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EDITORIAL

Dear Colleagues,

This is the last issue of 2024.

Our journal is becoming more and more known every year. You can observe that not only studies in Turkey but also studies conducted in different centers of the world are submitted to our journal.

I would like to remind you that our journal is indexed in DOAJ, Scopus and ESCI. When writing the results of your research, I remind you not to forget to take a look at similar articles published in the Archives of Epilepsy.

I wish you all a healthy new year in advance.

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

Archives of Epilepsy

Review

Sex Differences in Epilepsies: A Narrative Review

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Abstract

Epilepsy affects people of all ages and sexes. The aim of the current narrative review was to summarize the sex differences in patients with epilepsy. In January 2024, we systematically searched PubMed for relevant articles. The following keywords were used: "Epilepsy" or "Seizure" and "Sex". The prevalence and symptomatology of many neurological conditions, including epilepsy syndromes, may differ between male and female patients. The reasons behind these sex differences are not yet clear. It is likely that sex hormones, neurosteroid, and sex chromosome gene differences play roles in the development of this phenomenon. The existence of sex differences in epilepsy is well recognized, but there is little discussion of their mechanisms and therapeutic implications. Future research should investigate the exact roles of sex hormones, neurosteroid, and genes in the development of sex differences in epilepsy. Similarly, future studies should investigate whether sex differences exist in seizure characteristics (e.g., seizure frequency, semiology, response to treatment, outcome) in different syndromes. These issues may have important clinical implications for designing appropriate sex-specific treatment strategies for various syndromes and conditions. Furthermore, sex should be considered as a biological variable in basic and clinical research.

Keywords: Epilepsy, gene, hormone, seizure, sex

INTRODUCTION

Gender and sex disparities exist in all aspects of human life; they may represent biology, bias, or both. In general, "sex" refers to the biological differences between males and females, while "gender" refers to the role of a male or female in society.[1] Sex differences in the characteristics of neurological conditions may be explained by the actions of sex hormones and also by sex chromosome gene-related brain differences.[2] These sex differences may influence the clinical characteristics, management, and even outcomes of neurological conditions.[3]

Evidence from human and animal studies supports a bidirectional relationship; the role of sex on seizures and epilepsy, as well as changes in the endocrine system and levels of sex hormones by epilepsy.[4] The aim of the current narrative review was to summarize the biological reasons for sex differences in people with epilepsy.

In January 2024, we systematically searched PubMed for relevant articles. The following keywords were used: "Epilepsy" or "Seizure" and "Sex". We included all original studies and articles written in English. Both authors independently participated in the screening, eligibility, and inclusion phases of the study. The authors collected the full manuscripts for all publications that appeared to meet the inclusion and exclusion criteria. The inclusion criteria were all human studies on sex differences in epilepsies (i.e., retrospective, cross sectional, case-control, case series, prospective trials, etc.), review articles, and articles written in English. The exclusion criterion was gray materials (i.e., letters, etc.) Because this was a narrative review, we did not follow the recommendations of the preferred reporting items for systematic reviews and meta-analyses statement; therefore, we did not track the number of identified papers in each step of the work.

Sex Differences in Patients with Epilepsy

The prevalence and symptomatology of many neurological conditions, including epilepsy syndromes, may differ between male and female patients. Although the sex differences in the incidence of epilepsy do not reach a significant difference, consistent trends across many

studies suggest that the incidence and prevalence of epilepsy are slightly higher in males than in females, in general.[4,5] Sex differences in seizure susceptibility may result from differences in factors, such as steroid hormone levels, cytochrome P450 activity, and biological factors in the brain.[6,7] These differences are most likely multifactorial phenomena, and many factors may contribute to these differences (e.g., environmental factors and lifestyle). In this review, we focused on the neurobiology of sex differences in various epilepsy syndromes.

Idiopathic Generalized Epilepsy

Female patients often outnumber male patients with idiopathic generalized epilepsy (IGE). The sex (female to male) ratio of the whole cohort of patients with IGE was approximately 1.5 in various studies.[8-10] This sex disparity is to some extent syndrome-related in patients with IGEs; the female-to-male ratio was significantly higher in patients with juvenile myoclonic epilepsy (JME) (of 1.8) compared with those in other syndromes of IGE (e.g., 1.33 in childhood absence epilepsy) in one study.[10] It is likely that sex hormones, neurosteroid, and sex chromosome gene differences play a role in the development of the aforementioned phenomenon (Figure 1).[11-13] Considering the peripubertal onset of JME, it is plausible to assume that the expression of genes that increase susceptibility to myoclonic seizures is regulated or affected by sex steroids.[14] In addition, it is hypothetically possible that mutant epilepsy genes have greater penetrance in females and males.[15]

Both female and male sex steroid hormones may influence brain excitability. Progesterone and its metabolites are anticonvulsants, whereas estrogens are mainly proconvulsants. The results from clinical studies have been supported by several animal studies that have demonstrated increased and decreased seizure frequencies after estrogen and progesterone administration, respectively.[11]

Androgens have more varied effects, although a generally antiseizure effect has been suggested; testosterone increases the electroconvulsive threshold in males at low doses and in both sexes at higher doses.[11] The effects of sex hormones on neuronal excitability and seizures involve complex mechanisms that are difficult to separate, as they range from regulation of gene expression to rapid effects via activation of various membrane receptors or acting as ligands on neurotrophin and ion-channel coupled receptors.[4] Furthermore, sex hormone surges during distinct maturation periods may also affect brain function and seizure outcomes (e.g., by inducing sexual differentiation of regions responsible for seizure control or initiation, or brain maturation).[4] Some epilepsy syndromes may either remit (e.g., childhood absence epilepsy) or have onset (e.g., JME) around the adolescence ages, indicating the likely influence of sex hormone changes and brain maturation occurring around puberty.[4]

Neurosteroids are key endogenous molecules in the brain that can affect many neural functions.[12] Neurosteroids are known for their nongenomic effects via the direct modulation of N-methyl-D-aspartate and gamma-aminobutyric acid (GABA)-A receptors. Neurosteroids are mainly responsible for the "fine tuning" of neuronal excitability by acting at synaptic and extrasynaptic receptors.[4] The neuronal GABA-A receptor chloride channel is a prime molecular target of neurosteroid.[12] At low concentrations, neurosteroid potentiate GABA-A receptor currents, whereas at higher concentrations, they directly activate the receptor.[16,17] Allopregnanolone-like neurosteroid are potent allosteric agonists and direct activators of synaptic and extrasynaptic GABA-A receptors.[12] The resulting chloride current conductance generates a form of shunting inhibition that controls brain network excitability and seizures. These mechanisms of neurosteroid provide potential innovative therapies for epilepsy and epilepticus.[12]

Finally, while sex differences in the brain have been largely attributed to the effects of sex hormones, it is becoming increasingly clear that brain sex differences are also mediated by the complement of genes encoded on sex chromosomes.[13] Sex chromosome gene expression is sexually dimorphic in the brain in a region-specific and cell type-specific manner.[13] Genes on the sex chromosome may influence neurological diseases by modifying the differentiation process of neurons, encoding proteins, neurotransmitter biosynthesis, and synaptic transmission (Figure 1).[13] Interestingly, evidence suggests the preponderance of female sex in the transmission of seizure liability in IGEs.[18] In one study of families with 82 index cases with IGEs, the highest risk for siblings was conferred by an affected mother. If a father was affected, the risk for proband siblings was almost equal to that in families with both parents unaffected.[18]

The relationship between menstrual cycle and seizure susceptibility in women is a well-known phenomenon (catamenial epilepsy); this is greatly influenced by hormonal fluctuations associated with the menstrual cycle phases. Catamenial seizures are considered neurosteroid withdrawal symptoms.[19] The pathophysiology of perimenstrual catamenial epilepsy involves withdrawal of progesterone-derived GABA ergic neurosteroid due to a decline in progesterone levels at the time of menstruation.[20] However, other mechanisms such as changes in water content, fluctuations in calcium levels, interactions between anticonvulsant drugs and steroid hormones, and thyroid hormone deficiency have also been implicated in the pathophysiology of perimenstrual catamenial epilepsy 4. A detailed review of catamenial epilepsy is beyond the scope of this manuscript, and readers should refer to other studies on this topic.[11,19,20]

Most of the abovementioned discussions on the neurobiology of sex differences in epilepsy also apply to other types of epilepsies [e.g., focal epilepsies, genetic epilepsies, status epilepticus (SE)]. Below, we highlight some sex differences that are specific to other epilepsy.

Focal Epilepsy

Generally, men may have a greater predisposition to behaviors that cause brain injury and acquired epilepsy.[21] In addition, animal studies have implicated that the presence of testosterone in intact and gonadectomized males with testosterone replacement increases their susceptibility to seizure. Seizures were either stronger (full limbic) or more frequent in animals with testosterone compared to animals devoid of testosterone.[22] In contrast, women

MAIN POINTS

- Systematically, PubMed was searched in January 2024.
- Keywords: "Epilepsy" or "Seizure" and "Sex".
- Epilepsy syndromes are affected by sex hormone, neurosteroid, and sex chromosome genes-related brain differences.

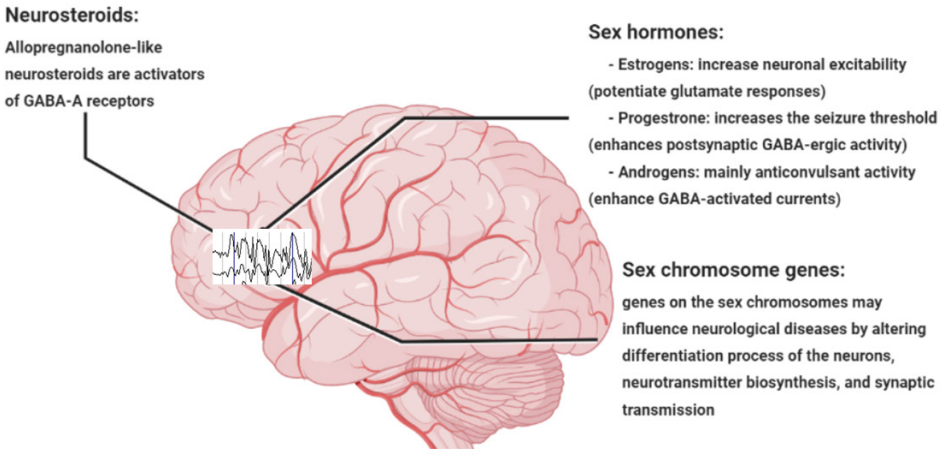

Figure 1. Potential reasons for sex differences in epilepsy

may be protected from brain injury by the neuroprotective effects of estrogens and progesterone.[21] Furthermore, some symptomatic (structural) focal epilepsy may be more frequent in men (e.g., focal cortical dysplasia, perinodular heterotopia).[7,21] In one study of non-acquired focal epilepsy, no sex differences were observed for seizure types with or without altered consciousness or progression to bilateral tonic-clonic seizures. However, autonomic, psychic, and visual symptoms are more frequently reported in females than in males.[3]

In temporal lobe epilepsy (TLE), which is the most common type of focal epilepsy, the sex distribution is almost similar between males and females,[23] but some clinical aspects appear to differ between men and women (e.g., auras are more common in women).[21,24] Interestingly, one study suggested the existence of sex differences in the spatial distribution of brain dysfunction in patients with mesial TLE, perhaps reflecting sexual dimorphism in regional cerebral connectivity.[25] Male patients more often exhibited frontal lobe hypometabolism ipsilateral to the seizure onset zone and epileptiform activity spread to this region. By contrast, female patients more often exhibited hypometabolism and ictal spread to the contralateral temporal lobe.[25]

Investigating sex differences in focal epilepsies may have important clinical implications; for example, in designing individualized sex-specific surgical plans for patients with drug-resistant mesial TLE, considering the extent of cerebral dysfunction in different sexes.

Symptomatic (Structural-Metabolic-Genetic) Generalized Epilepsy

Lennox-Gastaut syndrome (LGS) is the prototype of symptomatic (structural-metabolic-genetic) generalized epilepsy. Male patients often outnumber female patients in LGS. In one study, the sex (female to male) ratio of patients with LGS was 0.6;[26] this was consistent with other studies.[27] Male preponderance has also been reported in other epilepsy syndromes, such as Landau-Kleffner syndrome, epilepsy with myoclonic absences, Ohtahara syndrome, and Dravet syndrome.[4-7] Sex-dependent genetic disorders (e.g., X-linked syndromes such as Rett syndrome and fragile X syndrome) may explain some of these sex differences in symptomatic (structural-metabolic-genetic) generalized epilepsies.[28-31]

Status Epilepticus

SE is more prevalent in males than in females. In one large study from the USA, a higher incidence, earlier age at onset, and higher mortality of SE were observed among males.[32] In another study conducted in Taiwan, the male-to-female ratio of SE incidence rate was 1.57;[33] however, the in-hospital mortality was significantly lower in males (7.4%) than in females (11.1%).[33]

Sex Differences in the Adverse Effects of Antiseizure Medications

A recent systematic review suggested a higher frequency of general adverse effects of antiseizure medications in girls (than that in boys).[34] Higher risks of overweight, hyperammonemia, and carnitine deficiency were suggested in girls taking valproic acid. Similarly, an increase in height and an increased risk of weight loss were suggested to occur in girls on topiramate. Finally, a higher risk of retinal toxicity was observed in boys taking vigabatrin. However, the authors concluded that the effect of sex on the susceptibility to adverse effects of antiseizure medications is poorly investigated.[34]

The choice of antiseizure medications may have direct effects on hormonal cycles, hormonal contraception, pregnancy, fetal risk of major congenital malformation, and lactation in adolescents and adults with epilepsy. A detailed review of these issues is beyond the scope of this manuscript, and readers are encouraged to refer to other references.[35-37] For a comprehensive review of the molecular mechanisms of sex differences in epilepsy and seizure susceptibility in terms of chemical, genetic, and acquired epileptogenesis, readers may refer to the review by Reddy et al.[38]

CONCLUSION

The existence of sex differences in epilepsy is well recognized, but there is little discussion of their mechanisms and therapeutic implications. Future research should investigate the exact roles of sex hormones, neurosteroid, and genes in the development of sex differences in epilepsy. Similarly, future studies should investigate whether sex differences exist in seizure characteristics (e.g., seizure frequency, semiology, response to treatment, outcome) in different syndromes. These issues may have important clinical implications

for designing appropriate sex-specific treatment strategies for various syndromes and conditions. Furthermore, sex should be considered as a biological variable in basic and clinical research.

