated. Significant variations in rearing behavior were observed in GAERS rats injected with GAERS during pregnancy, contrasting pre-injection levels [F(2, 16)=8.89, p=0.003, Figure 2A]. Analysis of freezing behavior revealed statistically significant differences attributed to treatment: F(2, 16)=7.3, p=0.006 during pregnancy and F(2, 16)=8.27, p=0.003 postpartum, specifically with LEV in comparison to the saline group (Figure 2B).

In terms of head dipping frequency, significant treatment effects were observed: F(2, 16)=9.3, p=0.002 during pregnancy and F(2, 16)=4.69, p=0.025 postpartum, both indicating that LEV-treated rats differed from the saline group (Figure 2C), according to two-way ANOVA.

The results from the hole-board test displayed a tendency toward reduced rearing and hole exploration, coupled with heightened freezing behavior in the saline and VPA-treated groups. Conversely, the LEV-treated group exhibited increased freezing behavior and diminished hole exploration.

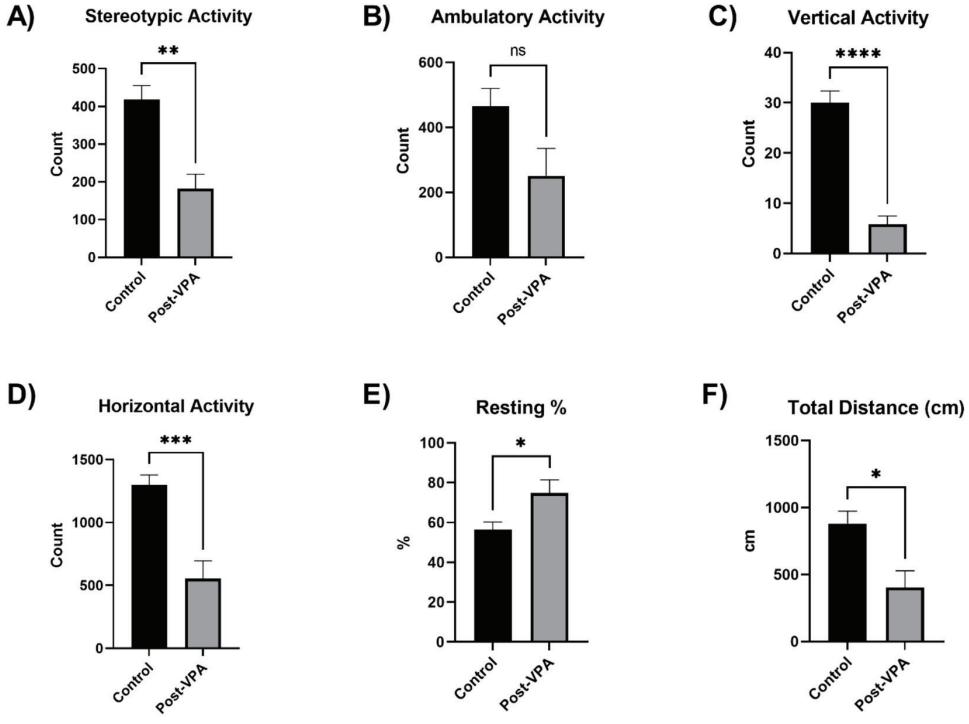

Figure 1. Comparison of locomotor activity parameters and behavioral traits in GAERS before and after VPA injections. The locomotor activity parameters of GAERS were evaluated before and after VPA injections. The figures present the distinct activity parameters and behavioral traits analyzed in this study. (A) Stereotypic activity was significantly altered following VPA injections; p=0.001, indicating changes in repetitive, non-goal-directed behaviors; (B) Ambulatory activity exhibited a trend toward modulation in response to VPA injections; (C) Vertical activity displayed a substantial decrease, indicating decreased vertical movements; (D) Horizontal activity was significantly decreased by VPA injections; (E) Resting behavior of pregnant GAERS exhibited a significant increase post-VPA injections; (F) Total distance traveled by pregnant GAERS also displayed a significant decrease following VPA injections. Error bars represent SEM
GAERS: Genetic Absence Epilepsy Rats from Strasbourg, VPA: Valproate, LEV: Levetiracetam, SEM: Standard errors of the mean

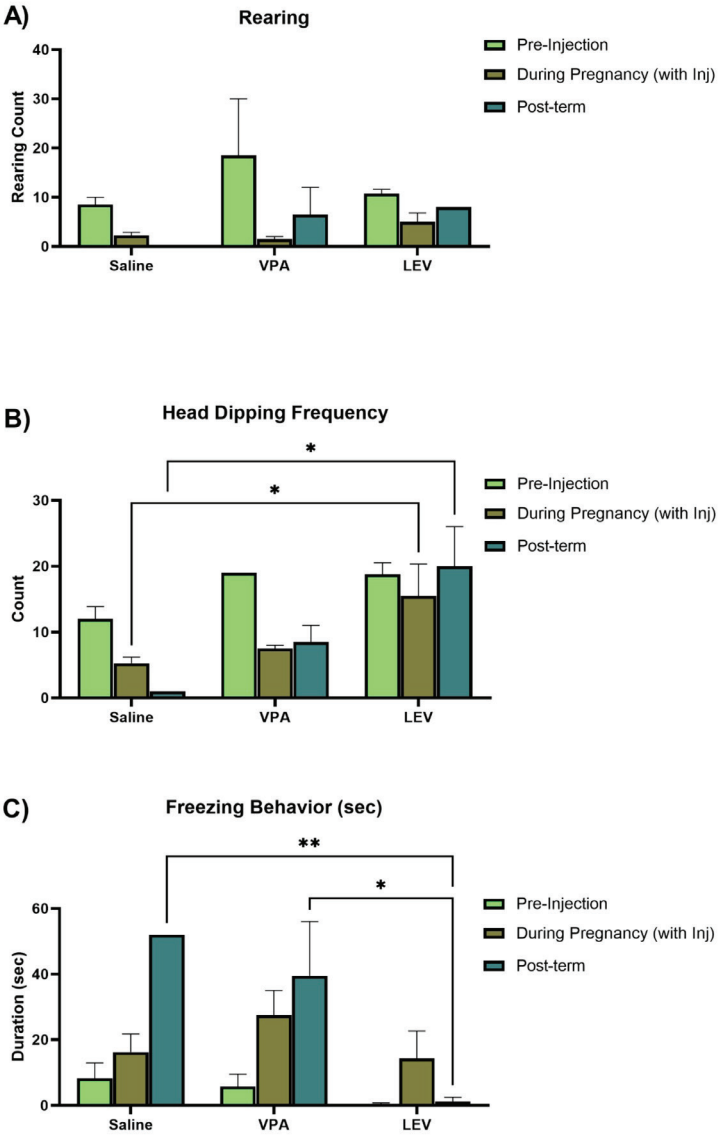

Figure 2. Effects of pharmacological treatments on maternal behavior and anxiety-related responses in female GAERS. Rearing behavior, freezing behavior, and head-dipping frequency of female GAERS were assessed following treatment with saline, VPA, and LEV during different phases of pregnancy and postpartum. Pregnant rats (n=6 per group) were administered saline, VPA (200 mg/kg), or LEV (50 mg/kg), while pre-injection pregnant rats served as controls (n=4 VPA, n=6 LEV). Behavioral variations were analyzed using two-way ANOVA. (A) Rearing behavior displayed significant differences among GAERS rats injected with treatments during pregnancy compared with pre-injection levels; (B) Freezing behavior exhibited treatment-specific effects during pregnancy and postpartum. LEV-treated rats showed increased freezing behavior in contrast to the saline group; (C) Head dipping frequency during pregnancy and postpartum revealed significant treatment effects. LEV-treated rats displayed distinct head dipping behavior compared with the saline group GAERS: Genetic Absence Epilepsy Rats from Strasbourg, VPA: Valproate, LEV: Levetiracetam, SEM: Standard errors of the mean

DISCUSSION

Our findings demonstrate: (1) decreased stereotypic, overall activity, and increased resting behavior of pregnant GAERS with chronic VPA treatment; (2) decreased rearing and hole exploration coupled with heightened freezing behavior in the saline and VPA-treated groups; (3) increased freezing behavior and diminished hole exploration in the LEV-treated group.

