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Review

The S100B Protein in Epilepsy

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Abstract

Epilepsy is a chronic disease caused by an increased excitability of nerve cells in the brain, characterized by two or more unprovoked seizures, which can be attributed to genetic or acquired causes. There are currently more than 50 million people worldwide who have epilepsy, and this number is continuously increasing. Although significant advancements have been made regarding the diagnosis and treatment of epilepsy in recent years, our knowledge about the cellular and molecular mechanisms underlying the development of epilepsy or epileptogenesis is still insufficient. The absence of a specific biomarker for diagnosis makes epilepsy relatively challenging to diagnose. Therefore, the discovery and implementation of specific markers are important for the diagnosis and early treatment of epilepsy. The S100 protein family is a group of low molecularweight proteins that are localized in the cytoplasm and/or nucleus of various cells. These proteins play a regulatory role in various intracellular processes, including the cell cycle, by localizing within the cytoplasm and nucleus of the cell. S100B is a member of the S100 family. Its functions are highly concentration-dependent, at physiological concentrations, it exhibits a neuroprotective function, supporting neural survival and stimulating dendrites and axons. However, at high concentrations, it induces neuronal apoptosis, activates pro-inflammatory cytokines, and stress-induced inflammatory enzymes. When brain cells are damaged or destroyed, S100B proteins are released from the cells and can be detected in the blood. S100B can be considered as a prognostic biomarker that can be used for diagnosing epilepsy in clinical practice. This review summarizes the role of the S100B protein in epilepsy.

Keywords: Biomarker, epilepsy, S100B

INTRODUCTION

Since antiquity, epilepsy has been a known and researched disease. Even though Hippocrates and Galen maintained that epileptic seizures developed because of various etiologies in the brain, epilepsy had always been attributed to supernatural causes until philosophers and physicians in the 19th century began conducting research on brain function.[1] Because of all these studies, epilepsy is now defined as a chronic disease caused by an increased excitability of nerve cells in the brain (neuronal hyperexcitability), characterized by two or more unprovoked seizures, which can be attributed to genetic or acquired causes.

Epilepsy is a common neurological disorder that can affect individuals of all age groups. There are currently more than 50 million people worldwide who have epilepsy; nearly 80% of them live in low- and middle-income countries. This number is continuously increasing, with approximately 2.4 million people being newly diagnosed each year.[2] Although significant advancements have been made regarding the diagnosis and treatment of epilepsy in recent years, our knowledge about the cellular and molecular mechanisms underlying the development of epilepsy or epileptogenesis is still insufficient.[3]

Although monotherapy is sufficient for seizure control in most epilepsy patients, seizures cannon be effectively controlled in 30% of patients despite the availability of over 20 types of antiepileptic drugs.[4] Some patients may require combination therapy, resective surgery, or neurostimulation device application. Due to comorbid mood and psychiatric disorders, cognitive deficits, and the side effects of drugs used during treatment, epilepsy can significantly impair the quality of life. In addition, seizures can be fatal due to their direct effects on autonomic and arousal functions and the indirect effects caused by suffocation or other accidents that may occur during seizures.

One of the biggest obstacles hindering the development of treatment options in epilepsy is the heterogeneity of epilepsy. Different genetic and pathophysiological factors [such as stroke, traumatic brain injury (TBI), perinatal and prenatal injuries, central nervous system (CNS) malformations or tumors] may be underlying causes of epilepsy seizures.[1] The presence of so many different factors indicates that different

mechanisms can cause epileptogenic focus and that there are potentially different mechanisms of functional impairment and seizure formation.

The absence of a specific biomarker for diagnosis makes epilepsy relatively challenging to diagnose. No biomarker has yet been found that can be used to reliably assess epileptogenesis. Pitkänen and Engel[1] have defined a biomarker that can be used for epileptogenesis as "an objectively measurable characteristic of a biological process that reliably identifies the development, presence, severity, progression or localization of an epileptogenic abnormality". Therefore, the discovery and implementation of specific markers are important for the diagnosis and early treatment of epilepsy.[4,5]

S100 Proteins

The S100 protein family is a group of low-molecular-weight proteins that is localized in the cytoplasm and/or nucleus of various cells in vertebrates and contains two calcium-binding regions in a helix-loop-helix structure. They are involved in the regulation of various cellular processes, including cell cycle progression and differentiation. The S100 family proteins consist of two subunits, alpha and beta, and exist as homo or heterodimers depending on the subunit status. However, they typically exhibit homodimeric structure. Dimerization of S100 proteins is significant in terms of displaying their biological activities. When Ca^{2+} binds, the helix structure changes.[6,7] The Ca^{2+} binding region of each S100 monomer contains a separate binding region for the target protein. Binding of these target proteins to the S100 proteins produces a strong reduction of the S100 protein. This is due to the structural changes of the helices.[8,9]