Footnotes

Authorship Contributions

Concept: A.A.A-P., Design: A.A.A., Data Collection or Processing: A.A.A., M.A., N.M.D., K.F.D., Analysis or Interpretation: A.A.A., Literature Search: A.A.A., M.A., N.M.D., K.F.D., Writing: A.A.A., M.A., N.M.D., K.F.D.

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The Influence of the Hydroalcoholic Extract of *Polypodium vulgare L.* on Pentylenetetrazole-induced Seizures and Its Comparison with the Impact of Sodium Valproate in a Rat Model

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Abstract

Objective: Epilepsy affects over 1% of the global population. *Polypodium vulgare L.* has emerged in studies, suggesting its potential antiepileptic effect. This study evaluated the anticonvulsant efficacy of the hydroalcoholic extract of *Polypodium vulgare L.* in a pentylenetetrazole (PTZ)-induced epilepsy model in rats. This research aimed to determine the optimal dosage for delaying seizure onset and reducing seizure severity. This study investigated whether the active compounds offer a viable alternative for epilepsy management, mainly through their potential interaction with GABAergic mechanisms.

Methods: We randomly selected four groups of 10 and 2 groups of 8 male Wistar laboratory rats. The reference and control groups received PTZ and distilled water, respectively. In contrast, experimental groups 1 and 2 received the hydroalcoholic extract of *Polypodium vulgare L.* at doses of 300 and 500 mg per kg of body weight. Experimental groups 3 and 4 received 150 and 300 mg per kg dose. Chemical kindling was induced in all groups via intraperitoneal injection of PTZ. Data analysis was conducted using Statistical Package for the Social Sciences version 20 software.

Results: The hydroalcoholic extract of *Polypodium vulgare L.* exerted a pronounced mitigating effect on convulsions induced by PTZ administration, specifically at a dosage of 300 mg/kg of body weight. It effectively prolonged the time necessary for seizure onset.

Conclusion: The administration of a 300 mg dose of the hydroalcoholic extract of *Polypodium vulgare L.* demonstrated superior efficacy compared with its 500 mg counterpart and both the 300 and 150 mg doses of sodium valproate in addressing PTZ-induced epilepsy. The results suggest that the hydroalcoholic extract of *Polypodium vulgare L.* has promise as an effective treatment for epilepsy.

Keywords: Polypodium vulgare, epilepsy, sodium valproate, valproic acid, kindling

INTRODUCTION

Neurological disorders are the second leading cause of global mortality, accounting for 11.6% of disability-adjusted life years and contributing to 16.5% of all deaths.[1] Epilepsy is a notable neurological disorder characterized by its prevalence, and the risk of its occurrence notably increases with the progression of age.[2] The global prevalence of this disease has been reported to encompass nearly 46 million individuals.[3] Epilepsy is a chronic central nervous system (CNS) disorder that affects individuals of all ages and exhibits a global distribution. Despite the existence of various disease mechanisms that can contribute to epilepsy, the cause remains unknown in approximately 50% of cases globally.[4] Seizures resulting from epilepsy are linked to various complications and issues, including diminished quality of life,[5] job-related challenges and difficulties,[5] cognitive disorders,[6] depression,[7] and bone fractures.[8] Therefore, given the numerous consequences associated with epilepsy, the management of epilepsy should prioritize the prescription of anticonvulsant drugs, addressing the underlying causes, and mitigating the systemic consequences to prevent damage induced by seizures.[9,10]

In recent years, numerous antiepileptic drugs have been tested and utilized, with over 80% of patients experiencing epileptic seizures receiving at least one of these medications.[11] Sodium valproate is a commonly prescribed medication widely used for the treatment of epileptic seizures. Nevertheless, the use of this drug is linked to various side effects, including digestive problems (nausea, vomiting, diarrhea, etc.), drowsiness, headache, and dizziness. Several complications have been identified, leading to non-adherence by patients.[12]

The most common animal model is chemical kindling, which is used to study epilepsy. The kindling model shares strong similarities with different types of human epilepsy.[13] When applied repetitively and intermittently, a subconvulsive stimulus (either chemical or electrical) leads to a process called Kindling. It can eventually produce full-blown convulsions.[14] Goddard[15] first proposed the kindling model in the late 1960s. The kindling model is usually used for seizure development and epilepsy. Then, the behavioral involvement and duration of induced seizures increase repeatedly.[16] PTZ kindling finally leads to potentially irreversible long-lasting changes in the structure of neuronal networks.[10]

Nature is a rich source of diverse biological and chemical substances, with numerous plants exhibiting anti-anxiety, analgesic, anti-depressant, and anti-convulsant effects.[17] Among these plants, *Bisfaij* (*Polypodium vulgare L.)* stands out, and its antiepileptic effects have been mentioned in a few studies.[17,18] *Bisfaij* plant has been reported to possess various antioxidant, antimicrobial, analgesic, and antibiotic characteristics.[19] Additionally, it has been demonstrated that *Polypodium vulgare L.* exerts an effect on nerve activity by reducing the activity of the CNS.[18]

Polypodium vulgare L. contains organic substances such as resin, tannin, steroids, flavonoids, alkaloids, glycosides, proteins, and reducing sugar. Moreover, studies have shown that this plant also contains minerals such as calcium, magnesium, potassium, iron, sulfur, and chloride.[20,21] It has been reported that *Polypodium vulgare L.* exhibits a protective effect against drug-induced catalepsy. This suggests that it may enhance the transmission of dopamine in the CNS and could be explored for its potential impact on Parkinsonism disorders. Furthermore, considering the activity and reduction of the effect of *Bisfaij* plant extract on the CNS, the possibility of an antiepileptic impact on this plant has also been raised.[21,22] On the one hand, the butyric acid present in the stem and root of *Bisfaij* serves as a precursor to the neurotransmitter gamma-aminobutyric acid (GABA). On the other hand, sodium valproate exerts its anticonvulsant effects by increasing the levels of this neurotransmitter. Therefore, it seems plausible that the bisfaij stem extract, which contains butyric acid, could potentially contribute to seizure control through a similar mechanism.[23]

Pentylenetetrazole (PTZ) is employed as a selective antagonist of $GABA_A$ receptors, whereas phaclofen serves as a selective antagonist of $GABA_B$ receptors.[24] GABA receptors function as target sites for drugs such as benzodiazepines. Classical benzodiazepines exert their therapeutic effects by binding to the benzodiazepine site of the GABA receptor, promoting chloride flow through the ion channel complex. However, this mechanism is linked to a broad spectrum of side effects.[25] Considering that antiepileptic drugs often require prolonged usage, sometimes for a lifetime, and acknowledging the potential side effects and risks associated with chemical drugs, their extended use may result in adverse effects and even drug poisoning. However, these limitations could compromise the efficacy of these treatments in achieving the desired therapeutic outcome.[26]

Considering the medicinal and therapeutic properties traditionally attributed to the *Bisfaij* plant for the treatment of epilepsy, as well as the side effects associated with chemical drugs commonly used for this purpose, this study explored the therapeutic effects of the *Bisfaij* plant in alleviating symptoms and treating epilepsy.

MAIN POINTS

- One strength of our research lies in the use of the animal kindling method. To enhance the scope of our investigation, we administered two distinct doses of *Polypodium vulgare L.* extract and compared them with a standard anticonvulsant medication commonly used for this condition.
- Another highlight of our study was the thorough observation and precise recording of animal behaviors, which ensured detailed behavioral analysis.
- Additionally, a comparison between intervention groups treated with the hydroalcoholic extract of *Polypodium vulgare L.* and those treated with an anticonvulsant drug revealed a novel aspect of our approach.

METHODS

Plant Collection

The study was approved by the Fasa University of Medical Sciences Research Ethics Committees (approval number: e-9210, date: 01.10.2013). The plant was obtained from a local perfumery in Shiraz city and was subsequently submitted to the Department of Pharmacy at Shiraz University for purity confirmation. The pharmaceutical department endorsed and assigned voucher number PM12983- to this plant, identifying it as *Polypodium vulgare L.* of the family *Polypodiaceae*.

Extraction

The Department of Pharmacy at Shiraz University prepared the hydroalcoholic extract. After cleaning and drying in the air, the resulting solution was ground and powdered. The second step in preparing hydro-alcohol extract was percolation with 70% ethanol, which was poured into the percolator device. The extract was then concentrated using a rotatory evaporator and dried in a vacuum oven. The Bisfaij hydroalcoholic extract was diluted with distilled water to produce two different concentrations for this study. The *Bisfaij* group 300 received an oral gavage of 300 mg/kg of body weight, whereas the *Bisfaij* group 500 received a concentration of 500 mg/kg. These doses are administered to rats.

Laboratory Animals

For this study, 56 Wistar male rats, aged between 2 and 3 months, were randomly chosen. The rats' weights fell within the range of 180 to 220 g. The rats were housed in containers and provided ample food and water. They were subjected to a 12-hour light and 12-hour dark cycle with suitable temperature and humidity conditions.

Pentylenetetrazole

PTZ with the commercial formula C6H10N4 was procured from Kiagene (IRAN) for use in this study.

Sodium Valproate

The pharmacy dispenses sodium valproate in 500-mg tablets. Subsequently, it undergoes crushing using a designated mortar and is diluted in two distinct ratios with distilled water for application in the research investigation.

***In vivo* Treatments**

No manipulation was executed on the control group. The reference group was administered seven complete doses of PTZ at varying levels (25, 30, 35, 40, 45, and 50 mg per kilogram of rats' weight). These doses were dissolved in distilled water at a volume percentage of 1% and administered through subcutaneous injections every other day.

The *Bisfaij* group 300 received 300 mg/kg of the Bisfaij hydroalcoholic extract for body weight 30 minutes before PTZ administration. This dosage was prepared by diluting it with distilled water to a concentration of 1%.

Bisfaij group 500 received a dosage of 500 mg/kg hydroalcoholic extract of *Bisfaij* of body weight 30 minutes before the administration of PTZ. This dosage consisted of the hydroalcoholic extract of *Bisfaij*, which was orally administered using a gavage syringe and diluted to 1%. Similarly, sodium valproate groups 150 and 300 received 150 and 300 mg sodium valproate, respectively, diluted with distilled water at a concentration of 1% per kilogram of body weight 30 minutes before PTZ injection. Oral administration was performed using a gavage syringe. Subsequently, the movements of the rats within 30 min were meticulously recorded by a camera and subjected to behavioral assessments focusing on seizure severity and seizure onset time.

The severity of seizures was evaluated according to the following criteria:[27]

- *Score 0: Absence of any observable reaction.*

- *Score 1: Facial and ear twitches.*

- *Score 2: Myoclonic jerks of the body.*

- *Score 3: Clonic movements involving the front limbs.*

- *Score 4: Generalized clonic seizures, leading to the animal turning to one side.*

- *Score 5: Generalized tonic-clonic seizure.*

- *Score 6: Equivalent to animal demise.*

Ultimately, all rats were anesthetized via intraperitoneal injection of 80 mg/kg ketamine (Sigma Aldrich Co.) and sacrificed under the Helsinki Declaration of 1975.

Statistical Analysis

Data are presented as means±standard error of the mean. The comparison between groups was done with a one-way analysis of variance (ANOVA) test, followed by Tukey's post-hoc test. P values <0.05 were considered as statistically significant. The data were analyzed using IBM Statistical Package for the Social Sciences software version 22 (IBM Co. Armonk, NY). Additionally, Microsoft Excel (version 2013) was used to create tables and graphs to represent the results visually.

RESULTS

Upon examining the relationship between the average seizure onset time across the studied groups, the results indicated a lack of significant differences in seizure onset time between the second and third injections (p value >0.05). However, in the fourth iteration, the findings revealed a substantial increase in seizure onset time for the *Bisfaij* 300 (p value=0.007) and *500* (p value=0.004) compared to group sodium valproate 300. This disparity did not reach significance for any of the groups compared to the reference group. In the fifth injection round, a notable reduction in the mean and standard deviation of seizure onset time was observed in the sodium valproate 150 group compared with the bisfaij 300 group, and this difference was statistically significant (p value=0.006).

In the sodium valproate 150, the seizure onset time was 7.50±9.38 minutes. However, even during this time, there was no significant reduction in the seizure onset time compared with the reference time. In the sixth injection, groups of sodium valproate 150 and sodium valproate 300 exhibited a significant decrease in seizure onset time compared with group *Bisfaij* 300 (p values of 0.03 and 0.02, respectively). Moving on to the seventh injection, group *Bisfaij* 300 displayed a prolonged seizure time compared with group sodium valproate 150, and a statistically significant difference was observed between these two groups (p value=0.002). Furthermore, significant differences were reported between group *Bisfaij* 300 and the reference group and between group sodium valproate 300 and the reference group. Detailed information on seizure onset and its intergroup relationships is presented in Figure 1.