Behavioral assessments offer valuable methods for analyzing the potential effects of drugs and concurrent psychiatric irregularities. This is particularly significant in our investigation because of the relevance of the GAERS model as an accurate portrayal of human absence epilepsy, exhibiting documented social, behavioral, and psychiatric deviations.[28,29]

The findings of our study suggest differential effects of VPA and LEV on maternal behavior and anxiety-related responses in GAERS rats during pregnancy and postpartum periods, especially with the hole-board test. The results indicate anxiety-like behaviors and a general decrease in activity. Previously, we performed behavioral tests on male adult GAERS to analyze if any changes in arousal could be observed in the locomotor activity at baseline. Elevated stereotypic activity was observed in the GAERS group treated solely with a vehicle in contrast to the Wistar group, and the alpha antagonist drug also suppressed these stereotypic activities.[30] Stereotypic behavior, which is linked to excessive dopaminergic activity, is known to be mitigated by D1 receptor antagonism.[31] This mitigation of stereotypic activity could imply an indirect stabilization of the dopaminergic system.[32] VPA induces dopamine release in the amygdala without stimulation, dopamine release triggered by a conditioned stimulus, and dopamine release during methamphetamine sensitization.[33] In another study, VPA led to a rise in depressive symptoms and deterioration of dystonia in D2 supersensitivity.[34] Therefore, VPA may decrease the increased stereotypic behavior of the GAERS model. On the other hand, increased resting behavior and decreased activity may indicate depressive symptoms.[35]

LEV-induced psychiatric symptoms are reported as hypomanic symptoms,[36] aggression, depression,[22] and some of them are found to be irreversible.[37] On the other hand, recently, the LEV has been shown to have cognitive advantages,[38] with increased activity in the prefrontal cortex.

Study Limitations

As a limitation to our study, we only had the chance to observe throughout pregnancy, where physiological inactive states occur, and this will decrease the interpretation of locomotor activity data. Another limitation is that we could not perform locomotor activity tests on LEV-treated animals, and because many studies in the literature report dose-dependent teratogenicity,[39-41] and as a rule of thumb, dose-dependent influences on anxiety,[21] our study is limited due to the use of single doses

CONCLUSION

The available research suggests that both LEV and VPA may exhibit beneficial effects in mitigating abnormalities associated with dopaminergic excess. However, it is important to approach their usage cautiously, particularly in cases involving depressive states during pregnancy. The current body of literature concerning maternal mental health during pregnancy remains limited, warranting more comprehensive investigations into the potential behavioral and mood-related alterations resulting from the

administration of antiseizure drugs among pregnant women. Further studies in this domain are imperative to better understand the intricate interplay between medication use, dopaminergic modulation, and maternal mental well-being throughout pregnancy.

Ethics

Ethics Committee Approval: The study was approved by the Marmara University Ethical Committee for Experimental Animals (protocol number: 108.2018.mar, date: 03.12.2018).

Informed Consent: Animal experiment.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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Archives of Epilepsy

Original Article

Role of Platelet Indices in Pregnant Women with Epilepsy

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Abstract

Objective: This study aimed to investigate the inflammatory platelet (Plt) indices; Plt/lymphocyte, Plt/monocyte ratio (PMR), and Plt/neutrophil ratio (PNR) in maternal epilepsy patients.

Methods: Patients diagnosed with maternal epilepsy in a tertiary center between 2019 and 2022 were included in this retrospective case-control study. Consecutive uncomplicated healthy pregnant women constituted the control group. Complete blood count (CBC) parameter results and Plt indices during the first trimester of pregnancy were recorded. Neonatal outcomes, seizure history of epilepsy patients during pregnancy, and antiepileptic drugs used were also recorded.

Results: One hundred thirteen pregnant epilepsy patients were included in this study. As a control group, 339 healthy pregnant women were included. While the Plt was $271x10^9$/L in the epilepsy group, it was $249x10^9$/L in the control group (p=0.029). PMR and PNR were significantly higher in the epilepsy group. Fifty of the epilepsy patients had seizures during pregnancy (44.2%). When compared, no significant difference was found between epilepsy patients with a seizure history or not, as to demographic features and CBC parameters during the 1st trimester of pregnancy (all p>0.05).

Conclusion: Pregnant women with epilepsy have low-grade inflammation during the first trimester. Inflammatory Plt indices may be used in combination with other parameters for the management of pregnancy. Further studies are required.

Keywords: Epilepsy, pregnancy, inflammation, platelet, complete blood parameter indices

INTRODUCTION

Epilepsy is the most common chronic neurological disease with an incidence of 0.3-0.7% in pregnant women.[1] Epilepsy was shown to be stable in almost more than half of the patients during pregnancy. However, in 25-30% of the patients, the frequency of epileptic seizures was shown to be increased, and the fetal-neonatal outcomes remain obscure.[2]

In animal models, inflammation has been shown to trigger epileptic activity.[3] The pathological examination of brain tissues of children with epilepsy operated due to intractable seizures was reported to have inflammatory changes.[4] Additionally, antiepileptic drugs such as steroids act as anti-inflammatory interactions.[3,5] Marchi et al.[6] evaluated the inflammatory pathways in seizure disorders, suggesting that inflammation plays a role in the etiology of epilepsy.

Inflammatory maternal blood count parameters that are easily accessible have been studied in the obstetric field to predict adverse outcomes.[7-9] Neutrophil lymphocyte ratio (NLR) and platelet (Plt) lymphocyte ratio (PLR) were assessed in patients with epilepsy. An increase in NLR was shown to be associated with epileptic seizures.[10] In a systematic review, patients with epilepsy in the acute phase of the disease had higher NLR values.[11] In contrast, in another study, no difference was observed in NLR and PLR levels in epilepsy patients compared with healthy controls.[12] Systemic inflammatory markers were evaluated in patients with brain pathologies. No statistical difference was seen between the temporal lobe epilepsy patients and the control group in terms of inflammatory markers. NLR and PLR values were found to be lower in the temporal lobe epilepsy patients than in the meningioma and glioma patients.[13] Epilepsy was shown to have chronic low-grade inflammation, not severe acute inflammation, suggesting stable levels of inflammatory markers.[14] The results in the literature are contradictory regarding inflammatory markers and epilepsy.[15] Therefore, in this study, we aimed to investigate the

inflammatory Plt indices; PLR, Plt/monocyte ratio (PMR), and Plt/neutrophil ratio (PNR) in maternal epilepsy patients.

METHODS

This case-control study was approved by the Ankara City Hospital Institutional Review Board (decision no: E2-23-3634, date: 15.03.2023). Patients diagnosed with maternal epilepsy between 2019 and 2022 were included in the study group. Randomly assigned consecutive uncomplicated healthy pregnant women constituted the control group. The data of the patients were obtained retrospectively.

Pregnant women with complete blood count (CBC) results in the first trimester of pregnancy (<14 weeks) were included. Excluded were pregnant women with alcohol and cigaret consumption, chronic diseases, drug use except for epilepsy, maternal infection, thrombophilia, and fetal structural and chromosomal anomalies.

Maternal age, gravidity, parity, and neonatal outcomes (gestational age at delivery, birth weight, and APGAR scores) were recorded as study parameters. The pregnant women's CBC parameters until the 14th week of gestation were recorded. Hemoglobin (Hb), hematocrit (Hct), Plt, white blood cell (WBC), lymphocyte (Lym), monocyte, and neutrophil levels were recorded from the CBC results. Additionally, PLR, PMR, and PNR, which are inflammatory markers, were calculated and recorded. The seizure history of patients with epilepsy during pregnancy and the antiepileptic drugs they used were recorded.

Statistical Analysis

To analyze the data, the Statistical Package for the Social Sciences 24 program was used. The conformity of the data to the normal distribution was analyzed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. As the data did not show normal distribution, non-parametric methods were used for the analysis. The Mann-Whitney U test was used to compare the parameters between the groups. Non-normally distributed data are shown as median (minimum-maximum). Categorical data are shown as numbers (n) and percentages (%). A p-value <0.05 was set as a significant.

RESULTS

One hundred thirteen pregnant epilepsy patients were included in this study. As a control group, 339 healthy pregnant women were included.

Table 1, the comparison of clinicalodemographic features and CBC results in the 1st trimester of pregnancy. No statistically significant difference was found between the groups' maternal age and the number of gravidities. As for the CBC results during the 1st trimester, whereas the Plt was 271x10^9/L in the epilepsy group, it was 249x10^9/L in the control group (p=0.029). PMR and PNR were also significantly higher in the epilepsy group accordingly (p=0.011, p=0.014 respectively). No significant difference was seen in Hb, Hct, WBC, Lym, monocytes, neutrophils, and PLR (all p>0.05).

Epilepsy patients were divided into two groups as those with seizure history during pregnancy and not. In Table 2, the comparison of epilepsy patients according to seizure history is shown. Of the 113 epilepsy patients, 50 had a seizure history during pregnancy (44.2%). No significant difference was found between epilepsy patients with or without a seizure history or not as to demographic features and CBC parameters during the 1st trimester of pregnancy (all p>0.05).

Antiepileptic drugs were questioned. Seven of the epilepsy patients received polytherapy, 94 received monotherapy, and 12 were followed without medication during pregnancy. The most commonly used drug in epilepsy patients receiving monotherapy was levetiracetam, with 56 patients (49.6%). The second most common drug used was lamotrigine (n=17). Epilepsy patients receiving monotherapy and polytherapy were compared in terms of neonatal outcomes. There was no significant difference in gestational age at birth, APGAR scores, and birth weight between these groups (all p>0.05).