S-100 proteins are found in cells originating from the neural crest (Schwann cells, melanocytes, and glial cells), chondrocytes, adipocytes, myoepithelial cells, macrophages, Langerhans cells, dendritic cells, and keratinocytes.[10] They have many intracellular and extracellular regulatory activities. These proteins play a regulatory role in various intracellular processes including the cell cycle by localizing within the cytoplasm and nucleus of the cell. Proteins in the S100 family regulate the enzymatic activities by interacting with numerous effector proteins, influence the structural dynamics of the cytoskeleton, regulate cell growth-differentiation, motility and cell cycle, as well as maintain Ca^{2+} homeostasis.[11] Extracellular S100 proteins act as regulators in inflammatory cells, neurons, astrocytes, microglial, endothelial, and epithelial cells. Ultimately, S100 proteins are multifunctional proteins involved in the regulation of various cellular activities.[12,13]

The S100 protein genes consist of at least 13 members located as a cluster on chromosome 1q21. However, the S100B gene is located on 21q22.3.

MAIN POINTS

- When brain cells are damaged or destroyed, S100B proteins are released from the cells and can be detected in the blood. This protein has also been shown to increase in blood and cerebrospinal fluid especially after seizures.
- It is believed that S100B can be considered as a biomarker that can be used for epilepsy in clinical practice.

S100B

S100B, a 21 kDa protein, is a member of the S100 family. The alpha- and beta-beta heterodimers are defined as S100B proteins. It functions as a Ca^{2+} receptor inside the cell and as a neuropeptide outside the cell. The alpha-beta isoform is in glial cells, whereas the beta-beta isoform is found in brain astrocytes and Schwann cells. The S100B protein is the most abundant member of the S100 protein family in the CNS, accounting for 96% of total S100 proteins in human brain.[14-16]

It is considered to be specific to glial cells and is thought to be primarily expressed in astrocytes. When produced and released by astrocytes at physiological concentrations, it has a neurotropic effect on nerve regeneration and development. In addition to regulating intracellular signal transmission, intercellular communication, energy metabolism, and cell growth, it exerts autocrine and paracrine effects on neurons and glial cells. This protein is believed to play a regulatory role in axon elongation, stimulation of calcium influx, inhibition of protein kinase C-mediated phosphorylation, astrocytosis, and inhibition of axonal proliferation and intracellular microtubule formation. It exhibits neurotropic behavior in the developing central nervous system, stimulating cell proliferation and migration within the cell, while inhibiting apoptosis and differentiation. This is important for brain development and repair. It also functions in the regulation of certain enzymes. The extracellular activities of S100B are effective on neurons, astrocytes, microglia, macrophages and other cells.[14,16,17]

The increase in intracellular Ca^{2+} and Zn^{2+} concentrations causes the release of S100B from glial cells into the extracellular environment via vesicular transport. S100B displays cytokine-like functions in the extracellular environment.[18] These functions are highly concentration dependent; at nanomolar (nM) levels, it exhibits a neuroprotective function supporting neural survival and stimulating dendrites and axons. However, at micromolar (μM) concentrations, it induces neuronal apoptosis, activates pro-inflammatory cytokines, and stress-induced inflammatory enzymes.[19-21] In other words, it has dose-dependent neurotropic or neurotoxic effect. These effects occur via receptor for advanced glycation end products (RAGE) in the brain. S100B produces its neurotoxic effect by inducing apoptosis. μM concentrations of S100B interact with RAGE leading to an increase in ROS. As a result, cytochrome-C is released, inducing the caspase cascade and resulting in apoptotic neuronal cell death. It also induces apoptosis by increasing the permeability of L-type Ca^{2+} channels and 'up-regulating' a series of apoptosis genes (c-fos, c-jun, bax, bcl-x).[22-26]

When brain cells are damaged or destroyed, S100B proteins are released from the cells and can be detected in blood.[27] In cases of brain injury and neurodegenerative diseases, they activate astrocytes.[17]

When the cytosol of the glial and Schwann cells is structurally damaged, the S100B protein is released into the cerebrospinal fluid (CSF) and bloodstream. In vitro studies of its release into the extracellular space have shown that it is released from astroglial cells in several different ways. Activation of adenosine glutamate receptors is very rapid, occurring within 1 hour; there is stimulation of astroglial 5-hydroxytryptamine 1A (5-HT1A) receptors or a mediated release of adrenocorticotropic hormone

and corticotropin-like peptide. S100B can also be released from proliferating astrocytes.[28]