In the current investigation, seizure intensity was assessed using a rating scale ranging from 0 to 6, and the study aimed to explore the correlation between average seizure intensity across different groups. In the second injection round, the findings indicated no significant difference in seizure severity among the groups (p value >0.05). In the third injection round, the seizure intensity in group *Bisfaij* 300 was notably lower than in the sodium valproate 150 (p value=0.03). However, this difference was not statistically significant when comparing *Bisfaij* 300 with the reference group. During the fourth injection round, the intensity of seizures in the Bisfaij 500 group was significantly lower than that in the sodium valproate 150 and 300 (p value=0.01). There were no significant differences in seizure severity among the intervention groups for the fifth and sixth injections. However, in the seventh injection, the intensity of seizures in group *Bisfaij* 300 was significantly lower than in the reference group and the *Bisfaij* 500 and sodium valproate 150. The graphical representation illustrates that group *Bisfaij* 300 exhibited the lowest seizure intensity during the fifth and seventh injections compared with the other groups (0.7±0.47 and 0.6±0.42, respectively) (Figure 2).

DISCUSSION

Sodium valproate is a relatively side-effect-free compound routinely used.[28] However, its side effects, especially its teratogenicity, are attracting increasing attention. The term "fetal valproate syndrome" indicates that multiple organ malformations have been observed.[29] In one study, the authors further confirmed the teratogenetic effects of sodium valproate on fetuses when pregnant mice were exposed to this compound during the gestational period of organ formation, i.e., gestational day 6 to day 9 in mice.[30] A hypoplastic right ventricle has been reported in a fetus exposed to valproate.[31]

Sodium valproate has a broad spectrum of anticonvulsive properties. The most commonly reported side effects involve

the gastrointestinal tract, including nausea, vomiting, abdominal cramps, and diarrhea. Sodium valproate can also have transient effects on the CNS, such as drowsiness and sedation. Most patients report an overall feeling of increased alertness. Sodium valproate inhibits the secondary phase of platelet aggregation. Consequently, prolonged bleeding times and thrombocytopenia have been reported in some cases, primarily in children.[32]

The advent of newer anticonvulsants has expanded therapeutic options, with new drugs showing fewer interactions and reduced hypersensitivity compared to older medications. However, these newer drugs have not been effective in decreasing the prevalence of drug-resistant epilepsy or in preventing epilepsy in high-risk individuals. There is an urgent need for renewed efforts in antiepileptic drug development to discover more effective treatments for drug-resistant epilepsy, including severe and catastrophic forms.[33]

The use of complementary and alternative medicine, including among patients with epilepsy, is increasing. Herbal medicines, one of the most popular alternative medicines, are perceived by many users as safe and effective.[34] Although herbal treatments are widely employed in epilepsy management, solid evidence supporting their efficacy and toxicity profiles is lacking. Therefore, herbal remedies must undergo evidence-based evaluation.[35]

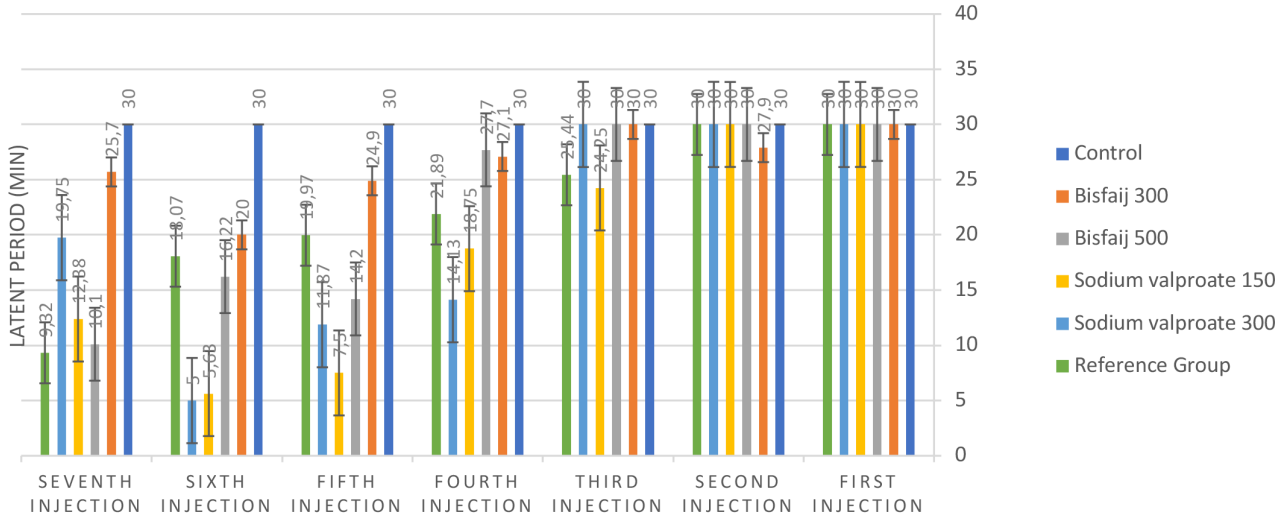
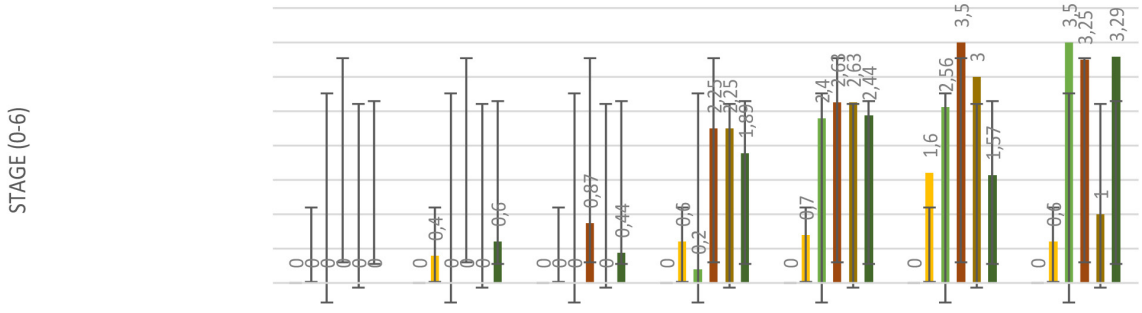


Figure 1. Comparison of seizure onset times in the studied groups from the first to seventh injection of pentylenetetrazole
- In the seventh injection, 19.75 and 25.7 values indicate the significance of the difference between the mean values of each group and the reference group
- In the seventh injection, values of 10.1, 12.38, and 19.75 indicate the significance of the difference between the mean values of each group and the control group



	First Injection	Second injection	Third Injection	Fourth Injection	Fifth Injection	Sixth Injection	Seventh Injection
Control Group	0	0	0	0	0	0	0
Bisfaij 300	0	0,4	0	0,6	0,7	1,6	0,6
Bisfaij 500	0	0	0	0,2	2,4	2,56	3,5
Sodium valproate 150	0	0	0,87	2,25	2,63	3,5	3,25
Sodium valproate 300	0	0	0	2,25	2,63	3	1
Reference Group	0	0,6	0,44	1,89	2,44	1,57	3,29

Figure 2. Comparison of seizure severity in the study groups from the first to seventh injection
- In the seventh injection, 0.6 and 1 indicate the significance of the difference between the mean value of each group and the reference group
- In the seventh injection, the 3.5, 3.25, and 3.29 values indicate the significance of the difference between the mean values of each group and the control group

The current study, employing a behavioral approach, investigated the impact of the hydroalcoholic extract of *Polypodium vulgare L. (Bisfaij)* on PTZ-induced epilepsy using the kindling method. The findings suggest that administration of a 300 mg dose of *Polypodium vulgare L.* extract per kilogram of body weight and time at the onset of seizures demonstrated greater efficacy regarding both the onset time and intensity of convulsive attacks than other intervention groups. The study's outcomes regarding the average seizure onset time revealed that group 1 exhibited a longer average seizure onset time than the other intervention groups. Consequently, group 1, which received a 300 mg dose of *Polypodium vulgare L.* hydroalcoholic extract, demonstrated more favorable results than the other drug groups and notably outperformed group 2. Moreover, the mean intensity of epilepsy was lower in group 1 than in the other four groups.

In light of these findings, it can be concluded that the therapeutic efficacy of the hydroalcoholic extract of *Polypodium vulgare L* is more pronounced at a dose of 300 mg/kg than at a dose of 500 mg/kg. Additionally, behavioral observations from this study indicate that the 300 mg dose of hydroalcoholic extract of *Polypodium vulgare L.* resulted in a lower average epilepsy score among the animals in the intervention groups. This suggests a more significant reduction in the intensity of explosive attacks than in the other intervention groups.

Based on these findings, it can be deduced that the therapeutic effects of the 300 mg dose of *Polypodium vulgare L.* surpass those of the 500 mg dose. Within the sodium valproate intervention groups, the study results indicated that a dose of 300 mg per kilogram exhibited greater therapeutic efficacy than a 150 mg per kilogram dosage concerning the onset time of seizures and intensity of convulsive attacks in animals. Ultimately, the 300 mg dose of *Polypodium vulgare L.* demonstrated superior effectiveness to its 500 mg dose and the 300 and 150 mg doses of sodium valproate in treating PTZ-induced epilepsy. This superiority was reflected in the reduction of convulsive attack intensity and its delayed onset.

The research on the antiepileptic effects of the *Bisfaij* plant is notably limited. Phytochemical investigations have revealed that the rhizome of the *Bisfaij* plant harbors various medicinal compounds, such as *Polypodin A* and *Polypodin B*. These compounds exert protective effects against neurological and neurodegenerative disorders. Furthermore, it has been noted that the caffeine content of *Bisfaij* exhibits a stimulating effect on adrenergic receptors and possesses antioxidant properties. While these findings suggest the potential therapeutic benefits of *Bisfaij*, further comprehensive studies are warranted to elucidate and validate its antiepileptic properties.[36]

One study suggested that *Polypodin A*, a compound found in the *Bisfaij* plant, reduces the neuroleptic effect of apomorphine in laboratory animals. This implies that *Polypodin A* may modulate or mitigate the neuroleptic effects induced by apomorphine in experimental settings.[37] GABA is a gamma-amino acid with a molecular structure that includes a butanoic acid backbone, where the amine group is substituted at the C-4 position. GABA is a neurotransmitter that plays a pivotal role in human metabolism. It serves as an inhibitory neurotransmitter in the CNS, exerting influence over diverse physiological processes, such as regulating neuronal excitability and modulating mood. GABA's inhibitory actions contribute to maintaining a balance in neural activity and preventing excessive neuronal firing.[38] Given the existence of butyric acid within the rhizomes of the *Bisfaij* plant[18] and its structural correlation with the neurotransmitter GABA, there may be a linkage between the presence of this compound and the mechanism underlying the anticonvulsant effects attributed to the *Bisfaij* plant. This observation paves the way for future research investigations, emphasizing the importance of exploring this connection in subsequent studies.

Study Limitations

A notable strength of this study lies in its use of the animal kindling method, which provides a robust foundation for investigations. Additionally, including two distinct doses of the *Bisfaij* plant juxtaposed against conventional anticonvulsant drugs for disease management adds depth to the research design. However, certain limitations should be acknowledged. The present study did not examine serum factors implicated in epilepsy development, suggesting the need for subsequent laboratory analyses in future research.

CONCLUSION

This study demonstrated that the hydroalcoholic extract of *Polypodium vulgare L.* (*Bisfaij*) has significant therapeutic potential for treating PTZ-induced epilepsy in animal models. These findings suggest that *Polypodium vulgare L.* may offer a promising alternative treatment for epilepsy, possibly because of its active compounds, such as *Polypodin A* and caffeic acid, which may interact with GABAergic mechanisms. However, further studies are needed to elucidate the precise mechanisms of action and explore this extract's potential clinical applications in epilepsy management. The mechanism underlying the anticonvulsant effects of bisfaij plants remains unexplored in this study, representing another avenue for future investigation.

Ethics

Ethics Committee Approval: The study was approved by the Fasa University of Medical Sciences Research Ethics Committees (approval number: e-9210, date: 01.10.2013).

Informed Consent: Animal experiment.

Footnotes

Authorship Contributions

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

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

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Effects of Perampanel on Electroencephalography

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Abstract

Objective: Perampanel (PER), a noncompetitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonist, has been approved as adjunctive therapy for focal and generalized epilepsy. Limited information is available regarding the measurable impact of anti-seizure medications (ASM). In this study, we aimed to investigate the effects of PER on electroencephalography (EEG) background activity and interictal epileptic discharge.

Methods: This study included all patients with a clinical diagnosis of epilepsy who underwent routine EEG before and after PER treatment between 2018 and 2023. EEG findings were examined according to their background activity and clinical features such as risk factors of epilepsy, the occurrence of sleep-related seizures, sleep disorders, intellectual disability, abnormality of magnetic resonance imaging and EEG, multifocal features on EEG, the duration between EEG and initiation of PER treatment, frequency of seizures before and after PER treatment (seizure freedom or >50% reduction in seizures), previous epilepsy surgery, the number of current and previous ASM, and dosage of PER.

Results: In a total of 11 patients, epilepsy type was focal in 8 (73%), all of the patients were on polytherapy, and 4 of them had undergone epilepsy surgery. PER treatment resulted in seizure freedom in 36% of patients and a >50% decrease in seizures in 55% of patients. There was no statistically significant relationship between background activity, phase reversal, and equipotential in EEG before and after PER treatment. In addition, pre- and posttreatment responses to activation procedures and disruption in sleep structure did not differ significantly. The relationship between seizure freedom and phase reversal decrease after PER treatment was statistically significant. The relationship between a >50% decrease in the frequency of seizures and epileptic discharges also reached statistical significance.