DISCUSSION

Epilepsy is a neurological disease that generally has a stable course during pregnancy; however, in some patients, seizures may be aggravated and neonatal outcomes are not clear.[2] In the current study, CBC parameters and Plt indices were evaluated in pregnant epilepsy patients and compared with healthy pregnant controls. We found that Plt, PMR, and PNR was significantly higher in

Table 1. Clinicodemographic features and CBC results of epilepsy and control groups

Variables	Epilepsy group (n=113)	Control group (n=339)	p value
Age (year)	28 (18-42)	28 (17-44)	0.787
Gravidity (n)	2 (1-9)	2 (1-8)	0.935
Parity (n)	2 (1-6)	1 (0-6)	**0.001**
Hemoglobin (g/dL)	12.2 (9.3-16.5)	12.2 (8.9-15.4)	0.608
Hematocrit (%)	36.8 (28.1-44.5)	36.5 (23.2-44.9)	0.792
Platelet (x10^9/L)	271 (90-511)	249 (118-442)	**0.029**
WBC (x10^9/L)	8.83 (4.49-16.67)	9.04 (4.23-14.61)	0.346
Lymphocyte (x10^9/L)	1.88 (0.67-6.30)	1.75 (0.49-5.61)	0.271
Monocyte (x10^9/L)	0.42 (0.16-1.17)	0.42 (0.14-1.54)	0.350
Neutrophil (x10^9/L)	6.09 (1.93-14.27)	6.51 (2.47-13.05)	0.201
PLR	146.80 (60.05-402.48)	139.73 (60.08-501.82)	0.344
PMR	622.50 (249.25-2319.05)	571.43 (22.92-2635.72)	**0.011**
PNR	43.37 (16.18-264.77)	38.76 (12.48-118.34)	**0.014**

Values were given as median (minimum-maximum).
p<0.05 was considered statistically significant.
CBC: Complete blood count, WBC: White blood cell, PLR: Platelet/lymphocyte ratio, PMR: Platelet/monocyte ratio, PNR: Platelet/neutrophil ratio

MAIN POINTS

- Epilepsy is the most common chronic neurological disease with an incidence of 0.3-0.7% in pregnant women.
- Epilepsy was shown to have chronic low-grade inflammation.
- Inflammatory platelet indices may be used in combination with other parameters for the management of pregnancies complicated with epilepsy.

Table 2. Clinicodemographic features and CBC results of epilepsy patients according to seizure history during pregnancy

Variables	Seizure + group (n=50)	Seizure - group (n=63)	p value
Age (year)	28 (19-42)	27 (18-40)	0.537
Gravidity (n)	3 (1-9)	2 (1-6)	0.051
Parity (n)	2 (1-6)	2 (1-4)	0.224
Hemoglobin (g/dL)	12.1 (9.9-16.5)	12.2 (9.3-14.7)	0.722
Hematocrit (%)	36.65 (28.6-44.5)	37.1 (28.1-43.4)	0.512
Platelet ($x10^9$/L)	256 (180-487)	290 (90-511)	0.454
WBC ($x10^9$/L)	8.47 (4.49-16.67)	8.90 (4.97-14.49)	0.945
Lymphocyte ($x10^9$/L)	1.77 (0.80-3.98)	1.94 (0.67-6.30)	0.118
Monocyte ($x10^9$/L)	0.40 (0.16-0.81)	0.44 (0.18-1.17)	0.383
Neutrophile ($x10^9$/L)	6.08 (3.09-14.27)	6.09 (1.93-11.32)	0.775
PLR	142.92 (60.05-402.48)	147.18 (73.49-276.42)	0.529
PMR	622.90 (313.16-2319.05)	615.15 (249.25-1663.64)	0.801
PNR	41.49 (19.32-111.19)	46.27 (16.18-264.77)	0.481
Gestational age at birth (weeks)	38 (25-41)	38 (25-40)	0.314
Birth weight (grams)	2970 (530-3840)	3130 (690-4400)	0.148
APGAR5	9 (6-9)	9 (5-10)	0.182

Values were given as median (minimum-maximum).
$p<0.05$ was considered statistically significant.
CBC: Complete blood count, WBC: White blood cell, PLR: Platelet/lymphocyte ratio, PMR: Platelet/monocyte ratio, PNR: Platelet/neutrophil ratio

the epilepsy group during the first trimester. PLR did not differ between the groups. No significant differences were seen in terms of demographic features between the epilepsy and control groups and between epilepsy patients having seizures during pregnancy and not.

In a study conducted by Güneş and Büyükgöl,[10] inflammatory markers such as NLR, PLR, and C-reactive protein (CRP) were evaluated in patients with epilepsy during the acute phase of seizures. NLR and CRP were increased during epileptic seizures. However, the PLR did not differ between epilepsy and controls. This study evaluated non-pregnant individuals. The results were suggested to be due to the lower Plt levels in the epilepsy patients. In our study, pregnant women diagnosed with epilepsy were included, and the Plt of the epilepsy patients was shown to be higher than that of the controls. Pregnancy has a complex course in terms of adaptive and immunological processes. Although an immune process accompanies placental invasion and inflammation during the first trimester, the immune tolerance mechanism also prevents the fetus and conception material from being rejected.[16,17] Another conflicting situation during pregnancy is altered CBC parameters.[18] Epilepsy was shown to have chronic low-grade inflammation, not severe acute inflammation, suggesting stable levels of inflammatory markers.[14] In our opinion, the findings of the current study may be due to low-grade inflammation during the first trimester.

In a recently published review, patients with epilepsy had higher NLR values during the acute phase of the disease.[11] This review assumed that epileptogenesis was the result of local and systemic inflammatory responses and thought that inflammatory markers that are easily accessible may be reasonable to be studied in epilepsy patients to help clinicians better follow up epilepsy patients under control. Conversely, Faruk Ozdemir et al.[12] evaluated preoperative inflammatory markers in epilepsy patients undergoing surgery and found no statistical difference as to NLR and PLR. They concluded that systemic inflammatory markers were not to be used as indexes in epilepsy patients. This study included some epilepsy patients (n=21). However, all these studies were conducted in the non-pregnant population and in the acute phase of epilepsy. The literature lacks information on pregnant women with epilepsy regarding inflammatory markers.

In our study, patients with epilepsy were mostly under monotherapy, and the most common drug used was levetiracetam to almost half of the patients concurrent with the literature.[19] No major congenital malformations were detected in epilepsy patients. All pregnant women enrolled in this study had a live birth. Although 50 patients (44.25%) had seizures during pregnancy, no significant difference in terms of neonatal outcomes suggests that the epilepsy was under control.

Study Limitations

The main strength of our study was the high number of epilepsy patients (n=113) and healthy pregnant controls (n=339). Our hospital is a referral center for complicated and high-risk pregnancies. Inflammatory markers were evaluated in the first trimester to determine whether there was a relationship between adverse neonatal outcomes. However, the study was conducted retrospectively. Another limitation was the lack of CBC results at the time of labor and/or delivery.

CONCLUSION

In conclusion, we believe that pregnant women with epilepsy have low-grade inflammation during the first trimester. Pregnancy has a complex course with altered CBC parameters. Inflammatory Plt indices may be used in combination with other parameters for the management of pregnancy. Further studies are required.

Ethics

Ethics Committee Approval: The study was approved by the Ankara City Hospital Institutional Review Board (decision no: E2-23-3634, date: 15.03.2023).

Informed Consent: Retrospective case-control study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: D.T.E., Ö.Ü., M.Y., O.Ö., Concept: D.T.E., Ö.Ü., M.Y., O.Ö., G.K., A.T., D.Ş., Design: D.T.E., Ö.Ü., M.Y., O.Ö., G.K., D.Ş., Data Collection or Processing: D.T.E., Ö.Ü., M.Y., O.Ö., G.K., Analysis or Interpretation: D.T.E., G.K., Ö.K., Literature Search: D.T.E., G.K., Ö.K., A.T., Writing: D.T.E., G.K., A.T., Ö.K., D.Ş.

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Archives of Epilepsy

Original Article

Changes in the Maternal Serum Inflammatory Parameters of Pregnant Women with Epilepsy

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Abstract

Objective: This study investigated the third-trimester maternal serum inflammatory status of pregnant women with epilepsy (PWWE).

Methods: One hundred-two PWWE and 102 healthy pregnant women were included in the study. Data were retrospectively collected from hospital records between May 2020 and 2023. The results of monocyte, neutrophil, lymphocyte, platelet counts, neutrophil-to-lymphocyte ratio (NLR), and serum C-reactive protein (CRP) levels were recorded. The systemic immune inflammation index (SII) and systemic inflammation response index (SIRI) were calculated. The presence of seizures and receiving antiseizure medications during pregnancy were recorded.

Results: Gestational age at delivery and birth weights of neonates were significantly lower in the epilepsy group than in the control group ($p<0.001$). The median NLR was 4.79 (2.36-10.50) in the polytherapy group and 2.87 (2.40-4.05) in the drug-free group, and this value was found to be statistically higher in the polytherapy group ($p=0.025$). No statistical significance was observed for NLR, CRP, SII, and SIRI values between the epilepsy group and the control group ($p>0.05$).