High levels of this protein in the CSF, which can be up to 40 times that of the serum, are generally associated with damage to the nervous system. Kinetic studies have shown that the half-life of S100B is approximately 1.5 h *in vivo*, for this reason, it has been accepted by some researchers as an early indicator of the function of the blood-brain barrier (BBB).[16] Extracellular high S100B concentrations have been associated with various neurological diseases such as Alzheimer's, multiple sclerosis, amyotrophic lateral sclerosis, schizophrenia, epilepsy and TBI.[14,29]

S100B and Epilepsy

In epilepsy, there is evidence indicating an increase in S100B levels, particularly after seizures. It has been reported that normal S100B levels attenuate epileptogenesis and that there is a relationship between high S100B concentrations and the severity of temporal lobe epilepsy (TLE). After surgical intervention in patients with refractory TLE, it has been reported that there was a threefold increase of S100B-immunoreactive astrocytes in neocortical sections, indicating a potential involvement of S100B in the pathophysiology of epilepsy.[30-32] Elevated S100B- levels have been demonstrated in adults and children with TLE. In one study, S100B was found to be higher in female TLE patients than in males, which was thought to indicate a possible interaction between S100B and sex hormones.[30,33] Khamis et al.[34] showed that S100B levels were higher in children with more severe epilepsy and structural changes on their MRI and were significantly increased in generalized epilepsy than in focal seizures. Therefore, they suggested that the observation of elevated S100B levels in children with epilepsy was associated with the presence and severity of brain damage of epileptic seizures.

In a randomized controlled study conducted by Maiti et al.[35] on 60 patients with focal seizures, it was determined that the S100B protein was significantly higher in epilepsy patients with focal seizures compared to normal individuals, and serum S100B values measured 2 and 4 weeks after starting antiepileptic therapy were found to be significantly lower. Moreover, it was determined that treatment with carbamazepine resulted in greater decrease in serum S100B levels compared to oxcarbazepine. It has been suggested that serum S100B can be used as a prognostic biomarker in focal seizures.[35,36] It has also been reported that long-lasting behavioral abnormalities with lithium-pilocarpine-induced SE during development in rats may be associated with elevated S100B levels in CSF.[37]

On the other hand, some studies do not support these findings. While studies have stated that there is no significant difference between epilepsy and control groups,[38,39] there are also studies reporting a decrease in serum S100B levels in epilepsy.[40,41] These stated that the short half-life (25-113 minutes) of S100B affected the reliability of the measurement. In their study on S100B, Atici et al.[42] also did not observe a significant increase in the sera of 39 pediatric patients with febrile convulsions compared to the control group.

However, out of the studies conducted so far, positive studies seem to predominate. Two recent large meta-analyses support-elevated levels of S100B protein in people with epilepsy.[8,21] In the detailed meta-analysis studies conducted by Simani et al.[36], 22 studies related to S100B were evaluated. In this study, it was established that S100B levels in patients with epilepsy were significantly increased compared to control group, which was consistent with other meta-analyses.

Experimental and clinical studies show that inflammation in the CNS is critical to epileptogenesis and induction of seizures. Neuroinflammation is thought to play a critical role in the pathogenesis of epilepsy. It contributes to disease progression, neurological comorbidities, frequency, and duration of seizures.[36,43] BBB dysfunction is thought to be triggered by neuroinflammation as inflammatory cytokines and other mediators affect the trans- and para-cellular pathways.[44] In addition, excessive epileptic discharge generation triggers BBB leakage and glial activation, which increases neuroinflammation. Thus, in epilepsy, there is a relationship between seizures and inflammation responsible for progression and tissue damage. Therefore, increased levels of brain biomarkers such as S100B could be indicative of BBB degradation and degree of neuroinflammation.[36]

CONCLUSION

In conclusion, although the precise mechanisms underlying epilepsy pathogenesis are not fully understood, there is an increasing body of evidence suggesting that oxidative stress, dysfunction of the BBB, inflammation, and neuronal and glial damage contribute to the development of epilepsy disorders. The S100B protein has also been shown to increase in blood and CSF after these pathologies, especially after seizures. Thus, S100B can be considered as an important biomarker for epilepsy.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.E.S., D.T.A., G.K., Design: A.E.S., D.T.A., G.K., Literature Search: A.E.S., Writing: A.E.S.