Conclusion: To summarize, seizure freedom following PER treatment appears to be associated with reduced epileptic discharge, and EEG monitoring might help determine prognosis.

Keywords: Perampanel, epileptic discharges, epilepsy, treatment response

INTRODUCTION

The effects of anti-seizure medications (ASM) on electroencephalography (EEG) have attracted interest since the discovery of scalp EEG in 1924.[1] Changes in alpha rhythm and mental processes after the use of various medications have been defined.[2] In studies of healthy subjects, phenytoin, phenobarbital, valproate, carbamazepine, oxcarbazepine, and gabapentin slow down the background rhythms on EEG.[3-6]

Traditionally, the frequency of seizures reported by patients or relatives is used to measure response to ASM.[7] Nevertheless, patients are usually unaware of up to 60% of their seizures when they are awake and up to 80% of their seizures during sleep.[8,9] In addition, patients might not be aware of epileptiform activity when they appear.[10,11] Accordingly, the epileptiform discharge burden on EEG rather than the declared seizure frequency might be a more reliable measure of disease activity.[12-17] Given these factors, long-term EEG recordings that assess epileptiform discharge burden might provide a more objective indicator of prognosis and improvement after ASM initiation.[11-18]

Perampanel (PER), a non-competitive α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, receptor antagonist, received approval from the European Medicine Agency (EMA) for use as an adjunctive therapy for both focal and generalized epilepsy, and it has demonstrated efficacy in various off-label clinical scenarios, from myoclonic epilepsy to status epilepticus.[19-22] Among all available ASMs, PER is the sole medication that directly inhibits glutamatergic pathways.[23]

Little is described about the measurable effect of ASM on epileptiform discharge in focal and generalized epilepsy. Few studies have investigated the effects of newer ASMs. This study aimed to evaluate the effects of PER on EEG.[24] Our results might provide a different

perspective on the effects of PER on the central nervous system and the potential use of EEG to monitor the efficacy of PER.

METHODS

This study included all patients with a clinical diagnosis of epilepsy who underwent routine EEG before and after PER treatment between 2018 and 2023. Patients whose EEG data were unavailable before or after treatment were excluded from our study. A structured recording protocol was used. All outpatient EEG recordings consisted of 2h of awake and sleep periods, and all patients underwent hyperventilation and intermittent photic stimulation at the beginning and end of the recording twice per 5 min.

Gold EEG electrodes were placed at Fp1, Fp2, F3, F4, F7, F8, T3, T4, T5, T6, C3, C4, Fz, Cz, Pz, P3, P4, O1, and O2 according to the international 10-20 system, and EEGs were recorded on a 21-channel digital machine. The Oz electrode was applied as a system reference during recording. Bandpass was 0.3-70 Hz. Gains (all channels) were adjusted for each subject to optimize the range of the analog-to-digital converter. All EEG data were reported by a well-experienced epileptologist and clinical neurophysiologist (C.G.). EEG endpoints were assessed by manual counting. Phase reversals and equipotential were counted by a clinical neurophysiologist (İ.E.).

EEG findings were examined according to background activity and clinical features such as risk factors of epilepsy (febrile seizures, head trauma, perinatal injury, central nervous system disorder, stroke, consanguinity, family history of epilepsy or febrile seizures), occurrence of sleep-related seizures, sleep disorders, intellectual disability, abnormality of magnetic resonance imaging (MRI) and EEG, multifocal features on EEG, duration between EEG and initiation of PER treatment, frequency of seizures before and after PER treatment (seizure freedom or >50% reduction in seizures), previous epilepsy surgery, number of current and previous ASM, and dosage of PER.

The primary endpoint of this study was the number of phase reversals and equipotential, as well as the change in the frequency of background EEG rhythms (alpha, theta, beta and delta) before and after PER treatment. The secondary endpoint was reduced seizures by more than 50% and seizure freedom after PER treatment.

Statistical Analysis

Categorical variables are presented as numbers (%), and continuous variables are presented as medians [minimum (min) and maximum (max)]. If non-parametric variables showed normal distribution, the independent samples t-test was used; if they did not, the Mann-Whitney U test was used. When parameters did not show normal distribution, the Wilcoxon test was used to assess statistical differences in continuous variables. The χ^2 test or Fisher's exact test was used to assess statistical differences in categorical variables. All statistical analyses were performed using the Statistical Package for the Social Sciences 22.0. A p value of <0.05 was considered statistically significant.

This study was approved by the Institutional Review Board of the Faculty of Medicine, Koç University (decision no: EMA/sk/258/2024, date: 20.02.2024). Oral informed consent was obtained from all patients. In a total of 11 patients, there were five female patients; the mean age was 30 [standard deviation (SD): 15.3, min: 8, max: 61], median age at epilepsy onset was 14 (min: 4, max: 20), and mean duration of epilepsy was 11 years (SD: 17.1, min: 0, max: 57). Epilepsy type was focal in 8 (73%) patients: all patients were on polytherapy and 4 of them had undergone epilepsy surgery. The patients' medical history consisted of febrile seizures in 2, head trauma in 3, cerebrovascular disease in 1, and central nervous system disorder in 1 of the patients. Family history of febrile seizures and epilepsy in 1 and epilepsy in 6. There was an intellectual disability in 4 of the patients. The demonstration features are detailed in Table 1.

PER treatment resulted in seizure freedom in 36% of patients and a >50% decrease in seizures in 55% of patients. EEG abnormalities were found in 91% of patients, multifocal EEG findings were described in 46%, and MRI was abnormal in 55% of patients. The mean duration from the initiation of PER treatment to the EEG recording was 221 days, and the mean duration from the PER treatment to the second EEG recording was 185 days. The median number of ASM was 4.2 (SD: 1.2), and the mean number of previous ASM use was 3.7 (SD: 2.3).

Table 1. Baseline characteristics of all patients (n=11)

Baseline characteristics	Findings
Mean age (SD) (years)	30 (±15.3)
Female gender; n	5
Median age at seizure onset (years)	14
Mean duration of epilepsy (years)	11 (±17.1)
Epilepsy type-focal (%)	8 (73%)
Number of current ASMs (median)	4.2
Seizure freedom after PER (%)	36%
>50% reduction in seizures	55%
Perampanel dosage (median) (mg)	4.5
Risk factors for seizures	
Febrile seizures (n)	2
Head trauma (n)	3
Central nervous system disorder (n)	1
Cerebrovascular disease (n)	1
Consanguinity (n)	0
Family history of epilepsy (n)	6
Febrile seizures in children	1

SD: Standard deviation, PER: Perampanel, ASM: Anti-seizure medications

MAIN POINTS

- Perampanel (PER), a non-competitive alpha-amino-3-hydroxy-5-methyl-4-isooxazole-propionic acid receptor antagonist, received approval from the European Medicine Agency for use as an adjunctive therapy for both focal and generalized epilepsy.
- The decreased rate of phase reversals was correlated with seizure freedom and a >50% reduction in seizures.
- Electroencephalography may be a valuable tool for evaluating patient response rates to PER.

RESULTS

The mean number of phase reversals on EEG were 722 and 411 before and after PER, respectively. The mean number of equipotential before and after PER was 74 and 323, respectively. There was no statistically significant relationship between background activity, phase reversal, and equipotential in EEG before and after PER treatment. In addition, pre- and posttreatment responses to activation procedures and disruption in sleep structure did not differ significantly. Beta activity was present in 4 patients on different ASM that were known to cause this activity on EEG. When we combined equipotentials and phase reversals as epileptic discharges, the pre-and post-treatment statistical results were not significant.

On the other hand, the relationship between seizure freedom and the decrease in phase reversals after PER treatment was statistically significant (p=0.03). The relationship between a >50% decrease in the frequency of seizures and epileptic discharges also reached statistical significance (p=0.0058).

The decrease in phase reversal and equipotential was not related to the dosage of PER, epilepsy type, age, sex, age at seizure onset, occurrence of intellectual disability, duration of epilepsy, abnormalities in MRI and EEG, number of current ASMs, number of previous ASMs, risk factors of epilepsy, and occurrence of sleep-related seizures.

DISCUSSION

Interictal spikes on EEG are strongly associated with the existence of epilepsy, and spikes reflect inhibitory mechanisms.[25] This study investigated the effects of PER on EEG in patients with epilepsy and showed that seizure freedom after PER treatment is related to a decrease in epileptiform discharge (phase reversals) on EEG. The findings of this study suggest that phase reversals may be a valuable marker of ASM response.

Interictal spikes are particularly indicative of epilepsy because they result from the paroxysmal discharges of large groups of neurons.[26,27] However, the connection between spikes and seizure generation remains contentious because of conflicting evidence.[28-30] Although earlier research examining short-term EEGs showed a limited link between seizure management and epileptiform discharges, recent studies investigating extended EEGs have demonstrated that a decrease in epileptogenic discharge burden is associated with enhanced seizure control.[13-15,17] The variations in the outcomes of these studies might be attributed to the disparity in the duration of EEG recordings utilised.[31] Extended EEG recordings might offer a more precise evaluation of epileptic discharge burden because they can account for fluctuations occurring within ultradian and circadian cycles.[32,33] In our study, even if the EEGs were not long-term monitoring, they were longer than the routine 20-min EEGs. Because we monitored only one sleep cycle, we believe we could measure ultradian fluctuations correctly. We observed synchronous and symmetrical sleep-related EEG activities in 90% of the patients. The efficacy of sleep did not change after treatment.

Similar to our findings, a recent study demonstrated that PER is more effective against epilepsy presenting with second bilateral synchrony on EEG and other epileptic discharges. Another study investigating the effect of PER on EEG spectral power and connectivity showed an increase in theta power, and researchers linked this interaction to increased sleepiness among PER users.[34] However, our study did not confirm this finding because we observed no remarkable change in background activity. In addition, one study reported increased beta activity among PER users, whereas another study did not replicate this finding, which is similar to our study.[34,35]

The current literature suggests that valproic acid, ethosuximide, and levetiracetam might decrease the epileptic discharge burden in both treatment-naive and treatment-resistant genetic generalized epilepsies.[31] Similarly, levetiracetam has been reported to create a consistent long-term reduction in interictal spikes over 4-18 months.[16,36] A study conducted with patients with focal epilepsy demonstrated that interictal epileptiform discharges decreased during treatment with carbamazepine. Moreover, the decreased interictal discharges were found to be related to seizure freedom.[37] In our study, a decrease in phase reversal among patients with seizure freedom was statistically significant, and the rate of decrease in seizures by >50% was nearly statistically significant. These findings might be interpretable in follow-up EEGs in patients with epilepsy, which provide valuable data regarding seizure outcomes.

Earlier research proposed the use of quantitative EEG (qEEG) to identify ASM-induced neurotoxicity.[4,38] However, qEEG has not been extensively used in neurological practice, and it is usually confined to research laboratories.[39] Therefore, the practical application of qEEG is limited. As in our study, even if visual inspection might be time-consuming in clinical practice, it provides valuable information about treatment response in patients with epilepsy.

Study Limitations

There are limitations to our study. First, only a small number of patients are eligible to be included in the study. Since PER is not within the scope of reimbursement by the social security institution and not all patients have undergone pre- and post-treatment EEG, this study included a small sample to analyze. Finally, this study could not isolate the exclusive impact of PER alone because it has not been approved for use as a monotherapy, which poses a potential constraint in our study. Additionally, variability in the PER dosage was observed because of personalized treatment approaches.

CONCLUSION

In conclusion, seizure freedom after PER treatment seems to be related to decreased epileptic discharge, and EEG monitoring might help determine prognosis. Conclusive findings could not be obtained regarding this matter because of the limited number of patients included in this study. Additional research is required to address this issue in a more extensive cohort.

Ethics

Ethics Committee Approval: This study was approved by the Institutional Review Board of the Faculty of Medicine, Koç University (decision no: EMA/sk/258/2024, date: 20.02.2024).

Informed Consent: Oral informed consent was obtained from all patients.

Footnotes

Authorship Contributions

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

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

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Archives of Epilepsy

Original Article

The Importance of Epileptiform Activities in Breach Rhythms

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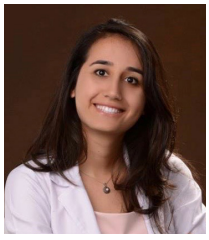

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Abstract

Objective: The breach rhythm is a benign activity variant that can be confused with epileptiform discharges. We aimed to investigate the relationship between breach rhythms and seizures, even though they are known as benign variants. In addition, to identify whether the seizure was related to seizures and which conditions should be considered by electroencephalographers.

Methods: Electroencephalograph records recorded between October 2017 and March 2021 were re-examined. Breach rhythms were classified for localization, frequency, morphology, and presence/absence of sporadic epileptiform discharges. The placement of skull defects, etiology of skull defects, presence of encephalomalacia, symptomatic seizures, and anti-seizure medication use were documented. Statistical analysis was performed using Statistical Package for Social Sciences software version 26.0.

Results: We included 71 recorded breach rhythm activities. All breach rhythms had a similar placement to skull defects. Twenty-three (32.4%) patients had an epileptiform abnormality with a breach rhythm in the same area. The presence of epileptiform abnormalities was associated with seizures more than 4.5 times [p=0.004, odds ratio (OR): 4.667]. The theta frequency was related to the presence of sporadic epileptiform activity exceeding 3.3 times (p=0.029, OR: 3.316).