Conclusion: This study revealed that maternal serum inflammatory parameters did not differ between PWWE and healthy pregnant women. Having epileptic seizures or being seizure-free during pregnancy did not alter the maternal serum inflammatory status. Prospective large population studies conducted in the postictal acute and interictal phases are needed to reveal the effect of seizures on the inflammatory process in PWWE.

Keywords: Epilepsy, inflammation, pregnancy

INTRODUCTION

Epilepsy affects almost 1% of the general population and is the most common neurological disorder in pregnancies. The use of multiple antiseizure medications (ASMs), the frequency and severity of epileptic seizures, and drug-resistant epilepsyirectly affect the risk status of pregnant women with epilepsy (PWWE).[1] At least 9 months of seizure-free time before pregnancy is associated with a high rate of remaining seizure-free during pregnancy.[2] The risk of mild preeclampsia during pregnancy is 1.8 times, the risk of gestational hypertension is 1.5 times, the risk of vaginal bleeding in late pregnancy is 1.9 times, and the risk of preterm delivery is 1.5 times increased in PWWE using ASMs compared with healthy pregnant population.[3]

Inflammation may contribute to seizures, and anti-inflammatory therapies may treat seizures.[4] Some ASMs, such as valproate and levetiracetam, have anti-inflammatory effects by reducing serum levels of the C-C motif ligand 2.[5] It has also been found that glucocorticoids are effective in pediatric drug-resistant seizures and reduce the frequency of seizures.[6]

The neutrophil-to-lymphocyte ratio (NLR) is a reliable, cheap, and easy-to-apply marker of the immune response. NLR is influenced by many medical conditions such as chronic diseases, stroke, diabetes, cancer, and stress. NLR helps distinguish severe diseases from milder one.[7] NLR has been found to be higher in the acute and subacute phases of seizures than in healthy people. Elevated NLR is accepted as

a biomarker of inflammation and epilepsy.[8] The systemic immune inflammation index (SII) and systemic inflammation response index (SIRI) are derived from inflammatory maternal blood count parameters, positively associated with systemic inflammation, and reflect local and systemic immune responses. SII and SIRI have been used to estimate the risk of ischemic stroke, cardiovascular diseases, and overall survival of patients with cervical cancer.[9,10]

We hypothesized that the inflammatory process in epilepsy may affect maternal serum blood parameters. We aimed to investigate whether there is an association between inflammatory parameters and the occurrence of seizures by evaluating maternal serum inflammatory parameters such as C-reactive protein (CRP), NLR, SII, and SIRI in PWWE.

METHODS

This study was designed as a retrospective case-control study. The study was conducted on 102 PWWE and 102 healthy pregnant women who attended Ankara City Hospital's antenatal and perinatology outpatient clinic. Pregnant women who were diagnosed with epilepsy and followed up routinely between May 2020 and 2023 were included in the study group. Randomly selected healthy pregnant women without any systemic disease were used as the control group. Taking any medication except for ASMs, smoking, having no systemic or pregnancy-related disease, and having multiple pregnancies were exclusion criteria. The data of the patients were retrospectively obtained from the hospital records. Ethical approval was obtained from the University of Health Sciences Turkey, Ankara Bilkent City Hospital Institutional Review Board (no: E2-23-4486, date: 12.07.2023) for this study.

Third-trimester maternal serum complete blood count results were recorded for all patients. The results of monocyte, neutrophil, and lymphocyte counts, platelet counts, NLR, and serum CRP levels were recorded. SIRI was calculated by the formula (SIRI=monocyte counts × neutrophil counts/lymphocyte counts) and the SII index was calculated by the formula (SII=peripheral platelet counts × neutrophil counts/lymphocyte counts. The presence of seizures and receiving ASMs during pregnancy were recorded. Maternal age, obstetric history, gestational age at birth, birth weight of neonates, and hospitalization information in the neonatal intensive care unit (NICU) were recorded.

Statistical Analysis

IBM Statistical Package for the Social Sciences version 25.0 software (IBM Corp. Armonk, NY, United States) was used for statistical analyzes. The variables were analyzed using the Kolmogorov-Smirnov test to determine whether they were normally distributed or not. Descriptive analyzes were performed using medians (minimum-maximum) for non-normally distributed variables and mean standard deviation for normally distributed variables. The Mann-Whitney U test was used to compare two independent non-normally distributed variables. The variables with a normal distribution were compared using a parametric test (Student's t-test). The chi-square test was used for categorical variables. The Kruskal-Wallis test was used to compare more than two non-normally distributed independent variables. A p value of 0.05 was considered to show statistically significant results.

MAIN POINTS

- Pregnant women with epilepsy (PWWE) under polytherapy had a higher neutrophil-to-lymphocyte rate than drug-free pregnant women with epilepsy PWWE.
- Having epileptic seizures or being seizure-free during pregnancy did not alter the maternal serum inflammatory status.
- Maternal serum inflammatory parameters were not different between PWWE and healthy pregnant women.

RESULTS

Obstetric and clinical features of the epilepsy and control groups are shown in Table 1. The mean age, number of gravidas, and abortus were similar between the groups. Gestational age at delivery and birth weights of neonates were significantly different between the groups (p<0.001). While the NICU hospitalization rate was 21.6% in the maternal epilepsy group, it was 2.9% in the control group. This result was statistically significant (p<0.001). No statistical significance was observed for NLR, CRP, SII, and SIRI values (p>0.05).

A comparison of serum inflammatory parameters according to the presence of seizures is shown in Table 2. PWWE were divided into two groups according to whether they had seizures during pregnancy or not. No seizure was observed during pregnancy in 54.9% of the patients, whereas 45.1% of the patients had one or more seizures during pregnancy. NLR, CRP, SII, and SIRI values were similar (p>0.05).

In Table 3, epilepsy patients were divided into subgroups as monotherapy, polytherapy, and drug-free during pregnancy. Eleven of 102 patients (10.78%) did not take any medication during pregnancy. Eighty-four of 102 (82.35%) were treated with monotherapy, with 50 (49.01%) receiving levetiracetam, 14 (13.72%) receiving carbamazepine, 14 (13.72%) receiving lamotrigine, 5 (4.90%) receiving valproate, 1 (0.98%) receiving

Table 1. Obstetrics and clinical features of epilepsy and control group

	Epilepsy group n=102	Control group n=102	p value
Age	28 (18-42)	27 (18-39)	0.599[a]
Gravida Primigravid/multigravid	39/63	39/63	1.0[b]
Abortus	0 (0-6)	0 (0-3)	0.206[a]
Gestational age at birth (weeks)	37.5±2.62	38.8±1.31	**<0.001**[c]
Birth weight (grams)	2971±616	3289±409	**<0.001**[c]
NICU administration Yes (%)/No (%)	22 (21.6%)/80 (78.4%)	3 (2.9%)/99 (97.1%)	**<0.001**[b]
NLR	3.30 (0.74-10.65)	3.59 (1.16-11.17)	0.831[a]
CRP	5.15 (0-150)	10 (0-40)	0.961[a]
SII	870 (323-3130)	905 (344-2535)	0.751[a]
SIRI	1.40 (0.34-8.63)	1.42 (0.35-4.97)	0.442[a]

[a]Mann-Whitney U test; results were presented as median (min-max).
[b]Chi-square test; results were presented as number (%).
[c]Student's t-test; results were presented as mean±standard deviation.
p<0.05 values were presented in bold.
NICU: Neonatal intensive care unit, NLR: Neutrophil-to-lymphocyte ratio, CRP: C-reactive protein, SII: Systemic immune inflammation index, SIRI: Systemic inflammation response index, min-max: Minimum-maximum

Table 2. Comparison of serum inflammatory parameters according to the presence of seizures

	Seizure free group n=56 (54.9%) Median (min-max)	Seizure group n=46 (45.1%) Median (min-max)	p value[a]
NLR	3.26 (0.74-7.86)	3.73 (1.35-10.65)	0.114
CRP (mg/L)	5.15 (0-100)	4.90 (0-150)	0.398
SII	874 (382-2114)	870 (323-3130)	0.431
SIRI	1.48 (0.34-4.17)	1.38 (0.43-8.63)	0.809

[a]Mann-Whitney U test; results were presented as median (min-max).
NLR: Neutrophil-to-lymphocyte ratio, CRP: C-reactive protein, SII: Systemic immune inflammation index, SIRI: Systemic inflammation response index, min-max: Minimum-maximum

Table 3. Comparison of serum inflammatory parameters according to anti-seizure medication type

	Drug free group n=11 (10.8%) Median (min-max)	Monotherapy group n=84 (82.4%) Median (min-max)	Polytherapy group n=7 (6.9%) Median (min-max)	p value[a]
NLR	2.87 (2.40-4.05)*	3.30 (0.74-10.65)	4.79 (2.36-10.50)*	**0.025**
CRP	5.30 (0-20)	4.95 (0-150)	10 (0-20)	0.876
SII	717 (515-1766)	879 (323-3130)	1341 (698-2507)	0.100
SIRI	1.17 (0.67-3.0)	1.38 (0.34-8.63)	2.25 (1.32-8.01)	0.099

[a]Kruskal-Wallis test. p<0.05 values were presented in bold.
*The difference is statistically significant.
NLR: Neutrophil-to-lymphocyte ratio, CRP: C-reactive protein, SII: Systemic immune inflammation index, SIRI: Systemic inflammation response index, min-max: Minimum-maximum

oxcarbazepine. An additional 7 (6.86%) patients were treated with polytherapy, including various combinations of levetiracetam, carbamazepine, lamotrigine, valproate, and lacosamide, to control the seizures during pregnancy. The NLR was 4.79 (2.36-10.50) higher in the polytherapy group than in the drug-free group 2.87 (2.40-4.05) and this difference was statistically significant (p=0.025). The other serum inflammatory parameters (CRP, SII, and SIRI) did not differ between the groups.