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Effect of Antiepileptic Drug Sodium Valproate on Stomach Tissue Glycoproteins: The Protective Role of Moringa Extract

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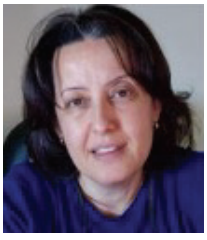

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Abstract

Objective: Sialic acid, hexoses, hexosamines and fucose are components of glycoprotein, glycolipid and/or ganglioside. These glycoconjugates are essential components of cellular membrane and receptors, which are required for normal cellular activities. The levels of these aforementioned glycans are likely to be obstructed under biological conditions (such as oxidative stress) that leads to cellular and tissue damage. Despite the efficacy of valproate as a broad-spectrum antiepileptic drug, it administration is linked to oxidative stress and multiple organ damage. *Moringa oleifera* leaves have been proven to be bioactive food with diverse biochemical benefits, that include antioxidant, wound healing and tissue protective effects.

Methods: In this study, female Sprague-Dawley rats were grouped into four. Group 1: control group given physiological saline; Group 2: animals given only 70% ethanol Moringa leaves extract (0.3 g/kg b.w./day); Group 3: animals that received only sodium valproate (0.5 g/kg b.w./day); Group 4: animals given similar dose of sodium valproate + Moringa extract. The treatments were administered orally for 15 days, and the animals were then fasted overnight and sacrificed. Stomach tissues collected were homogenized in ice-cold normal saline, using a glass homogenizer to make up 10% w/v tissue homogenate.

Results: Analysis revealed that valproate administration resulted in elevated levels of sialic acid, hexoses, hexosamine, and fucose in the stomach tissue homogenates. Conversely, the administration of Moringa extract mitigated the adverse effect of valproate on glycan levels.

Conclusion: Thus, Moringa leave extract can be a good candidate for attenuating valproate-induced toxicity on stomach tissue.

Keywords: Moringa, valproic acid, stomach, sialic acid, hexose, hexosamine, fucose

INTRODUCTION

The stomach is a vital organ of the digestive system involved in the digestion of food. Gastric juice (containing hydrochloric acid and the digestive enzymes pepsin) are secreted by gastric glands.[1] Hydrochloric acid in addition to intrinsic factors is secreted by the parietal cells of the stomach, while chief and neuroendocrine cells secrete pepsinogen and serotonin respectively.[2] The biological action of the fundic glands, cardiac glands, and pyloric glands protects the stomach against corrosion by gastric acid and proteolysis by pepsin at different junctions via secretion of a protective mucus layer. More so, bicarbonate secreted by fundic glands neutralizes excess gastric acid.[1,3]

The protective mucus layer of the stomach is chiefly composed of glycoproteins and glycolipids. In addition to protecting the stomach cells against microbial infiltration and toxins, digestive enzymes and gastric acid corrosion, these glycoproteins and glycolipids play other crucial biological roles that include transport, cell differentiation, cell regeneration, cells' recognition and cell.[4-6]

Sialic acids are a class of alpha-keto acid sugars made up of nine carbon atoms. There are primary components of glycoproteins, glycolipids and gangliosides that have diverse biological functions.[5] The most common member of the sialic acids is N-acetylneuraminic acid. Hexose on the other hand refers to monosaccharides with six carbon atoms. The most common aldohexoses of biological importance are glucose, mannose, and galactose. The biologically most important ketohexose is fructose.[7] The amino form of hexose, formed by the addition of an amino group to a hexose sugar is simply referred to as hexosamine. Essential among hexosamines are glucosamine, fructosamine, galactosamine, and mannosamine. These metabolites are essential substrates for protein glycosylation and the biosynthesis of UDP-N-acetylglucosamine. Altered levels of these metabolites in a tissue are an indication of biochemical derangement such as observed in cancer cells and nutritional stress state.[8-10] Fucose is a 6-deoxy hexose sugar found in found in several glycolipids and glycoproteins of mammalian cell origin. The sugar is unique an unusual because it exists in the L-configuration. Alterations of the fucose levels and structure are implicated in several biological derangements involving immunity and cancer.[11] Therefore, tracking fucose levels in tissue

samples can serve as a tool for the diagnosis and prognosis of tissue malfunction.

Moringa oleifera is a plant with plethora nutritional and diverse therapeutic benefits. The plant has received remarkable attention for use as nutraceuticals, food supplements and/or as herbs.[12,13] The antioxidant,[14] antiinflammatory,[15] wound healing,[16] enzyme inhibition[14,17] and protective effect on tissues such as liver,[18,19] kidney[20] and heart[21,22] make the plant a primary candidate for studies related to drug-induced toxicity.

In this study, the levels of sialic acid, hexose, hexosamine, and fucose in stomach tissue homogenates of valproic acid-administered rats were evaluated. Also, the protective effect of Moringa leaves extract against valproic-induced stomach damaged in rats was assessed.