Conclusion: Our study showed that breach rhythms are unrelated to seizure unless sporadic epileptiform activity is present. If the breach rhythm frequency is theta, the risk of sporadic epileptiform activity is higher than the alpha or beta frequency breach rhythm. According to our study results, the breach rhythm is a benign variant, unless accompanied by sporadic epileptiform discharges.

Keywords: Benign variants, breach effect, breach rhythm, epileptiform discharges, seizure

INTRODUCTION

The primary aim of all electroencephalographers is correct detection of epileptiform activities. Before we decide whether the activity is an epileptiform discharge, we consider whether there are artifacts, benign variants, or graph elements in the sleep. Breach rhythm or "breach effect" is classified as a benign variant, as described by Cobb et al.[1] in 1979. It is known to occur because of skull defects. The presence of bone prevents electrophysiological activity from the brain to the scalp.[1,2] The morphology of breach is typically sharply countered, with a higher amplitude, and generally 6-11 Hz but may have a faster or slower frequency.[1-4] Breach rhythms can be intermittent or continuous. If they are intermittent, this may lead to misdiagnosis as epileptiform activity. The irregular and sharp counter morphology can lead to misdiagnosis of epileptiform activity. On the other hand, the irregular morphology of breach rhythms may mask epileptiform activity in the same places. In addition, according to a three-case series, skull defects may also lead to the consideration of epileptiform discharges as artifacts on electrodes near defects.[5] Although breach rhythms are described and classified as a benign variant owing to skull defects, a few case reports have shown that the breach rhythm appears in patients with osteolytic skull involvement. In addition, breach rhythms may disappear due to seizures, recurrence, or enlargement of tumors.[6-9]

Identifying breach rhythms with/without sporadic epileptiform activity is essential in determining whether patients should be treated according to seizure risks. Our study aimed to investigate the relationship between breach rhythms and seizures, even though they are known as benign variants. In addition, to identify whether they were related to seizures and which conditions should be considered by electroencephalographers.

METHODS

Patients

The clinical data of patients were collected from the hospital archives. Demographic data, seizure history, places of cranium defects, presence of encephalomalacia, and use of anti-seizure medications (ASMs) were recorded.

The study was approved by the Dokuz Eylül University Local Ethics Committee (decision no: 2021/08-38, date: 08.03.2021).

Procedures and Definitions

Electroencephalography (EEG) records obtained between October 2017 and March 2021 from the epilepsy center of Dokuz Eylül University were re-examined, retrospectively. Datasets were re-analyzed if patients had a history of a skull defect or a "breach rhythm/effect" was reported. The investigators collected the data and re-analyzed all EEG records.

For the routine EEG records, the electrodes were placed according to the universal 10-20 system (Fp1, F3, F7, T3, T5, C3, P3, O1, Fz, Cz, Pz, Fp2, F4, T4, C4, P4, O2). The EEG device filters were LFF 0.3 Hz and HFF 70 Hz with a sensitivity of 100 V. The page sweep rate was 10 mm/s. All records considered at least three montages: monopolar, double banana, and transverse. If necessary, Laplacian and other montages were also used. Breach rhythms were described with higher amplitudes than those of the other electrodes and had an irregular sharp or sinusoidal morphology. The frequency, morphology, and continuity of activities were recorded.

The frequency was classified as theta, alpha, and beta. If there was a mixture of frequencies, we considered the lowest frequency for classification. The presence of sporadic epileptiform activity in the breach rhythm was noted. The instances in the EEG records are shown in Figures 1, 2.

All demographic data were documented. Skull defects were classified as frontal, temporal, parietal, or occipital. Additionally, encephalomalacia, the etiology of skull defects, symptomatic seizures, and ASM use were documented. The clinical course and neuroimaging findings of all included patients were re-analyzed.

Statistical Analysis

The statistical analysis was performed using IBM Statistical Package for Social Sciences software version 26.0.[10] The Kolmogorov-Smirnov test was performed for ages (p=0.2), and the histogram distribution was considered for normality tests. Missing data were assigned a missing value when statistical analyses were performed.

Descriptive statistics present the mean and standard deviation for age distribution as a normal variable. Fisher's exact test and the chi-square test were used for categorical variables. Bonferroni correction was used if the variables were more than two. Spearman's correlation analysis was used to determine which variables could be included in the regression analysis model. A binary logistic regression model was used to investigate independent risk factors. The 95% confidence intervals and $p<0.05$ were considered statistically significant.

MAIN POINTS

- Higher amplitude and sharply irregular morphology are the main structures to describe the breach rhythm, which could have any frequency.
- The breach rhythm is not associated with seizures unless it is accompanied by sporadic epileptiform discharges.
- The presence of the theta frequency is associated with a higher risk of sporadic epileptiform discharges in the breach rhythm.

RESULTS

Seventy-one recorded breach rhythm activities were obtained from different patients.

All breach rhythm activities recorded a similar placement as skull and bore hole defects regarding the area of the defects. The descriptive data are summarized in Table 1.

There was no statistical significance for age and sex in the seizure and seizure-free groups (Table 2).

Morphology of Breach Rhythm During Seizure

The breach rhythm morphology was categorized as theta, alpha, mu, and beta. Twenty-one (29.6%) patients had a beta-breach rhythm, 10 (14.1%) patients had an alpha-breach rhythm, eight (11.3%) patients had a mu-breach rhythm, 13 (18.3%) patients had a theta breach rhythm, and 19 (26.8%) patients had and theta and beta breach rhythms. There were no significant differences in the presence of seizures between the subgroups (Tables 1, 2).

Frequency of Breach Rhythm During Seizure

Breach rhythm frequencies were categorized as theta, alpha, and beta. We ranked frequencies according to the lowest frequency if there were more than two differences, such as alpha, theta with or without beta. There were no significant differences between the three frequency subgroups and according to the presence of seizures (p=0.929). Although we categorized the breach frequency in two subgroups, the theta and alpha or beta rhythm, there are no statistically significant differences (p=0.861) (Table 2).

Frequency of Breach Rhythms in Patients with Encephalomalacia

There were no significant difference between the frequency of breach rhythms and the presence of encephalomalacia (p=0.703).

Frequency of Breach Rhythm with Epileptiform Discharges

When breach frequency was divided into two subgroups, the theta and alpha or beta frequency was related to the presence of sporadic epileptiform activity >3.3 times [odds ratio (OR): 3.316, 95% confidence interval (CI): 1.133-9.699; p=0.029] (Tables 3, 4).

Figure 1. A) Breach rhythm with beta frequency, B) Breach rhythm with alfa frequency, C) Breach rhythm with mü morphology, D) Breach rhythm with theta frequency

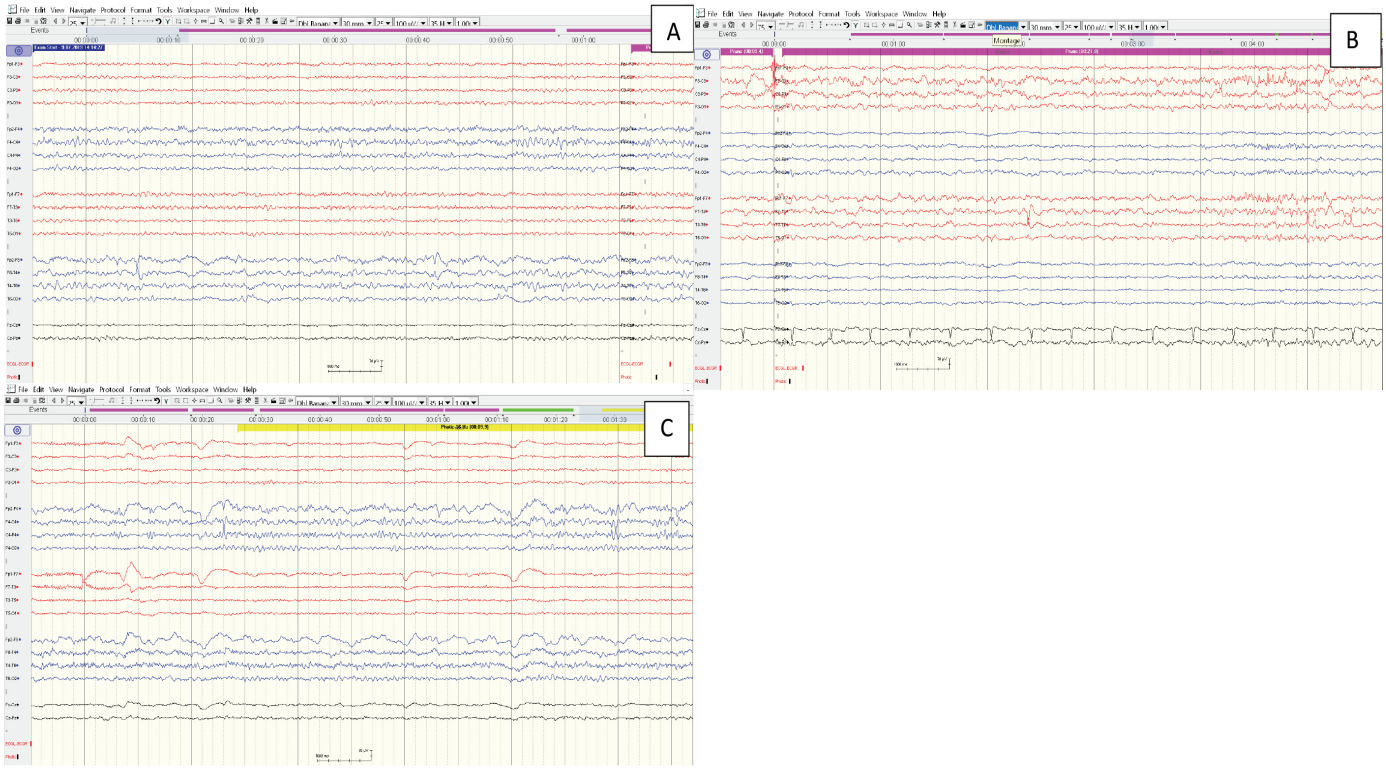

Figure 2. A-C) Breach rhythm with sporadic epileptiform abnormality

Table 1. Demographic and clinical data of patients with breach rhythm

Age, years (n=71)	**Mean±SD 52.55±15.36 (21.00-87.00)**	
Gender	**n**	**%**
Male	33	46.5
Female	38	53.5
Total	71	100.0
Seizure		
Yes	26	36.6
No	45	63.4
Total	71	100.0
ASMs		
Yes	63	88.7
No	8	11.3
Total	71	100.0
Breach morphology		
Theta	13	18.3
Theta-beta	19	26.8
Alpha	10	14.1
Mu	8	11.3
Beta	21	29.6
Total	71	100.0
Breach frequency		
4-7.99 Hz	21	29.6
8-12.99 Hz	18	25.4
>13 Hz	21	45.1
Total	71	100.0
Breach with epileptiform discharges		
Yes	23	32.4
No	48	67.6
Total	71	100.0
Localization of breach rhythm		
F3/4	13	18.3
F7/8	21	29.6
C3/4	10	14.1
T3/4	22	31.0
P3/4	4	5.6
O1/O2	1	1.4
Total	71	100.0
Encephalomalacia		
With encephalomalacia	58	88.1
Without encephalomalacia	8	11.9
Total	67	100.0
Missing	4	
Localization of cranium defect		
Frontal	30	44.8
Temporal	20	29.9
Parietal	15	22.4
Occipital	2	3.0
Total	67	100.0
Missing	4	
Etiology of skull defect		
Head trauma	7	10.1
Tumor surgery	37	53.6
Intracranial hemorrhage	19	27.5
Epilepsy surgery	6	8.7
Total	69	100.0
Missing	2	

ASMs: Anti-seizure medications, SD: Standard deviation

Breach Rhythms Associated with Epileptiform Activity and Seizures

The data were divided into two main groups according to breach rhythms with and without sporadic epileptiform activity (spike and/or sharp wave). Twenty-three (32.4%) patients had an epileptiform abnormality with breach rhythm in the same area, whereas 48 (67.6%) patients had only breach rhythm (Table 1). The presence of epileptiform abnormalities was associated with seizures more than 4.5 times (OR: 4.667, 95% CI: 1.613-13.498; p=0.004) (Table 5).

Localization of Breach Rhythm Associated with Epileptiform Activity

The localization of breach rhythm was categorized into temporal and extratemporal subgroups. There was no statistical significance regarding the localization of breach and the presence of sporadic epileptiform activity (OR: 2.832, 95% CI: 0.870-9.220; p=0.084) (Tables 3, 4).

DISCUSSION

Our study showed that breach rhythms were unrelated to seizures, except in cases with sporadic epileptiform activity. The presence of sporadic epileptiform discharges increases the independent risk of seizures by more than 4.6 times. In addition, lower frequency, as a theta breach rhythm, was associated with a 3.3-fold risk of sporadic epileptiform discharges with breach rhythm.

Identifying sporadic epileptiform discharges in the breach rhythm may be challenging for two reasons. One explanation is that irregular and sharp breach rhythms may mask epileptiform discharges. Second, artifacts in the same area may conceal sporadic epileptiform discharges that imitate natural phenomena. Mader et al.[5] highlighted the importance of using the 10-10 universal electrode system in patients with skull defects because artifacts can mask epileptiform activity. On the other hand, the breach effect appears in magnetoencephalography (MEG) less than EEG, so the authors suggested using MEG as an alternative.[11] The main requirement for evaluating sporadic epileptiform discharges is to follow the six rules in the International Federation of Clinical Neurophysiology glossary of terms.[12] In addition, sporadic epileptiform discharges have frequencies and amplitudes that differ from the breach rhythms.[4] Drowsiness and nonrapid eye movement sleep stages help evaluate physician-patient breach rhythms from sporadic epileptiform discharges.[13] Our study highlights these beneficial findings: breach rhythms with theta frequency have a higher risk of sporadic epileptiform discharges in the same area than other breach rhythms with higher frequencies.