DISCUSSION

In PWWE, the risk of perinatal complications and hospitalization increases during the antenatal, intrapartum, and postpartum periods. However, most women have a safe and normal pregnancy and delivery process. In our study, we found that the birth weight of newborns in the PWWE group was lower, the rate of admission to the intensive care unit was higher, and the gestational age at birth was lower. These findings were consistent with those reported in the literature.[11] Having epileptic seizures or being seizure-free during pregnancy did not alter the maternal serum inflammatory status or vise versa. PWWE who were treated with polytherapy had a higher NLR rate than women not taking any ASMs during pregnancy.

Overall, the theory that inflammation contributes to seizures is not clearly identified and is supported only by experimental studies. Impaired regulation of inflammatory cells is a critical and initiating step in the development of epileptogenesis. However, the pathophysiology remains unclear. Peripheral inflammation may damage the blood-brain barrier and initiate or aggravate epileptogenesis in systemic diseases such as SLE or RA. Controlling inflammation and prophylaxis in these disorders may reduce the risk of developing epilepsy.[4,12] Aronica and Crino[13] noted that the levels of inflammatory mediator cytokines, such as IL-6 and IL-1 receptor antagonists, reversibly increased both in the cerebrospinal fluid and serum of chronic epilepsy patients within 24 h after a tonic-clonic seizure. A study suggested that daily generalized motor seizures in children result in elevated IL-6 levels, leading to increased CRP.[14] Another study on rats observed that blood CRP and proinflammatory cytokine levels of rats with chronic seizures decreased after omega-3 treatment.[15] Our study did not find any statistical difference in serum CRP levels between the maternal epilepsy and control groups. The type of medication and presence of seizures during pregnancy did not change the CRP levels.

A recent systematic review that investigated NLR in epilepsy stated that elevated NLR values in the acute or subacute phase can be a good biomarker of inflammation for epilepsy.[8] Similarly, Güneş and Büyükgöl[16] found increased NLR values and blood cell inflammatory indices in the acute phase of epileptic seizures. A study of 116 enrolled patients noted that NLR could be a predictor and correlated with the length of hospitalization and need for ICU admission in adults with status epilepticus.[17] However, studies have also reported opposing views in the literature.[18,19] Faruk Ozdemir et al.[18] did not find any correlation between NLR and the duration and frequency of epilepsy in adult patients undergoing epilepsy surgery. Morkavuk et al.[19] did not find any difference in pre-and post-seizure NLR values in epilepsy patients. None of these studies were conducted in an epileptic pregnant population. In our study, NLR values were similar in both the epilepsy and control groups. However, the NLR values in both pregnant groups in our database were higher in the epilepsy and control groups. For example, the NLR value was found to be 2:66±3:70 in the epilepsy group and 1:83±0:49 in the control group in one study, and the pre-seizure NLR value was found to be 1.81 (0.88-3.71) in the generalized onset epileptic seizure group, 2.16 (0.83-3.67) in the focal onset epileptic seizure group, and 1.51 (0.84-3.64) in the PNES group in another study.[8,19] On the other hand, the placenta functions as a transient endocrine organ, and pregnancy may cause increased cortisol levels.[20] Cortisol may be a major driver of NLR variations because increased levels of cortisol are known to increase the neutrophil count while simultaneously decreasing the lymphocyte

count.[17] Combining these data that increased cortisol in pregnancy may be the factor that the NLR value both in epilepsy and control pregnant women are high in our data compared with the nonpregnant population in the literature. Bai et al.[21] found that SII and NLR in three pregnant trimesters increased in healthy pregnant women, which supports our findings. However, NLR rates were found to be higher in PWWE who received polytherapy during their pregnancy than in those who did not use drugs. One study found that ASMs did not affect NLR levels in epilepsy patients in the literature, and to the best of our knowledge, there is no data about the effect of ASM on NLR in epilepsy patients.[8] Studies are needed to reveal whether ASMs affect NLR values in patients with epilepsy.

Study Limitations

The major limitation of this study, we randomly collected blood samples and did not take samples at the acute or subacute phase of the seizure. We retrospectively examined serum inflammatory parameters from hospital records, and only the results of third-trimester serum blood samples were evaluated. Another limitation was the lack of subgroup analysis according to the type of antiepileptic drug used. The small number of the ASM-free and polytherapy groups was also a limitation, and a large number is needed for a more accurate evaluation in future studies.

CONCLUSION

To the best of our knowledge, this is the first study to evaluate serum inflammatory parameters such as SII, SIRI, and NLR values in PWWE. This study revealed that maternal serum inflammatory parameters do not differ between PWWE and healthy pregnant women. In addition, we did not find any association between maternal serum inflammatory parameters and seizures during pregnancy. Prospective large population studies conducted in the postictal acute and interictal phases are needed to reveal the effect of seizures on the inflammatory process in PWWE.

Ethics

Ethics Committee Approval: This case-control study was approved by the University of Health Sciences Turkey, Ankara Bilkent City Hospital Institutional Review Board (no: E2-23-4486, date: 12.07.2023).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.L.K., D.T.E., Ö.Ü., O.Ö., Ö.K., D.Ş., Concept: B.L.K., D.T.E., Ö.Ü., G.K., O.Ö., Ö.K., D.Ş., Design: B.L.K., D.T.E., Ö.Ü., G.K., O.Ö., Ö.K., D.Ş., Data Collection or Processing: B.L.K., D.T.E., Ö.Ü., O.Ö., Analysis or Interpretation: B.L.K., G.K., Ö.K., Literature Search: B.L.K., G.K., Ö.K., Writing: B.L.K., G.K., Ö.K., D.Ş.

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Original Article

Hitit University Epilepsy Outpatient Clinic Experience

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Abstract

Objective: Although epilepsy can be controlled with treatment; misperceptions are a disease that negatively affects life due to the lack of knowledge about the disease, even in individuals with epilepsy.

Methods: Individuals between the ages of 18 and 65 years with epilepsy who applied to the epilepsy outpatient clinic were included in the study using a random sampling method. All participants were evaluated by the same neurologist and psychiatric specialist.

Results: The mean age of 34 individuals with epilepsy was 30.0±10.4 years, the duration of the disease was 132.9±101.2 months, and the age of onset of the disease was 18.7±12.1 years. Of the patients, 40% were males and 60% were females. Of the cases, 93.9% had generalized seizures and 6.1% had focal seizures. Of the participants, 47.1% were under treatment with monotherapy and the others with polytherapy. The rate of patients without drug side effects was 57.1%. The rate of regular use of the drug was 85.7%. The median Epilepsy Disease Concealment Scale scores of the participants were 33.5, the median Epilepsy Stigma Scale scores were 65.0, and the median Quality of Life Scale in Patients with Epilepsy scores were 60.7. The median scores of Hamilton anxiety and depression were calculated as 3.0 and 5.0, respectively.

Conclusion: Although the patient population was limited, many findings in our study were consistent with the literature. Our study will shed light on future epidemiological data of Turkey and Çorum.

Keywords: Epilepsy, Stigma, Quality of Life Scale in Patients with Epilepsy, Epilepsy Disease Concealment Scale

INTRODUCTION

Is epilepsy, which affects the whole life, requires frequent follow-up, can be controlled with antiepileptics, but causes frightening misperceptions, or is it a lifelong disease that makes people feel lonely and helpless? Seizures that develop in social environments, lack of information about the disease, even in individuals with epilepsy, and false beliefs cause individuals with epilepsy to be stigmatized and their quality of life to decrease.