METHODS

Extract Preparation

M. oleifera leaves obtained from farms located in Sokoto town, Sokoto State of Nigeria were identified and authenticated at the Botany Unit of Biological Sciences Department, Usmanu Danfodiyo University Sokoto. The plant samples were dried under shade, at room temperature before pulverizing. This was followed by Soxhlet extraction using analytic grade 70% ethanol (150 mL) for each 10 g of leave powder. The extraction was performed until a clear siphon of the sample was observed. Under reduced pressure, a rotary evaporator was used to remove the solvent from the extract. The residues were kept at -20 °C in an airtight container until required for use.

Experimental Protocol

Approval of the experimental protocol was obtained from the Experimental Animal Local Ethical Committee of Marmara University (MÜHDEK) (protocol number: 11.2020.mar, date: 10.02.2020). Female Sprague-Dawley rats were randomly divided into four groups. Group 1: control group (n=8); Group 2: animals given only 70% ethanol extract of Moringa leaves for 15 days (0.3 g/kg b.w./day; n=8); Group 3: animals that received only sodium valproate for 15 days (0.5 g/kg b.w./day; n=15); Group 4: animals administered with similar dose of sodium valproate + Moringa extract for 15 days (n=15). Moringa extract and sodium valproate were administered orally. Group 1 were orally given a similar doses of physiologic saline. On the 15th day of the experiment, the animals were fasted overnight, sacrificed, then stomach tissues collected and homogenized in ice-cold normal saline, using a glass homogenizer to make up 10% w/v tissue homogenate.

MAIN POINTS

- The central nervous system (CNS) is primarily affected by epileptic conditions.
- The biochemical composition of epileptic individuals can be distorted either due to loss of coordination of the CNS, antiepileptic drug toxicity or due to injuries.
- Antiepileptic drugs such as valproic acid are associated with elevated oxidative stress levels, distortion of the cellular membrane, and multiple organ damage.
- *Moringa oleifera* is a plant with plethora nutritional and diverse therapeutic benefits.
- The plant has pronounced antioxidant effects, as well as antiinflammatory and wound healing effects.
- The administration of Moringa leaves extract mitigated the adverse effect of valproate on the glycoprotein levels.
- Moringa leaves can be a good candidate for attenuating valproate-induced toxicity.

Biochemical Analysis

The sialic acid levels in stomach tissue homogenates were estimated according to the method of Warren[23] (1959). The levels of hexose and hexosamine were estimated according to the Winzler[24] (1955) method. Fucose levels were measured based on the method of Dische and Shettles[25] (1948), while protein levels in the homogenates were quantified based on the method of Lowry et al.[26] (1951).

Statistical Analysis

Graph-Pad Prism 6.0 (GraphPad Software, San Diego, CA, USA) program was used to analyse obtained data, by using one-way analysis of variance (ANOVA). Differences between groups were determined with Tukey's multiple comparisons test. The results were expressed as mean±standard deviation. The significance of differences was taken at $p<0.05$.

RESULTS

The sialic acid levels in the stomach tissues of all experimental groups are presented in Figure 1. According to the results obtained, a significant difference ($p_{ANOVA}=0.0013$) was observed when the sialic acid levels of all experimental groups were compared with each other. Between the control group and the Moringa administered group, no significant difference ($p>0.05$) was observed. In comparison to normal control rats, the sialic acid of valproate administered rats was significantly increased ($p<0.01$). Interestingly, Moringa extract administration to the valproate group led to a significantly lower ($p<0.01$) SA level in the Moringa + valproate group compared to rats solely given valproate.

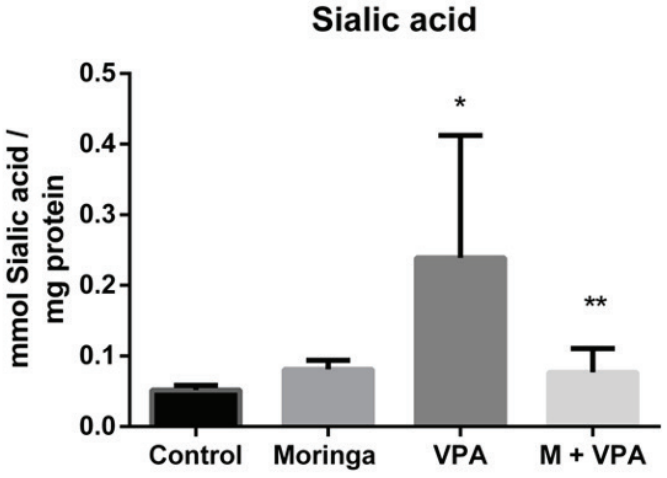

Figure 1. Sialic acid levels of the stomach tissue homogenates of experimental rats
*p<0.01 versus control group; **p<0.01 versus VPA group
VPA: Valproate, M: Moringa

As observed in Figure 2, a significant difference (p_{ANOVA}=0.0001) was observed between hexose levels of all experimental groups. The administration of Moringa leaves extracts to experimental control animals resulted in an insignificant increase (p>0.05) of hexose sugars levels in stomach tissue. In comparison to moreover, valproate administration resulted in a significant elevation (p<0.0001) of stomach tissue hexose sugar levels of control animals. In comparison to the valproate group, treatment of valproate rats with Moringa resulted in a significant decline (p<0.0001) of hexose concentration in the stomach tissue of Moringa + valproate group.