The area of breach rhythm recording was the same as that of skull defects. Our study results are concordant with these findings. The cause of breach rhythms is known as skull defect. Lyudmilov et al.[9] suggested that breach rhythms might be affected by the functional state of brain tissue based on a case report; during electrographic seizures, breach rhythms did not register in a patient with a skull defect, but after electrographic seizures were treated, breach rhythm appeared. In other cases, there were reports of changes in breach rhythms according to the performance of serial EEGs, and it was observed that the differences might be related to tumor growth.[7]

Table 2. Statistical analysis of seizure and its variables

	With seizure (n,%)	Without seizures (n,%)	p value
Age (years)	49.96±14.73*	54.04±15.67*	0.284[a]
Sex (female)	11, 28.9	27, 71.1	0.150[b]
Encephalomalacia (with)	24, 40.7	35, 59.3	0.242[c]
Breach frequency			
Beta-alpha	15, 37.5	11, 35.5	0.861[b]
Theta	11, 35.5	20, 64.5	
Breach localization			
Centro-temporal	12, 42.9	16, 57.1	0.379[b]
Extra-temporal	14, 32.6	29, 67.4	
Epileptiform discharges			
With	14, 60.9	9, 39.1	**0.003[b]**
Without	12, 5.0	35, 75.0	

*Mean±standartd deviation, [a]Independent samples t-test, [b]chi-square, [c]Fisher's exact test, p<0.05

Table 3. Statistical analyses of epileptiform discharges and variables

	With ED (n, %)	Without ED (n, %)	p value
Breach morphology			
Beta	4, 19.0	17, 81.0	
Alpha	4, 40.0	6, 60.0	
Mu	0, 0.0	8, 100.0	
Theta	6, 46.2	7, 53.8	
Beta-theta	9, 47.3	10 52.6	**
Breach frequency			
Beta	4, 19.0	17, 81.0	
Alpha	4, 22.2	14, 77.8	
Theta	15, 46.9	17, 53.1	0.028[a]
Breach frequency			
Beta-alpha	8, 20.0	15, 48.4	
Theta	32, 80.0	16, 51.6	**0.011[b]**
Breach localization			
Centro-temporal	5, 17.9	23, 82.1	
Extra-temporal	18, 41.9	25, 58.1	0.035[b,#]

**Small sample size, achi-square, linear by linear association p<0.016, Bonferroni correction, bchi-square, Pearson p<0.05.
[b,#]Differences were disappeared with logistic regression analysis.
ED: Epileptiform discharges

Table 4. Binary logistic regression analysis to predict the presence of epileptiform discharge with breach rhythm

Model-1				**-2 Log-likelihood=79.771**	
Model variables	B	SE	p value	OR	95% CI for Exp (B)
Constant	-2.013	0.574	<0.000		
Breach localization	1.041	0.602	0.084	2.832	0.870-9.220
Breach frequency-theta	1.199	0.548	**0.029**	**3.316**	**1.133-9.699**

Extratemporal, alpha-beta frequency, Omnibus p=0.008.
Hosmer-Lemeshow p=0.960.
SE: Standard error, OR: Odds ratio, CI: Confidence interval

Table 5. Binary logistic regression analysis to predict seizure in patients with breach rhythm

Model-1				**-2 Log-likelihood=4.773**	
Model variables	B	SE	p value	OR	95% CI for Exp (B)
Constant	-1.099	0.333	0.001		
Epileptiform discharges (with)	1.54	0.542	**0.004**	**4.667**	**1.613-13.498**

Without epileptiform discharges, Omnibus p=0.004.
SE: Standard error, OR: Odds ratio, CI: Confidence interval

These observations suggest that the functional state of brain tissue may lead to a breach rhythm. Our study findings did not include serial EEG recordings of the same patients, although in our cohort encephalomalacia did not differ in the morphology and frequency of breach rhythms. However, our cohort did not include patients with electrographic seizures or untreated tumors. These two cases and our case series all had skull defects, confirming that the single source of breach rhythms is skull defects.[5] However, more longitudinal studies with these patient groups must be performed to discuss the pathophysiology of breach rhythms, whether their only source is skull defects, or whether functional brain mechanisms may involve breach rhythm appearance.

Breach location can be anywhere on the skull. The temporal region was the most frequent location in our cohort, followed by the frontotemporal region and central region. Our results showed no differences in morphology and frequency according to location. In addition, no differences were observed among patients with signs of seizure or the presence of sporadic epileptiform activity in our cohort. However, the most critical limitations of this study are the not equal, even not similar, distributions of the subgroups. In addition, the temporal breach rhythm was the most frequent region of breach localization. Electroencephalographers should evaluate benign epileptiform variants more carefully because they can be localized more temporally than other locations, which can cause misdiagnosed wicket spikes.[5,14]

Study Limitations

Our study has several limitations. First, it included retrospective data, which led to missing values and a heterogeneous distribution of subgroups. Second, we did not perform a follow-up EEG, which might have allowed us to comment that the pathophysiologic source of the breach rhythms was skull defects alone. However, only a few studies have been conducted on this topic, which renders the results of these studies valuable.

CONCLUSION

In conclusion, our study showed that breach rhythms are unrelated to seizures unless sporadic epileptiform activity is present. If the breach rhythm frequency is theta, the risk of sporadic epileptiform activity is higher than that of alpha or beta frequency breach rhythms.

Ethics

Ethics Committee Approval: The study was approved by the Dokuz Eylül University Local Ethics Committee (decision no: 2021/08-38, date: 08.03.2021).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Medical Practices: D.M.D., İ.Ö., B.B., Concept: D.M.D., İ.Ö., B.B., Design: D.M.D., İ.Ö., B.B., Data Collection or Processing: D.M.D., Analysis or Interpretation: D.M.D., İ.Ö., B.B., Literature Search: D.M.D., İ.Ö., B.B., Writing: D.M.D., İ.Ö., B.B.

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Evaluation of Sleep Disorders in Patients with Epilepsy: A Case-control Study

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Abstract

Objective: There is a bidirectional relationship between sleep and epilepsy. In our study, we aimed to determine the prevalence of sleep disorders in patients diagnosed with epilepsy by evaluating sleep disorders using a questionnaire and to determine whether they are affected by epilepsy type, seizure frequency, and antiepileptic use.

Methods: In this study, 100 patients who were followed up in our epilepsy outpatient clinic and who did not have psychiatric or systemic diseases that may cause underlying sleep disturbance and 50 healthy control groups compatible with them were included. Epworth Sleepiness Scale, STOP-Bang obstructive sleep apnea screening (OSAS) questionnaire test, REM Behavior Disorder-Hong Kong Questionnaire, Swiss Narcolepsy Scale, restless legs syndrome (RLS) Diagnostic Form, Beck Depression Scale, and Beck Anxiety Scale were applied to the patients and controls.

Results: Increased daytime sleepiness was found in 30% of the patients, and up to 50% of these patients had seizures in the last 6 months. The risk of OSAS syndrome was significantly increased in patients with epilepsy, especially in patients with left temporal lobe epilepsy, males, and older patients (p=0.02).The prevalence of RLS was increased in patients with epilepsy, and the risk was higher in female epileptics(p=0.04). Insomnia was 33% in our patient group, and no correlation was found between insomnia and age, gender, and number of anti-seizure medications used. The rate of moderate and severe depression in patients with epilepsy in our study was 45%, which was significantly higher than that in the general population (p=0.03). Anxiety was present in 50% of the patients (p<0.01).

Conclusion: There is a complex relationship between sleep disorders, psychiatric comorbidities, and epilepsy, and the presence of these comorbidities may significantly impair the quality of life of patients. In order to understand this multifaceted relationship, comparative studies with more homogenous groups and patients are needed.

Keywords: Comorbidity, epilepsy, psychiatric disorders, sleep disorders

INTRODUCTION

Insomnia is common among individuals with epilepsy, with an estimated prevalence of up to 50%.[1] Sleep disturbances are approximately twice as common in people with epilepsy as in healthy controls, with approximately one-third of people with epilepsy reporting sleep disturbances.[2] Up to half of newly diagnosed children with epilepsy have sleep disorders upon diagnosis, suggesting a common underlying mechanism or link to the seizures themselves. In fact, sleep disorders are less common when seizures are well controlled.[3,4]

It is thought that cortical excitability increases in non-rapid eye movement (NREM) stage 2 sleep; therefore, seizures are mostly seen in this stage, and desynchronization in rapid eye movement (REM) sleep is antiepileptogenic.[5]

Even if seizures occur during the day or while awake, they may affect sleep and fragment the sleep structure. Fragmentation of sleep leads to decreased sleep quality, increased daytime sleepiness, and sleep deprivation, which may trigger epileptic seizures and increase seizure frequency.[6]

It is known that epileptic seizures may be triggered by sleep deprivation and may occur during sleep. Approximately 20% of epileptic seizures occur during sleep, and this rate increases to 60%, especially in epilepsies originating from the frontal lobe.[7,8]

The frequency and severity of seizures and side effects of antiepileptic drugs (AEDs) may change sleep patterns and decrease sleep quality.[9] This reciprocal relationship between epilepsy and sleep may lead to comorbid psychiatric problems, including depression and anxiety, which are more common in individuals with epilepsy.[10]

It is also important to recognize and treat sleep disorders, depression, and anxiety in patients with epilepsy. With appropriate treatment of these comorbidities, both quality of life and epileptic seizures can be significantly improved and controlled.

METHODS

Our study was conducted between September 2019 and February 2020 by applying questionnaire forms to patients diagnosed with epilepsy over the age of 18 years who had been followed up in the epilepsy outpatient clinic for at least 2 years and who regularly attended the controls. The study protocol was approved by the Ethics Committee of Eskişehir Osmangazi University (decision no: 19, date: 22.01.2019). Patients who presented with single or provoked seizures, those with incomplete differentiation of epileptic seizures, such as syncope or psychogenic seizures, those with severe mental retardation, and those with primary neurological diseases such as tumors, ischemia, demyelinating lesions, previous intracranial operations, or other neurodegenerative diseases causing seizures were not included in the study. Patients with known psychiatric disorders and anti-depressant use who were being followed up by the psychiatry department were also excluded.

A total of 100 patients were included in the study. Questionnaire forms were read and completed by the patients. In cases of incomprehensible questions, the patient was explained while filling out or handing over the questionnaire and was expected to answer. In addition, age, gender, seizure type, seizure frequency in the last 6 months, anti-seizure drugs (ASMs), use of multiple ASMs, and epilepsy syndromes that could be identified based on neuroimaging or video-EEG monitoring information were recorded.

Epworth Sleepiness Scale (ESS), STOP-Bang questionnaire obstructive sleep apnea screening test, REM Behavioral Disorder-Hong Kong Questionnaire (RBDQ-HK), SWISS Narcolepsy Scale, restless legs syndrome (RLS) Diagnostic Form, Beck Depression Scale, and Beck Anxiety Scale were applied.

Questionnaire Forms Used

Epworth Sleepiness Scale: ESS is a scale that evaluates daytime sleepiness.[11,12]

STOP-Bang Questionnaire: This questionnaire is used as a screening test for obstructive sleep apnea.[13]

MAIN POINTS

- Patients with epilepsy have a higher risk of psychiatric and sleep disorders.
- Because seizure frequency and antiepileptic drug use may change sleep structure and efficiency, sleep habits should be routinely evaluated.
- The risk of obstructive sleep apnea screening is higher in males and older adults, especially in patients with left temporal lobe epilepsy.
- Comorbid sleep and psychiatric disorders should be considered and treated.

The Diagnostic and Statistical Manual of Mental Disorders criteria were adapted to define insomnia based on a "yes" response to any of the following.[14]

Restless Legs Syndrome Diagnosis Form: The RLS Diagnosis Form, developed by the International Restless Legs Syndrome Study Group, was first created in 1995 and revised in 2012 in light of new data.[15]

REM Behavior Disorder Questionnaire-Hong Kong: The RBDQ-HK, which can be used as a screening test in REM behavior disorder to evaluate the severity of symptoms, has been shown to be an easily applicable, valid, and reliable test.[16]

SWISS Narcolepsy Scale: Narcolepsy or narcolepsy with cataplexy can be detected in some patients with daytime sleepiness. The Swiss narcolepsy scale has been proven to have high sensitivity and specificity in a study conducted in 2004.[17]

Beck Depression Scale: Beck Depression Scale was revised in 1996. Turkish validity and reliability study of the revised second version was conducted by Aktürk et al.[18]

Beck Anxiety Scale: Beck Anxiety Scale is a scale developed in 1988 that consists of 21 questions probing anxiety symptoms. The reliability and validity of this method have been proven, and its effectiveness in differentiating depression and anxiety has been demonstrated.

Statistical Analysis

The statistical analyses were performed using IBM Statistical Package for the Social Sciences version 23 software.

Descriptive analyses for parametric data are presented as mean and standard deviation. All data were re-recorded as dichotomous data, such as high-low, present-absent, above-below a specified score. The risk and scale results were analyzed using cross-tabulations according to the clinical characteristics and demographic data of the patients. The differences between the groups in terms of frequencies were compared using chi-square tests or Fisher's exact tests when the values observed in the cells did not fulfill the assumptions of the chi-square test. P values below 0.05 were considered as statistically significant results.

Multiple logistic regression analysis including relevant and potential confounding factors, such as age, gender, and type of antiepileptic used, was performed to analyze the association between epilepsy and sleep disorders, anxiety, and depression.