Stigma is defined as being marked as bad, being shamed, or being despised, and signs or traits that are recognized by outsiders that may lead to exclusion. People are stigmatized because they have undesirable features that are different from those of society, and those who are stigmatized are not seen as full human beings by normal people.[1,2] What is the current situation in one of the Central Anatolian provinces in epilepsy. In studies conducted in our country, it was determined that the social stigma will reveal the concealment of epilepsy.[3]

METHODS

In this study, patients with primary epilepsy were evaluated. Approval was obtained from the Hitit University Clinical Research Ethics Committee (decision no: 348, date: 23.12.2020). Participants were informed about the study, and a written consent form was obtained. The Declaration of Helsinki was complied with in this study. Patients under the age of 18 and over the age of 65, who had seizures due to secondary causes, had cognitive impairment, and had a history of psychiatric illness, were excluded from the study. Participants were included in the study using a random sampling method. Participants' age, gender, education levels, duration of disease, antiseizure medications, number of seizures in the last month, epilepsy, and seizure classification were questioned. The Epilepsy Disease Concealment Scale (EDCS), Epilepsy Stigma Scale (ESS), Quality of Life Scale in Patients with Epilepsy (EQoLS), Hamilton Anxiety Scale (HAM-A), and Hamilton Depression Scale (HAM-D) were administered by the same neurologist and psychiatrist.

Statistical Analysis

The evaluation of the data was done with the statistical package program (Statistical Package for the Social Sciences) 21.0. Descriptive tests were used for number, percentage, mean±standard deviation, median, range, and interquartile range values, and Spearman's correlation test was used to evaluate the relationship between data. The Mann-Whitney U test was used for group comparisons because the scale scores did not show a normal distribution. If the p values were below 0.05, it was considered statistically significant. r values were considered as no correlation between 0 and 0.25, weak correlation between 025 and 0.50, strong correlation between 0.50 and 0.75, and strong correlation between 0.75-1.00.

RESULTS

In the patient group we examined (n=34), the mean age was 30.0±10.4 years, the duration of the disease was 132.9±101.2 months, and the age of onset of the disease was 18.7±12.1 years. There were 40 (14) male and 60 (20) female participants in the study group. While the rate of patients with high school or higher education was 44.12% (n=15), the rate of patients with secondary education or below was 55.88% (n=19). It was learned that 37.2% (n=13) of the participants were unemployed, 20% (n=7) were housewives, and 17.1% (n=6) were working full-time. In terms of income level, 54.6% (n=19) of the patients were considered moderate, 21.2% (n=7) of them as bad, and the remaining group was considered good. 58.8% (20) of our patients were single, 41.2% (14) were married. It was found that 91.2% (31) of the individuals were followed up with generalized onset epilepsy and 8.8% (3) were diagnosed with focal onset epilepsy. The most common seizure type was generalized tonic-clonic seizure with 67.6% (n=23). The rate of patients without seizures for at least one year was 50% (n=17), 29.4% less than once a month (n=10), and the rate of patients who had seizures more than once a month was 20.6% (n=7). Unfortunately, none of the patients took precautions against accidents that may occur due to seizures, 17.6% (n=6) were victims of an accident during the seizure. Only one patient in the group developed disability due to a seizure. 47% (n=16) of the patients were under treatment with monotherapy and 53% (n=18) with polytherapy. Levetiracetam, valproic acid, lamotrigine, carbamazepine, and zonisamide were used in monotherapy. The rate of patients without drug side effects was 58.8% (n=20). The most common side effects were tremor 20% and forgetfulness 14.3%. Nervousness, weight gain, sedation sleep disturbances, and fatigue were the other reported side effects. When the drug dose was questioned; 97.05% of the participants (n=33) knew the drug dose they were using. The rate of regular drug use was 88.2% (n=30). Our rate of patients who were under regular doctor's control was 73.5% (n=25). Many patients who could not come to the controls came from outside the city. Apart from the physician's recommendations, five of the patients wore amulets and one patient had lead pour. The remaining 28 patients did not receive non-drug treatment, but all of them said that they had a positive view of the issue. Three patients had hypertension. 91.2% (n=31) of the patients had no other concomitant chronic disease. Unfortunately, no significant difference was found between the scales between the high school and above group and the lower high school groups according to the education level of the patients. The median EDCS scores of the participants were 33.5 (interquartile range 30.0-39.0), the median ESS scores were 65.0 (interquartile range 53.0-72.0), and the median EQoLS scores were 60.7 (interquartile range 41.6-84.6). The median scores of HAM-D and HAM-A were calculated as 3.0 (interquartile range 1.0-8.0), 5.0 (interquartile range 2.0-8.5), respectively (Table 1).

Table 1. Median, range, interquartile range values of the evaluation scales used

	Median (range)	Interquartile range
EQoLS	60.7 (10.9-95.2)	41.6-84.6
ECS	33.5 (22.0-47.0)	30.0-39.0
ESS	65.0 (43.0-108.0)	53.0-72.0
HAM-A	5.0 (0.0-31.0)	2.0-8.5
HAM-D	3.0 (0.0-27.0)	1.0-8.0

EQoLS: Quality of Life Scale in Patients with Epilepsy, ECS: Epilepsy Disease Concealment Scale, ESS: Epilepsy Stigma Scale, HAM-A: Hamilton Anxiety Scale, HAM-D: Hamilton Depression Scale

DISCUSSION

Epilepsy is a complex disease that affects individuals, families, and society in psychological and social terms. A lack of social knowledge has a significant impact on many aspects, including education, business life, marriage, and acceptance of patients in society as individuals.

Studies show that there are different levels of stigma in individuals with epilepsy and that it harms the individual at least as much as the disease itself. When the literature was examined, while stigma was found at different rates in studies conducted with stigma scales in epilepsy, risk factors for stigma were listed as seizure frequency, number of drugs used, low education and income level, patient age, and duration of disease.[4] In a study conducted in Turkey in 2022, the mean ESS was found to be 40.7±9.04, and the mean ESS was found to be 57.19±12.57.[5]

In a study among young people in Saudi Arabia, 31.2% of the participants thought that epilepsy was supernatural or black magic. In this study, 45.6% of the participants reported that they thought that epilepsy had an impact on their quality of life.[6]

In another study evaluating the stigma rates of 153 patients with first-diagnosis epilepsy, the rate that was 17.6% at the time of first diagnosis was found to be 30.7% in the first year.[7] In another study conducted in 2020, the mean of the fear of negative evaluation scale in Turkey was found to be 31.19±4.86, and the mean EDCS was found to be 46.93±9.55. It was noted that individuals with epilepsy have a high level of fear of negative evaluation by the society and a strong tendency to hide their epilepsy. In this study, the tendency of individuals with epilepsy to hide their diseases increased with age

MAIN POINTS

- Epilepsy is a complex disease that affects individuals, families, and society in psychological and social terms.
- Stigma harms the individual as much as epilepsy.
- Increasing social awareness and providing positive coping strategies to increase social support in patients with epilepsy may be effective in reducing stigma.

and seizure frequency. Surprisingly, fears of negative evaluations decrease as the concealment of their diseases increases.[8] In another study conducted in eastern Turkey, stigmatization rate was found in 62.4% of the participants, and some factors (being below the age of 30, being single, poor economic situation, living with parents and siblings, frequency of seizures, experience of harming someone due to epileptic seizure, and related accident experience) have been associated with a higher stigma score in patients with epilepsy. It has also been shown that there is a negative relationship between stigma score and social support score in patients with epilepsy.[9] The quality of life and stigma affect each other in the opposite direction.

The quality of life in adults with epilepsy is predominantly affected by psychosocial factors. The quality of life in epilepsy is a broad multidimensional concept. Clinicians prioritize treatment, side effects, and prognosis in patients with epilepsy, but the psychosocial dimension of the disease should not be overlooked. Effective epilepsy management requires more than seizure control.[10,11] Concomitant conditions in epilepsy, seizure frequency, severity, monotherapy or polytherapy, socioeconomic status, and stigmatization are important factors affecting the quality of life of patients. Cultural differences affect the quality of life outcomes between countries. Even within a country, different results can be obtained. Having general and accurate information about epilepsy is an important factor in coping with epilepsy.[12]

Depression and anxiety are two common comorbidities in patients with epilepsy.[13] Comorbidities of psychiatric diseases complicate the follow-up and treatment process of epilepsy. Although we did not detect significant anxiety and depressive symptoms in our current group, we believe that the compatibility of the stigma and disease concealment scales with the literature is related to the sociocultural structure and the inability to fully recognize the disease. In a study in which the mean HAM-D scores applied to epilepsy patients were calculated as 2.63±2.66; an inverse correlation was found between HAM-D scores and quality of life.[13] It is quite common for epilepsy to affect a person's quality of life, and additional psychiatric disorders will worsen the quality of life. Therefore, we believe that an early evaluation of patients with suspected psychiatric comorbidity by a psychiatrist would be beneficial in this regard.

A 2021 study showed that social phobia is positively associated with stigma in epilepsy. In individuals with epilepsy, psychiatric disorders are often under-recognized and their treatment can be ignored. Both conditions significantly impact the quality of life of patients.[14] Showing sensitivity to this issue is also required in outpatient clinics following epilepsy patients.