According to the results presented in Figure 3, comparison of hexosamine of all four groups indicated a significant difference (p_{ANOVA}=0.0001). The sole administration of both Moringa extract and valproate resulted in a significant rise in hexosamine levels in experimental rats (p<0.05, p<0.0001 respectively). In comparison to the solely valproate administered group, Moringa treatment to the valproate animals resulted in a significant decline (p<0.0001) of hexosamine level.

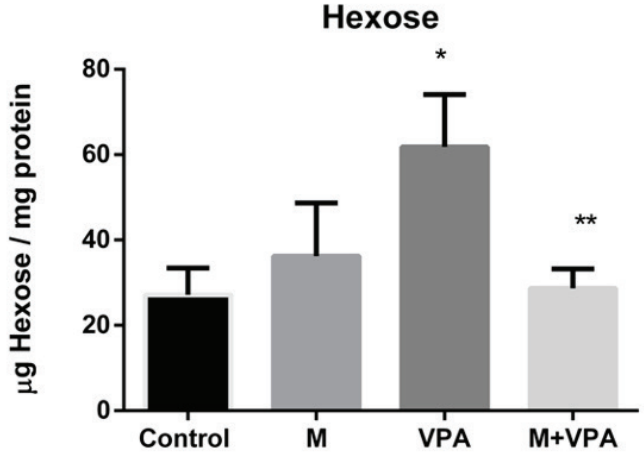

Figure 2. Hexose levels of the stomach tissue homogenates of experimental rats
*p<0.0001 versus control group; **p<0.0001 versus VPA group
VPA: Valproate, M: Moringa

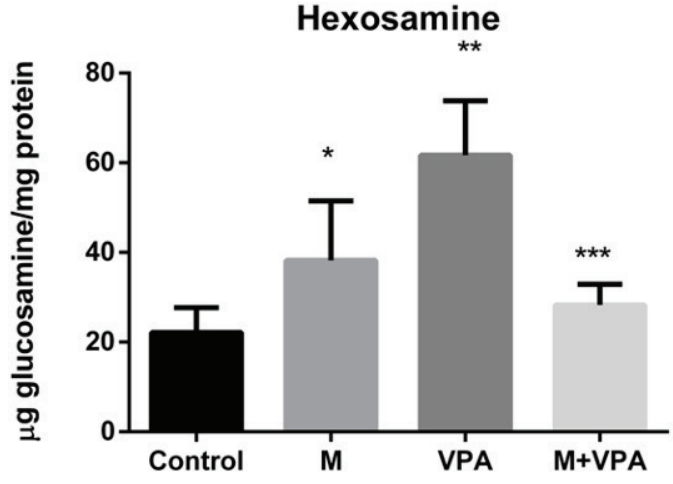

Figure 3. Hexosamine levels of the stomach tissue homogenates of experimental rats
*p<0.05 versus control group; **p<0.0001 versus control group; ***p<0.0001 versus VPA group
VPA: Valproate, M: Moringa

The fucose levels in the stomach tissue homogenates of all experimental groups are given in Figure 4. A significant difference (p_{ANOVA}=0.0001) was observed between all groups when statistically compared. In comparison to the normal control rats, the sole administration of either Moringa extract or valproate resulted in elevated fucose levels (p<0.05, p<0.0001 respectively). The fucose level of the Moringa + valproate group was significantly lower (p<0.0001) than that of the valproate group.

DISCUSSION

Generally, glycoproteins, glycolipids and gangliosides have critical biological roles essential for the normal function of cells, as well as its replication.[4-6,27] because these biomolecules are essentially made up of either proteins or lipids in combination to glycans (such as sialic acid, hexoses, fucose and/or their modified derivative), it is clear to expect abnormalities in glycan levels of tissues under any biological stress, pressure or trauma. The changes in tissue glycans levels can be a biomarker too for assessing the biological and physiological characteristics of the cell change and membrane damage.[28]

Despite the effectiveness and broad antiepileptic effect of valproate, the drug is associated with multiple organs and oxidative stress.[29-32] Moringa leaves on the other hand are rich in phytochemicals and antioxidants, which confers to it antioxidant,[17] antiinflammatory[15] and wound healing[16] effects. Thus, making it a suitable candidate for attenuating valproate-induced oxidative damage.