RESULTS

Demographic Characteristics

In our study, questionnaire forms filled out by 100 patients who were followed up in the neurology epilepsy outpatient clinic and came to regular controls were evaluated. Of the patients included in the study, 38 were male and 62 were female. The mean age of the patients was 30.48±10.0 years (18-58 years).

In total, 50 healthy adults (25 males and 25 females) were included as the control group. The mean age of the control group was

31.6±6.4 years (20-56 years). No significant differences were found between the groups in terms of age and gender (Table 1).

Among the patients, 64% had no seizures in the last 6 months, whereas 36% had at least 1 seizure. The mean number of seizures within 6 months was 12.53±13.12.

A total of 59 (59%) patients received single AED treatment. Of the 41 patients using more than one AED, 29 were dual, 11 were triple, and 1 was quadruple.

Regarding the antiepileptics used, 57 patients used levetiracetam, 29 used valproic acid, 33 used carbamazepine/oxcarbazepine, 16 used lacosamide/zonisamide, 10 used lamotrigine, 3 used topiramate, and 2 used clobazam.

The epilepsy syndromes of the patients were determined according to the International League Against Epilepsy 2017 epilepsy classification by evaluating clinics, electroencephalography (EEG), and neuroimaging findings during seizures. Of all patients, 47 and 53 had generalized and focal onset epilepsy. In patients with focal onset, imaging and EEG findings were compatible with frontal lobe-induced seizures in 18 patients and temporal lobe-induced seizures in 25 patients.

The rates of sleep disorders in the epilepsy and control groups are presented in Table 2.

Epworth Sleepiness Questionnaire

The mean ESS score was 6.83±6.74 in the epilepsy group and 5.94±4.49 in the control group. There were a total of 30 patients (30%), 20 females and 10 males, in the epilepsy group and 7 patients (14%), 5 females and 2 males, in the control group, with excessive daytime sleepiness ESS scores greater than 10 and increased daytime sleepiness.

When the epilepsy and control groups were compared, increased daytime sleepiness was significantly increased in the epilepsy group (p=0.3). No relationship was found between gender and AGU score (p=0.3).

Table 1. Demographic characteristics of the patient and control groups

	Epilepsy patients (n=100)	Control (n=50)	p value
Female/male	62/38	25/25	0.06
Age (mean±SD)	30.48±10.0	31.6±6.4	0.61
Duration of epilepsy (mean±SD)	12.10±8.03	-	-
Treatment of NPI		-	-
Monotherapy	59		
Polytherapy	41		
Epilepsy type		-	-
Generalized	47		
Focal	53		
Temporal	25		
Frontal	18		

NPI: Neuropsychiatric inventory, SD: Standard deviation

Table 2. Sleep disorders in the epilepsy and control groups

	Epilepsy patients (n=100)	Control (n=50)	p value
ESS	30	7	p<0.01
Insomnia	33	15	p=0.7
STOP-Bang Survey			
High risk	15	4	p<0.01
Medium risk	4	4	p>0.01
Low risk	81	44	p<0.01
Restless Leg Diagnosis Form	20	5	p<0.01
RBDQ-HK	12	1	p=0.01
Swiss Narcolepsy Scale	15	1	p=0.01
Beck Depression Scale			
Minimal	29	19	p>0.01
Mild	31	8	p<0.01
Moderate	14	-	p<0.01
Beck Anxiety Scale			
Minimal	20	15	p>0.01
Mild	21	5	p<0.01
Moderate	29	3	p<0.01

ESS: Epworth Sleepiness Scale, RBDQ-HK: REM Behavioral Disorder-Hong Kong Questionnaire, REM Sleep Behavior Disorder Questionnaire

When analyzed according to epilepsy groups, 13 (27.7%) patients with generalized epilepsy and 17 (32.1%) with focal epilepsy. No significant difference was observed between the two groups (p=0.6). However, when the focal epilepsy group was analyzed within itself, the AGI score of patients with frontal lobe epilepsy (10.22±8.40) was significantly higher than that of patients with temporal lobe epilepsy (5.66±4.83) (p=0.01) (Graphic 1). Unlike the other neuropsychiatric inventories, the AGU score increased in the carbamazepine/oxcarbazepine group, and daytime sleepiness was observed in almost half of the patients (45.5%) (p=0.01).

Insomnia

In our study, we did not apply a different questionnaire for insomnia, but 33 patients (33%) in the epilepsy group answered the question of not sleeping frequently and almost always. In the control group, 15 patients (30 per cent), 6 males and 9 females (30 per cent) who answered frequently and almost always to the question about insomnia. There were no significant differences between the control and epilepsy groups (p=0.7).

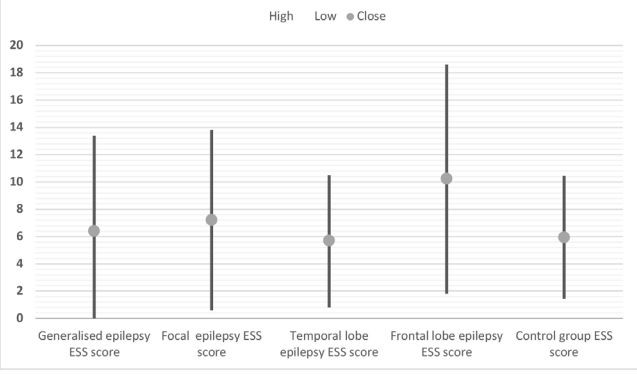
In 45.5% of the patients who complained of insomnia, seizures were present in the last 6 months; however, the result did not reach statistical significance (p=0.1).

STOP-Bang Survey

In our study, the number of patients who were evaluated using the STOP-Bang questionnaire and found to be at medium and high risk for obstructive sleep apnea syndrome (OSAS) was 19 (19%). Moreover, 28.9% of males and 12.9% of females were found to be at risk for OSAS. When the risk of OSAS was compared with the epilepsy type, the risk of OSAS was found to be higher in focal epilepsies, especially in focal epilepsies with left temporal lobe onset, than in generalized epilepsies (22.7% vs. 14.9%). However, this difference did not reach statistical significance (p=0.3).

Diagnosis Form for Restless Legs Syndrome

In 20 (20%) of 100 patients in the epilepsy group, answers compatible with RLS were provided in the RLS questionnaire. In the control group, RLS was found in 5 patients (10%), 3 females and 2 males. This rate was 2 times higher than that of the control group. Of the 20 patients, 17 (85%) were female and 3 (15%) were male, and a significant correlation was found between the risk of RLS and being female (p=0.01).



Graphic 1. Epilepsy types and mean Epworth Sleepiness Scale (ESS) scores

REM Behavior Disorder-Hong Kong Questionnaire

The mean score of patients on the RBDQ-HK was 16.33±12.27. There was no significant difference between genders in the mean score (mean score of males 15.53±12.69; mean score of females 16.82±12.09) (p=0.6).

The mean RBDQ-HK score of the control group was 11.72±8.33. The mean score of healthy women was 14.0±9.25, the mean score of healthy men was 9.25±6.52 and the mean RBDQ-HK score was found to be higher in the female gender (p=0.04).

Compared with the control group, the mean scores of the epilepsy group were significantly higher (11.7 vs. 16.3) (p=0.01).

SWISS Narcolepsy Scale

According to the Swiss Narcolepsy Scale, 15 patients (15%), 10 females and 5 males, had narcolepsy risk in the epilepsy group. In the control group, 1 patient (2%) was at risk of narcolepsy. The risk of narcolepsy was significantly increased in epileptics (p=0.01). There was no significant difference in the risk of narcolepsy in terms of gender (p=0.6).

The mean age of patients with and without narcolepsy risk was 32.07±7.66 years, while the mean age of the patients without narcolepsy risk was 30.14±10.33 years. No significant difference was found (p=0.4).

Approximately half (46.7-7%) of the patients with high risk of narcolepsy had a history of seizure in the last month. This rate increased to 75% (6 patients) in focal epilepsy. However, no statistically significant relationship between seizure in the last 6 months and narcolepsy was not found in any epilepsy group (p=0.2).

Beck Depression Scale

The mean Beck Depression Scale score of the control group was 11.06±7.34 and 16.77±10.26 in the epilepsy group.

When categorized as no depression, mild, moderate, and severe depression according to the scores, 26 patients with no depression, 29 patients with mild depression, 31 patients with moderate depression, and 14 patients with severe depression were found in the epilepsy group. In the control group, 23 patients did not have depression, 19 patients had mild depression, 8 patients had moderate depression, and no patient had severe depression.

The rates of moderate and severe depression were significantly higher in the epileptic group than in the non-epileptic group (45% vs. 8%) (p<0.01).

Moderate to severe depression was found in 69.4% of patients who had a seizure in the last 6 months. Having a seizure significantly increased the risk of depression (p<0.01).

Beck Anxiety Scale

When categorized according to Beck's anxiety scale scores, 30 of 100 patients in the epilepsy group had no anxiety, 20 mild anxiety, 21 moderate anxiety, and 29 severe anxiety. In the control group, 27 of 50 patients had no anxiety, 15 mild anxiety, 5 moderate anxiety, and 3 severe anxiety.

When the control and epilepsy groups were compared, the rates of moderate and severe anxiety were 50% and 16% in the epilepsy and control groups, respectively. The rate of anxiety was significantly increased in epileptics (p<0.01).

In the epilepsy group, 56.5% of women and 39.5% of men, and in the control group, 4.2% of men and 26.9% of women had moderate or severe anxiety, but no statistical relationship was found between gender and anxiety in the groups (p=0.09 and p=0.06).

DISCUSSION

In our study, we used questionnaire forms from 100 patients with epilepsy and 50 healthy controls who were followed up in our epilepsy outpatient clinic.

In patients with epilepsy, the complaint of increased daytime sleepiness is frequently encountered, and this is especially a subjective complaint. The rate of increased daytime sleepiness in patients with epilepsy has been reported to range between 10 and 47.5.[19] In our study, the proportion of patients with an ESS score >10 was 30%. In our study, we found no significant correlation between ESS score and other AEDs, except for increased daytime sleepiness (p=0.01) observed in carbamazepine/oxcarbazepine users. Although there are conflicting results in the literature, it has been reported that carbamazepine increases arousal, increases daytime sleepiness, increases slow-wave sleep (especially NREM stage 2), and increases REM latency.[19,20]

In patients with epilepsy, REM sleep behavior disorder (RBD) may be a comorbid condition and should be considered in the differential diagnosis of epilepsy. In the literature, it has been reported that RBD is more commonly observed in elderly, male, and cryptogenic epilepsy patients with sleep-related seizures.[21] In our study, we found that Rosai-Dorfman disease was significantly higher in patients than in control patients (p=0.01). We did not find any significant difference in terms of gender (p=0.6) and age (p=0.3). This may be attributed to the fact that patients older than 60 years were included in the study, and the mean age was 30.4 years in our study.

In our study, the rate of patients complaining of insomnia was found to be 33%, and rates of 24.6% and 43% are available in the literature.[22,23] We found no correlation between insomnia and age, gender, epilepsy type, and number of AEDs used by the patients, and our findings are consistent with the study of Im et al.[24] Other studies have also shown that NPI polytherapy is associated with increased insomnia scores.[23]

Of the 100 patients who were administered the Swiss Narcolepsy Questionnaire, 15 (15%) were evaluated as having a risk of narcolepsy with a negative score. Moreover, 10 of these patients responded positively to the cataplexy, emotional, triggering questions. The reported prevalence of narcolepsy in the normal population is 0.03-0.16%, and the rates in our study are considerably higher than those in the normal population. In a study evaluating the risk of narcolepsy in patients with epilepsy using a questionnaire, the risk of narcolepsy was found in 3 out of 100 patients; however, narcolepsy was not detected in any of them after the necessary evaluations.[25] In our study, there was 1 patient who was evaluated because of these complaints and then diagnosed with narcolepsy.

We believe that the diagnosis of narcolepsy may be overlooked; therefore, further evaluation with polysomnography and the multiple sleep latency test is important in patients with epilepsy who have a suspicious history or who are found to be at risk in screening tests.

The incidence of RLS in the Turkish population was 3.2%.[26] Öztürk et al.[27] analyzed the frequency of RLS in patients with epilepsy and found that it was 5.8%. However, they stated that this percentage may be lower than the actual rate because they did not include patients using drugs that may cause RLS or patients using gabapentin and pregabalin used in the treatment of RLS. RLS has been reported up to 28% in the literature.[28] In our study, we found the prevalence of RLS in patients with epilepsy to be 20%, which is quite high, and although none of the patients used gabapentin-pregabalin, this high prevalence suggests that the diagnosis of RLS may be overlooked in patients with epilepsy.