Although the social integration of these patients is associated with the development ranking of the countries, quality of life, stigma, and concealment of the disease, stigma continues in developed countries. In a study conducted in Norway, it was found that 56% of the participants felt stigmatized and 35% experienced discrimination related to the disease.[15]

In a study examining the effect of monotherapy or polytherapy on quality of life in epilepsy treatment, patients receiving polytherapy had a significantly higher prevalence of psychiatric comorbidity than patients receiving monotherapy, and patients receiving polytherapy scored significantly lower in the cognitive domain and overall quality of life in the epilepsy quality of life questionnaire.[16] When we examine the literature, studies from many countries of the world in which different rates of stigma and epilepsy have been determined.[17,18] As patients' knowledge about epilepsy and positive attitudes about the disease increase, stigma levels will decrease and the quality of life will increase.[19]

Study Limitations

Although the patient population was limited, many findings in our study were consistent with the literature. Our study will shed light on future epidemiological data of Turkey and Çorum.

CONCLUSION

The social stigma caused by epilepsy leads to the concealment of epilepsy and social isolation. It is important to determine the social perspective, epilepsy concealment, and the effects of stigma on the patient and quality of life. The data we obtained show that clinicians need to be about the existence of information pollution about the disease in epilepsy patients and in our society. Increasing social awareness and providing positive coping strategies to increase social support in patients with epilepsy may be effective in reducing stigma

Ethics

Ethics Committee Approval: Approval was obtained from the Hitit University Clinical Research Ethics Committee (decision no: 348, date: 23.12.2020).

Informed Consent: Participants were informed about the study, and a written consent form was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.E., S.A., A.K., F.U.T., E.Ö., Concept: S.E., F.U.T., E.Ö., Design: S.E., F.U.T., E.Ö., Data Collection or Processing: S.E., S.A., A.K., Analysis or Interpretation: S.E., S.A., Literature Search: S.E., Writing: S.E.

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Neuropsychological Evaluation of Visual Spatial Functions in Juvenile Myoclonic Epilepsy Patients

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Abstract

Objective: The main purpose of this research was to evaluate visual spatial functions in patients with juvenile myoclonic epilepsy (JME). The aim of this study was to determine the neuropsychological profile of subprocesses of visual spatial functions in JME patients.

Methods: Two different participant groups were included in the study. Twenty-two patients aged 18 years and older with a diagnosis of JME and 22 healthy volunteers with similar age, gender, and education status as the patient group were included as the control group. The Benton Face Recognition Test, Symbol Cancellation Test (SCT), Trail Making Test (TMT), and Judgment Line Orientation Test (JLOT) were used to evaluate visual spatial functions.

Results: The evaluation of neuropsychological tests showed that the JME patients underperformed in the JLOT and TMT compared with the control group, but the difference was not statistically significant. However, the results were statistically significant in some SCT sub-forms.

Conclusion: The results support the idea that JME patients have not only frontal lobe dysfunction but also a more global impairment in visual spatial functions.

Keywords: Juvenile myoclonic epilepsy, neuropsychological evaluation, visual spatial functions

INTRODUCTION

Juvenile myoclonic epilepsy (JME) is one of the most common forms of idiopathic generalized epilepsy, accounting for 5-10% of all epilepsy.[1] It typically begins during adolescence, between the ages of 12 and 18 although onset can occur between ages 6 and 22.[2] The condition is hereditary and affects both sexes equally.[1,3] JME is characterized by a triad; absence seizures, myoclonic jerks, and tonic-clonic seizures begin with age.[4] Seizures usually occur shortly after awakening or with sleep deprivation. Sleep deprivation is the most common seizure trigger, although other factors such as fatigue, alcohol consumption, stress, excitement, and premenstrual syndrome can also provoke seizures. Situations such as exams and travel may increase the likelihood of seizures.[5]

The effects of seizure types are often studied as causes of cognitive impairment in patients with epilepsy. While some patients do not experience cognitive impairment, others may have impairments in different functions.[6-8] It is commonly observed that patients with generalized seizures have lower cognitive scores. Some studies have reported learning difficulties throughout school life, even in those with normal intelligence and seizure control, in idiopathic generalized epilepsy.[7,9] There is a wealth of information on the cognitive effects of JME, which is the most common form of idiopathic generalized epilepsy and the focus of our study. Studies have shown that frontal lobe functions are especially impaired in patients with JME,[10,11] and that they also have impairments in visual and auditory attention and visual spatial functions.[12]

According to Piazzini et al.,[13] tests evaluating frontal lobe functions in patients with JME revealed cognitive impairment similar to with frontal lobe epilepsy. In another study by Sonmez et al.,[14] the cognitive performance of JME patients and healthy control groups were evaluated, and the patient group was found to have significant impairments in verbal and visual memory performance, frontal lobe functions, and visual spatial functions compared with the control group. Attention tests also showed that patients with JME had more difficulty maintaining attention than controls.[15-17] Multiple studies have reported that JME patients had worse results in verbal fluency tests and verbal and visual memory tests.[15] Executive functions associated with the frontal lobe have also been evaluated in previous research with findings related to JME. The objective of our study was to evaluate visual spatial functions using neuropsychological tests.

METHODS

Participants

The sample group for the study comprised 22 patients who were 18 years or older and who were diagnosed with JME. The patients were followed up at the neurology outpatient clinic of the Ondokuz Mayıs University Faculty of Medicine. Patients with other neurological, medical, or psychiatric conditions and those with persistent slow background activity on electroencephalography (EEG) were excluded from the study.

The study collected demographic information on the patient group, including age, gender, educational status, age at seizure onset, medication use, and psychiatric treatment history. A control group consisting of 22 healthy volunteers with similar demographic characteristics was also evaluated using the same cognitive and neuropsychiatric assessment protocol as the patient group. Participants who scored 14 or higher on the Hamilton Depression Rating Scale (HAM-D) were excluded from the study to minimize the impact of depression on the test results.

Neuropsychological Assessment

In this study, we applied neuropsychological tests; Trail Making Test (TMT), Symbol Cancellation Test (SCT), Benton's Face Recognition Test (BFRT), and Judgment of Line Orientation Test (JLOT), to the patient and control groups. Along with neuropsychological tests, patients' emotional states were measured using the HAM-D.

TMT consists of two parts. In part A, there are 25 numbered circles on a page. The subject is asked to connect the numbered circles sequentially with a pencil. In part B, 13 of the circles are marked with numbers and the others with letters. The subject is asked to combine the circles into a sequence of numbers and letters. The completion time of the task is the score received by the subject. This test provides information about visual attention, perseverance, and mental flexibility.

The SCT consists of four A4 sheets of regular letters, irregular letters, regular shapes, and irregular shapes. The subject is asked to mark certain letters and shapes on each page. Meanwhile, while the subjects are marking, the time is kept. Each page has 60 targets. It measures selective attention, visual spatial functions, and reaction time. Damage to the right posterior parietal hemisphere can result in impairment of SCT performance.

The BFRT requires the subject to identify 3 face photographs that match the stimulus face from 6 face photographs presented on a page just below it. The photographs are taken at different angles and brightness levels. The test measures the subject's ability to recognize faces, and the number of correctly matched faces determines the score. This test is sensitive to damage in the occipitotemporal cortical areas.

JLOT is a visual spatial orientation and perception test. The test includes 5 practice pages followed by 30 test pages. In this test, the subject is asked to match the two stimulus lines on the top with two of the eleven numbered lines on the bottom. The patient can score a maximum of 30 points. A high score indicates good visual spatial performance. JLOT is sensitive to injuries in the right posterior cortical regions.

HAM-D is a widely used clinician-based depression scale. It contains 17 items and is evaluated over 52 points.

Statistical Analysis

Kolmogorov-Smirnov and Shapiro-Wilk normality tests were applied to determine which test to use from the comparison tests. An independent two-sample t-test was used for two-category variables with a normal distribution, and a Mann-Whitney U test was used for two-category variables that did not show a normal distribution. The Kruskal-Wallis H test was used for variables that did not show normal distribution for variables with more than two categories. However, the Spearman's rank correlation coefficient was used for variables that did not show a normal distribution. The level of significance was set at $p \leq 0.05$. For statistical analysis, we used the Statistical Package for the Social Sciences version 22.0.

RESULTS

Patients with JME (n=22) and the control group (n=22) were evaluated. The patients and controls were similar to age, education, and gender distribution.

The mean age of the patients was 25.7±7.8; the mean age of the control group was 25.5±7.6 years. 63.6% of JME patients were female and 36.4% were male. The same pattern was observed in the control group. The education level of JME patients was as follows: 4.5% had primary school education, 36.4% had high school education, and 59.1% had university education. The education levels of the control group were as follows: 4.5% had primary school education, 9.1% had secondary school education, 31.8% had high school education, and 54.5% had university education (Table 1).

Neuropsychological Test Results

The group with JME scored lower than the control group on the two subforms of the SCT, which showed significant differences between the groups. The results from the TMT Part B and JLO tests were also lower than those of the control group, but the differences did not reach statistical significance (Table 2). All of the analysis results showed that patients with JME had lower scores than the control group. The control group outperformed the patients with JME, although the differences were not statistically significant.