In this study, valproate administration to experimental animals resulted in elevated levels of all four glycans (i.e., sialic acid, hexose, hexosamine and fucose) assessed from stomach tissue homogenates of rats. The pronounced increase in sialic acid level of the valproate rats is probably linked to an increase in the activity of the sialidase enzyme. The enzyme promotes the hydrolysis of sialic acid from glycoconjugates. Hence, higher levels of sialic acid can be observed in tissue homogenates. Studies have shown that oxidative stress promotes the activity of sialidase, thereby enhancing increased desialization.[33] The increase in sialic acid (a membrane component) levels in stomach tissue homogenates of the

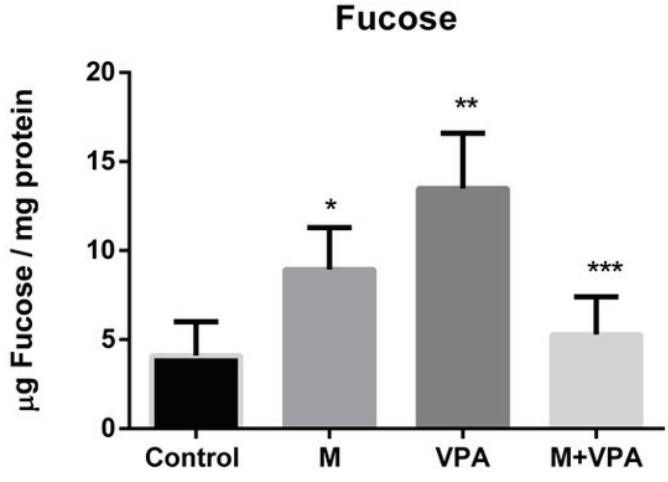

Figure 4. Fucose levels of the stomach tissue homogenates of experimental rats
*p<0.05 versus control group; **p<0.0001 versus control group; ***p<0.0001 versus VPA group
VPA: Valproate, M: Moringa

valproate group may be a direct consequence of cell membrane and tissue damage, which might have arisen due to valproate-induced oxidative damage. The administration of Moringa leaves extract in this study attenuated the negative effect of valproate on sialic acid level. This positive effect is likely because of the antioxidant, antiinflammatory, enzyme inhibition and wound healing potentials of Moringa extracts as earlier reported.[14-17]

Similarly, the concentrations of hexose, hexosamine, and fucose, which are glycoconjugate components of glycoprotein and glycolipids that makes up cell membrane and cellular receptors, were seen to have significantly increased upon administration of valproate to experimental rats. This is most likely a consequence of valproate-induced oxidative stress which damage cellular integrity and distort normal metabolic processes. Conversely, Moringa treatment to the valproate-treated animals mitigated the derangements in levels of hexose, hexosamine, and fucose of stomach tissue homogenates. Previous studies have indicated that antioxidants such naringin combined with vitamin C could prevent elevation of free glycan levels of both plasma, liver and kidney tissues streptozotocin-induced diabetes.[34] Similarly, vitamin U mitigate either amiodarone or D-galactosamine-induced hepatotoxicity, oxidative damage, as well as distortion of glycan levels.[35] Sacan et al.[36] (2021) and Turkyilmaz et al.[37] (2021) have demonstrated that antioxidant and antiinflammatory elements such as zinc could protect against cellular damage induced by streptozotocin. It also prevented oxidative stress and maintained normal levels of glycoconjugates. Just like Moringa extract, herbal formulations such as muthu marunthu[38] and convincing db[39] could protect tissue integrity and prevent the alteration of glycocomponents of glycoprotein levels in experimental animals. The ameliorative and positive biological action of Moringa against stomach tissue damage, as well as on glycoprotein glycan components is linked to it ample phytochemical components and antioxidant minerals. More so, the antioxidant potential of the plant extract must have played a vital role in preventing valproate-induced oxidative stress/damage to the stomach tissue of the experimental animals.

Study Limitations

The study limitation of this study is to fully lighten the beneficial effects of Moringa alcoholic extract on stomach biochemical parameter; thus, thus further stomach disease or toxicity models must be developed and protection of Moringa alcoholic extract must be examined on these models.

CONCLUSION

The administration of valproate to experimental rats distorted the levels of sialic acid, hexose, hexosamine, and fucose in the stomach tissue homogenate. Nevertheless, it coadministration with the Moringa extract offsets changes in tissue levels of the aforementioned glycans in the valproate group. Therefore, Moringa leaves can be a suitable candidate for mitigating valproate-induced toxicity/damage to stomach tissue.

Ethics

Ethics Committee Approval: Approval of the experimental protocol was obtained from the Experimental Animal Local Ethical Committee of Marmara University (MÜHDEK) (protocol number: 11.2020.mar, date: 10.02.2020).