In our study, the anxiety scores of epilepsy patients with high OSAS risk were also significantly higher (p=0.02). This finding is consistent with the literature, and in one study, anxiety about seizure was found to be higher in patients with epilepsy and OSAS, which may increase Beck Anxiety Scale scores.[29]

When the risk of OSAS was compared with the epilepsy type, the risk was found to be higher in focal epilepsies, especially in focal epilepsies with left temporal lobe onset, than in generalized epilepsies (22.7% vs. 14.9%). However, this difference did not reach statistical significance (p=0.3). Consistent with our study, 7 studies were examined in a meta-analysis in the literature, and the rate of OSAS in focal epilepsies (32.2%) was found to be higher in all studies compared to generalized epilepsies (28.2%), but none of the studies reached statistical significance.[30]

Although the relationship between resistant and controlled epilepsy and OSAS has been investigated; however, no relationship between seizure frequency and OSAS has been found. It has been shown in many studies that OSAS treatment reduces seizure frequency and provides significant benefits to epilepsy control; however, there is no evidence that seizure frequency is associated with OSAS.[31]

It is known that the prevalence of depression is higher in patients with epilepsy, which significantly affects the quality of life of these patients. One study has even shown that the risk of suicide increases up to 3 times in patients with epilepsy. In studies examining the prevalence of depression in epilepsy patients, rates of up to 32.6% have been reported.[32] In our study, 45 patients (45%) had moderate to severe depression according to the Beck Depression Questionnaire scores. Of the 45 patients, 12 were male and 33 were female, and there was a significant difference between genders (p=0.03). Consistent with the literature, the rate of depression was significantly higher in women with epilepsy than in men.[33,34]

As shown in many studies, seizure frequency was found to be associated with depression in our study.[35,36] In our study, 69.4% of the patients with depression had a seizure in the last 6 months, and the variable most associated with depression was the presence of a seizure in the last 6 months, as shown by the regression analysis.

In the literature, it has been reported that epilepsy patients with depression experience more side effects of the ASMs they use.[37]

In the relationship between ASM use and depression, particularly in patients with a higher risk of depression, care should be taken in this respect.

Study Limitations

The distribution of men and women in our patient group should be more homogeneous, and the number of patients should be increased. The patient group included in the study comprised mostly young adults, and patients with advanced age and poor educational status were not included in the study; therefore, the low number of resistant epilepsy cases is one of the limitations of the study. In addition, although sleep and sleep disorders were evaluated in detail with a long questionnaire used in this study, patients were often distracted while giving answers.

CONCLUSION

In conclusion, there is a complex relationship between sleep disorders, psychiatric comorbidities, and epilepsy. In order to understand this multifaceted relationship, comparative studies with more homogenous groups and patients are needed. Nevertheless, the necessity of questioning epilepsy patients in terms of sleep disorders, depression, and anxiety in clinical conditions in line with the information we have presented has been observed once again in this study. Effective questionnaire forms suitable for clinical conditions to be developed on these subjects may be used in this respect in the future.

Ethics

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of Eskisehir Osmangazi University (decision no: 19, date: 22.01.2019).

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

Footnotes

Authorship Contributions

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

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Case Report

Epilepsia Partialis Continua without Radiological Abnormalities in an HIV-infected Patient: A Case Report

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Abstract

Epilepsia partialis continua (EPC) without intracranial abnormalities is a rare presentation in patients with human immunodeficiency virus (HIV) infection. In our case report, the patient presented with left-sided clonic-myoclonic seizures that were resistant to initial anti-seizure treatment. This condition is classified as EPC. Lesions that could be linked to episodes of EPC were not evident on magnetic resonance imaging. Electroencephalography showed right-sided centroparietal epileptiform activity. After blood testing, the patient was diagnosed with HIV. Dual antiseizure medications were administered, leading to seizure cessation after three days.

Keywords: Epilepsia, epilepsia partialis continua, human immunodeficiency virus infection

INTRODUCTION

A retrovirus called human immunodeficiency virus (HIV) infects immune cells and destroys their function. In people with HIV, disorders of the central nervous system (CNS) arise either as a direct outcome of HIV itself or due to different opportunistic infections. Additionally, conditions like lymphoma, cerebral infarction, and immune reconstitution inflammatory syndrome are also observed in these patients. In imaging, there are various radiological findings, such as intracranial lesions, hydrocephalus, edema, infarcts, signal changes within the parenchyma, and contrast enhancement, etc. depending on the etiology.[1,2]

There are several potential causes for epilepsia partialis continua (EPC), which can be either localized or systemic. From a pathophysiological standpoint, EPC appears to involve a feedback loop characterized by alternating excitation and inhibition, though the precise mechanisms behind this process are not yet well understood.[3]

We report a case of a patient who presented with EPC, was diagnosed with HIV, and had no intracranial pathology.

CASE PRESENTATION

A 42-year-old woman from a foreign country presented to the emergency room (ER) with bilateral tonic-clonic seizures. She was admitted to the neurology inpatient clinic after receiving initial anti-seizure treatment in the ER. Although the patient's examination was suboptimal because of the language barrier, her neurological examination revealed decreased consciousness with no meningeal irritation or paresis. Blood tests indicated pancytopenia, elevated C-reactive protein, and positive anti-HIV staining. Serum antibodies for Borrelia, Toxoplasma, syphilis, and hepatitis were negative. No significant pathology was observed on cranial imaging (Figure 1). After reaching out to a relative of the patient, we learned that a lumbar puncture had been performed 5 days earlier at an external clinic for a differential diagnosis of encephalitis. Cerebrospinal fluid (CSF) investigations showed that biochemical indicators were within normal ranges, with no erythrocytes or leukocytes and a mildly elevated micro-total protein level. Follow-up observations indicated prolonged reaction time and ongoing clonic-myoclonic seizures with no response to diazepam infusion; therefore, levetiracetam treatment at a dose of 3000 mg/day was initiated for the patient. The patient was cooperative and oriented; however, his left-sided focal motor seizures persisted. Since the patient still had no response to treatment, the case was classified as EPC, and valproate treatment at a dose of 800 mg/day was added. As a result of candida esophagitis, additional antibiotic treatment was given after consulting with the infectious disease department. The electroencephalography (EEG) results revealed bioelectrical disorganization in both hemispheres and epileptic activity in the right centroparietal region (Figure 2).

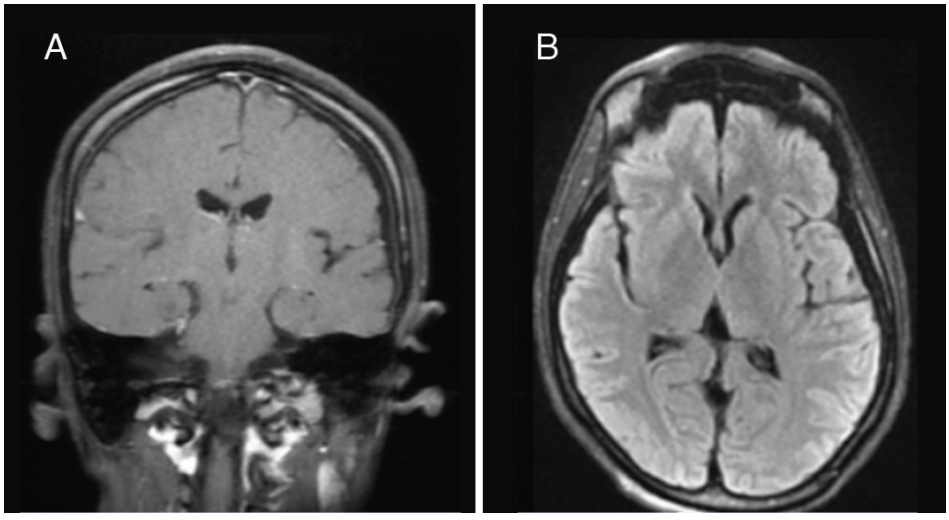

Figure 1. No parenchymal lesion or contrast enhancement is observed in (A) C+T1 coronal and (B) FLAIR axial sequences

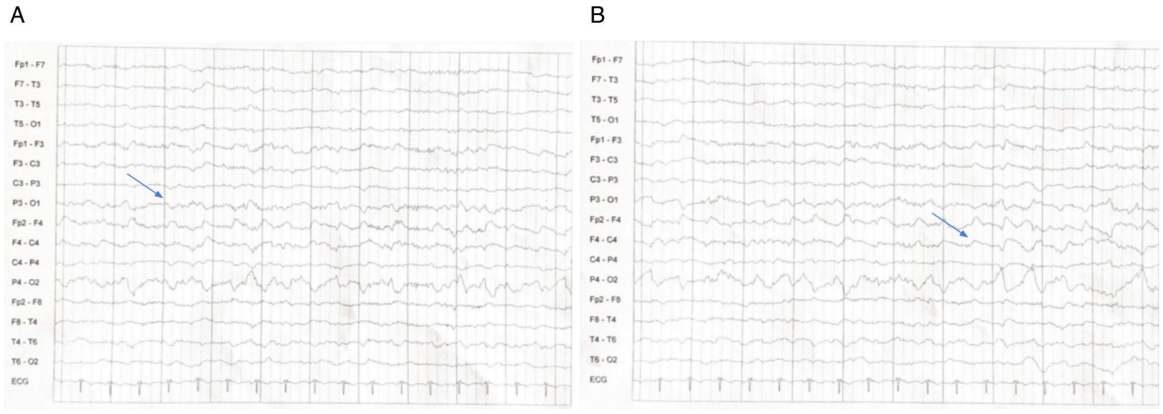

Figure 2. The EEG investigations (A) and (B) revealed bioelectrical disorganization in both hemispheres and epileptic activity in the right centroparietal region
EEG: Electroencephalography

During the follow-up, valproate was discontinued and replaced with low-dose lamotrigine due to worsening pancytopenia with valproate. The patient's seizures finally ceased and remained under total control on the third day after the initiation of anti-seizure treatment, and there was no pathology on the final neurological examination.

MAIN POINTS

- This case demonstrates a rare instance of epilepsia partialis continua (EPC) in an HIV-infected patient without central nervous system (CNS) pathology, highlighting the diverse neurological manifestations of human immunodeficiency virus (HIV).
- The pathophysiology of EPC in HIV-infected patients is thought to involve neurotoxic interactions among activated macrophages, astrocytes, and neurons, leading to neuronal death through increased glutamate activity and calcium influx, which disrupts the balance of excitatory and inhibitory neurotransmitters, thereby increasing seizure susceptibility.[4]
- This case emphasizes the need to consider HIV-related neurotoxicity as a potential cause of EPC in immunocompromised patients, even in the absence of radiological findings.

DISCUSSION

Garg[3] mentioned that new-onset generalized-type seizures are common manifestations in people infected with HIV. These seizures are mostly caused by CNS disorders.[4] Rarely EPC can be seen without any CNS pathology in people infected with HIV.

Mameniškienė and Wolf[4] describe that EPC represents a form of simple focal motor status epilepticus, characterized by frequent and repetitive muscle jerks. These muscle jerks usually lack a regular pattern. EPC can persist from one hour to years. Typically, it doesn't respond well to medical treatment. Benzodiazepines, levetiracetam and topiramate are some treatment options.[3]

The archetypical presentation of EPC is a continuous focal myoclonus involving the distal extremity. In our case, however, it had presented in both the upper and lower left extremities. The patient presented with EPC and mild loss of consciousness as the first manifestations of HIV-related encephalopathy without any radiological findings. Our CSF findings were inconclusive, with a lack of leukocytes and only a slight increase in CSF protein (49 mg/dL) and normal glucose levels, thereby ruling out any other

opportunistic infections. Epileptiform discharges in the right centroparietal region helped us localize the epileptic zone of EPC.

After ruling out HIV-associated opportunistic infections and space-occupying lesions we had come to the conclusion that newly onset EPC was the sole neurological manifestation in this patient. There have been many theories as to why seizures might occur in the absence of the previously mentioned causes. Garg[3] suggest that HIV or toxins related to immune deficiency cause macrophages, astrocytes and the neurons producing the neurotoxic substances to interact in a manner that indirectly results in neuron death.[4] The neurotoxic substances include eicosanoids, platelet-activating factor, quinolinate, cysteine, cytokines and free radicals. The macrophages that get activated by HIV-1 envelope protein gp120 also release similar toxins.

The final pathway, as described by Garg,[3] is through increased glutamate activity, which results in an influx of calcium into cells that leads to untimely death. This cascade of cell death results in an imbalance of excitatory and inhibitory neurotransmitters, which is coupled with neurotoxicity, resulting in a predisposition to seizures. It was our theory that these were the underlying mechanisms that caused the seizures in our patient.

Dawson's[5] research dating back to 1947 suggests that the waveforms commonly associated with EPC had a positive wave, followed by negative shifts with a train of superimposed spikes.

Inherent lateral inhibition in the neocortex is understood to keep specific pathway-associated responses precise. It has been suggested that this phenomenon might explain why seizures observed in EPC are localized and self-limiting compared with seizures that arise from the allocortex of the limbic pathways, which usually spread.[6] This phenomenon was observed in our patient as well, whose EEG revealed self-limiting sharp wave activities in the right centrotemporal region, which led us to believe that this region was affected at a neuronal level that could not be observed in magnetic resonance imaging (MRI).

While seizures are common manifestations of CNS involvement in HIV-infected patients, generalized seizures are the most common type.[4] Convulsive status epilepticus is also a common manifestation due to serum electrolyte abnormalities. While our patient had also presented with status epilepticus, after the serum abnormalities were quickly dealt with the only manifestation left was continuous clonic-myoclonic jerks with preserved consciousness.

HIV presenting with EPC is rare as is, with the first case being reported in 1999,[4] and the fact that our patient had no cerebral mass lesion to speak of made this a case worth documenting and presenting. While most patients who present with EPC have parenchymal lesions that can be viewed in an MRI, those who do not have any have also been reported. That is why while all common causes must be investigated when a patient presents with EPC, an immunocompromised state like HIV seropositivity, even without imaging findings, might be the underlying cause.

CONCLUSION

In summary, this case highlights the occurrence of epilepsia partialis in a patient with HIV infection. While generalized seizures, contrast enhancement, or parenchymal occupation on imaging are common among patients with HIV infection, this case stands out by presenting as focal seizures without detectable pathological brain findings on imaging.

Ethics

Informed Consent: Informal consent was obtained from the patient.

Footnotes

Authorship Contributions

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

Conflict of Interest: None of the authors has any conflicts of interest to disclose.

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