DISCUSSION

The aim of this study was to evaluate various visual spatial functions in patients with JME. In recent years, there has been increasing

MAIN POINTS

- In our study, neuropsychological evaluation was performed in myoclonic epilepsy (JME) patients.
- The aim of this study was to determine the effect of the disease on visual spatial functions.
- JME disease can cause disorders in different areas of the brain, including visual and spatial functions.

research on the cognitive profile of patients with JME.[18,19] Results from cognitive assessments revealed that patients with JME performed significantly worse in visual spatial skills than controls, which is consistent with previous research in the field.

It is well known that two functional pathways are involved in mediating visual spatial functions.[20] Both these pathways originate from the primary visual cortex. The ventral pathway (occipitotemporal pathway) is crucial for object perception, whereas the dorsal pathway (occipitoparietal path) is important for the perception of object parts, object position relative to other objects, and visual-based movements toward objects.[21] These functions are processed as a whole. Rao et al.[22] suggested that the "what" and "where" pathways of the prefrontal cortex play a unifying role in visual spatial functions. Therefore, even though occipitoparietal and occipitotemporal locations are primarily associated with visual spatial functions, the prefrontal cortex may also play a significant role in these functions.

In the current study, because the negative effect of depression on cognitive functions is a fact, the HAM-D scale was used before moving on to the neuropsychological tests that we applied with the patient and control groups. In this context, for example, in Ergin's[23] study, patients with depressed JME were found to have more significant impairments in the clock drawing and JLO tests, which reflect visual spatial functions, than patients with non-depressed JME.

Table 1. Demographic characteristics of the cases are given

Groups		JME n=22 (50%)	Control n=22 (50%)
Female		n=14	n=14
Male		n=8	n=8
Education	Primary	n=1 (4.5%)	n=1 (4.5%)
	Secondary	n=8 (36.4%)	n=2 (9.1%)
	High school	n=13 (59.1%)	n=7 (31.8%)
	University		n=12 (54.5%)
Age		min=19 max=46 25.7±7.8	min=19 max=46 25.5±7.6

JME: Juvenile myoclonic epilepsy, min: Minimum, max: Maximum

Table 2. Results of the cognitive assessment (patients and controls)

Test	JME (n=22)	Control (n=22)	p
BFRT	47.18	47.82	0.542
JLO	18.75	26.25	0.051
TMT-A time	39.95	34.45	0.128
TMT-B time	101.81	80.05	0.057
SCT1	98.14	89.45	0.172
SCT2	98.14	89.45	0.172
SCT3	95.77	81.00	0.015*
SCT4	82.82	67.36	0.034*

*p<0.05.

BFRT: Benton Facial Recognition Test, JLO: Judgment of Line Orientation, TMT-A time: Trail Making Test A form, TMT-B time: Trail Making Test B form time, SCT1: Symbol Cancellation Test form 1, SCT2: Symbol Cancellation Test form 2, SCT3: Symbol Cancellation Test form 3, SCT4: Symbol Cancellation Test form 4, JME: Juvenile myoclonic epilepsy

There was no statistically significant difference between the JME and control groups test mean values in the BFRT results reflecting complex visual perception functions of visual and spatial functions. There are studies in the literature that support this finding. Sonmez et al.[14] and Turan[16] are consistent with the research findings obtained in the current study. The consistency of the results with the literature is important because the study was conducted and used in the same population.

In our study, no statistically significant difference was found between the control and JME groups in the results of the JLO test, which evaluates the orientation of visual and spatial functions. However, according to the JLO scores, the mean of the group with JME was lower than that of the control group. Although the effect of depression was neutralized, we can say that there was a significant difference at the border. In another study, JME patients showed significantly worse results than the control group, even when the effect of depression was neutralized.[23] Despite this, the results are not significant in some studies.[14,24]

In the current study, the results of the analysis of TMT scores revealed a borderline significant difference, although not statistically significant, in the completion time of the TMT Part B form. It was observed that the JME group performed unsuccessfully by completing the form in a longer time than the control group. Such a performance of the patient group in terms of the duration score suggests that there is a slowdown in psychomotor speed and concentration in JME.[25] Studies on TMT reveal activation involving the medial and dorsolateral prefrontal cortex. This activation has been specifically associated with TMT, part B.[26] Regarding visual spatial skills, it has been reported in many studies that visual attention is impaired in the JME.[19,27] The findings obtained from TMT scores in JME patients are supported by the literature.[15,28-30] Similarly, Pascalicchio et al.,[31] in their study comparing JME and a healthy control group, emphasized that patients with JME were less successful in tests requiring attention function.

We observed significant differences between the JME and control groups in some sub-forms of the SCT results reflecting visual scanning and sustained attention functions. In the study, the values of JME and control groups participants were statistically significant compared according to each subtest of SCT. It was observed that the JME group took longer to complete the two forms. By looking at the test results, we can conclude that the visual selectivity, visual motor, reaction speed, visual scanning, and continuous attention functions of JME patients are impaired. Considering that SCT is a visual spatial perception and screening test with a spatial component, it agrees with research showing mild impairment in visual spatial functions of JME.

Study Limitations

The small number of cases and lack of video EEG monitoring are the limitations of our study. Because of the small number of cases, we could not evaluate the effects of drugs on cognitive functions.

Future studies are needed to comprehensively determine the visual spatial abilities linked to JME, comparing patients with different epilepsy, and evaluations can be made by having a larger sample size.

CONCLUSION

We found finding suggestive of parietal lobe involvement in patients with JME. Based on our results and extensive literature review, we can conclude that visual spatial dysfunctions are consistently and distinctly present in JME. In conclusion, when evaluating cognitive functions in patients with JME, it is recommended to consider that patients may have disorders in different areas of the brain, including complex visual spatial functions.

Ethics

Ethics Committee Approval: Ondokuz Mayıs University Social and Humanity Sciences Ethics Committee Decisions (decision date: 05.02.2020, decision number: 2020/11).

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: N.C., H.A.Ş., Design: N.C., Data Collection or Processing: N.J., N.C., Analysis or Interpretation: N.J., N.C., H.A.Ş., Literature Search: N.J., Writing: N.J., H.A.Ş.

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Archives of Epilepsy

Original Article

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

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Abstract

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

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

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

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

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

INTRODUCTION

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

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

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

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

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

METHODS

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

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

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

Statistical Analysis

The study criteria were defined as mean, standard deviation, frequency, and percentage values. Chi-square and Fisher's exact tests were used to compare frequencies and percentages between groups. To evaluate the means of variables with normal distribution, the t-test was used to compare two different groups, and the one-way ANOVA method was used to compare the means of more than two groups. Spearman's correlation, multivariate logistic regression, and Cox regression analyzes were performed to investigate the correlations between the variables and their model. In the interpretations, the limit of significance was taken as p=0.05. The Statistical Package for the Social Sciences (version: 22.0) package program was used for biostatistical analysis.

MAIN POINTS

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

RESULTS

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

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

DISCUSSION

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

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

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

*Significant at the p<0.05 level.
SD: Standard deviation, LTEEG: Long-term electroencephalography, MRI: Magnetic resonance imaging, GTC: Generalised tonic clonic seizure

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

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

SD: Standard deviation, LTEEG: Long-term electroencephalography

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

EEG, particularly prolonged EEG monitoring, is often used to predict the risk of ASM withdrawal. Few studies have compared routine EEG and LTEEG in seizure-free epilepsy patients planned for drug withdrawal. In one of these studies, both electrophysiological investigations, routine EEG, and LTEEG were performed in seizure-free patients. They found the rate of an interictal anomaly in LTEEG to be 28.6% in patients with normal routine EEG.[18] In other studies, the rate of epileptiform anomaly in routine EEG was reported as 10-20%.[19,20] Furthermore, the relapse risk was higher in patients with interictal epileptiform anomalies, and it was suggested to continue drug therapy. Although routine EEG was normal, evidence of abnormal neurological examination and epileptiform discharges in LTEEG is higher in trauma or other symptomatic epilepsy. Our study showed that symptomatic patients with epilepsy were probably more rated in LTEEG with interictal epileptiform anomalies, albeit statistically not significant. In another study that excluded symptomatic epilepsies, LTEE revealed unusual findings in 16 seizure-free patients out of 78 who formerly showed normal routine EEG.[21] On follow-up, 27% had relapsed yearly, which is lower than that in other studies. As a result, LTEEG is suggested in seizure-free patients planned for ASM withdrawal, even if the routine EEG is normal. Our patient group showed higher rates of abnormalities in LTEEG, reflecting the higher rate of symptomatic epilepsy included in our study.

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

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

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

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

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

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

Study Limitations

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

CONCLUSION

Our study showed that LTEEG is more sensitive in detecting epileptic discharges. Symptomatic patients with epilepsy were probably more rated in LTEEG with interictal epileptiform anomalies, albeit statistically not significant. Patients with frequent seizures had significantly higher LTEEG abnormalities. Our study results emphasize that LTEEG is beneficial in the treatment planning of seizure-free epilepsy patients.

Ethics

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

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

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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