Informed Consent: Animal experiment.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: U.F.M., S.M., Ö.S., R.Y., Design: S.M., Ö.S., R.Y., Data Collection or Processing: U.F.M., S.M., Ö.S., R.Y., Analysis or Interpretation: S.M., Ö.S., R.Y., Literature Search: U.F.M., Ö.S., R.Y., Writing: U.F.M., Ö.S., R.Y.

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

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Risk Factors for Clinically Overt Hypothyroidism in Unselected Population of Adult Epilepsy Patients

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Abstract

Objective: This study aimed to investigate the risk factors for hypothyroidism in patients with adult epilepsy patients.

Methods: Hospital charts of 530 patients were reviewed retrospectively. Patients with a definite diagnosis of hypothyroidism with persistent adherence to antiseizure medications (ASM) were included. An age and gender-matched group of 110 patients was selected as the control group.

Results: The rate of hypothyroidism was significantly higher in patients with epilepsy (p=0.01). The patients with epilepsy were separated into two groups-the patients with and without hypothyroidism. The distribution of other neurologic disorders was similar in epilepsy patients with and without hypothyroidism (p=0.46). The comparison of the two groups showed that, independent of the ASM type, receiving any polytherapy regimen was a significant risk factor for hypothyroidism (p=0.02) and epilepsy patients with hypothyroidism had a longer duration of epilepsy (p=0.03). Logistic regression analysis revealed that the only independent risk factor for hypothyroidism was being on a polytherapy regimen (p=0.02).

Conclusion: In this study, we found two major results: i) compared with an age and gender-matched control group, epilepsy is a major risk factor for hypothyroidism, ii) independent of the ASM type, receiving a polytherapy regimen is a predictive risk factor for hypothyroidism.

Keywords: Hypothyroidism, epilepsy, polytherapy

INTRODUCTION

Epilepsy has as an overall incidence of 0.2-4.1% amongst the adult population and causes a significant burden in all age groups.[1] Critically, the negative impact of epilepsy is disproportionate to its prevalence. Persons with epilepsy (PWE) have a lower quality of life compared with other chronically ill individuals.[2,3] When combined with the comorbidities, epilepsy becomes a more complicated disease.

Comorbidity is defined as the simultaneous presence of two or more diseases in the same individual more frequent than the chance expectation derived from an age-matched control cohort of healthy subjects.[4] Comorbidity does not always imply a directional relationship, although diseases may share common genetic or environmental risk factors, recent studies suggest that thyroid dysfunction should be regarded as a comorbidity of epilepsy.[5]

Therefore, in this study, we characterized the relationship between thyroid dysfunction and antiseizure medicines (ASM) in an unselected adult patient population with epilepsy.

METHODS

Patients

Hospital charts of patients aged more than 18 years old who were admitted to the epilepsy outpatient clinic of Akdeniz University between November 2017 and December 2018 were reviewed retrospectively. Patients who were diagnosed with epilepsy and receiving ASMs were included. Patients with the evidence of persistent nonadherence to medications were excluded from the study. An age and sex-matched group of patients those have attended the neurology outpatient clinic for other illnesses other than epilepsy were selected as the control group. Data regarding the seizure type, etiology, and epilepsy syndromes were classified according to the recommendations of the International League Against Epilepsy. Only the patients those have were evaluated by an endocrinologist and diagnosed with hypothyroidism in whom L-thyroxine replacement therapy was initiated were included in the patient group. The study was started with the

permission of the Akdeniz University Faculty of Medicine Clinical Research Ethics Committee with the decision dated 17/02/2022 and numbered 7090450.

Statistical Analysis

Continuous variables were expressed as mean±standard deviation and categorical variables as numbers and percentages. Significances of the differences between the groups were tested by the two-sided independent samples t-test for parametric data and by Mann-Whitney U test for non-parametric data. Pearson's chi-square test was used for categorical comparisons of nominal values. A binary logistic regression analysis was performed to identify the predictors of hypothyroidism in patients with epilepsy. A p value less than 0.05 was considered to be statistically significant. Data were analyzed using Statistical Package for the Social Sciences (SPSS) for Windows version 18.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Data of 530 consecutive patients with epilepsy and an age- and gender-matched group of patients consisting 110 individuals (those were selected as the control group) were reviewed retrospectively. ASMs used by the patients with epilepsy are listed in Table 1. The rate of hypothyroidism was significantly higher in patients with epilepsy (p=0.01) (Table 2). Patients with epilepsy were separated into two groups-patients with and without hypothyroidism. The distribution of other neurologic disorders was similar in epilepsy patients with and without hypothyroidism (p=0.46). A comparison of the two groups showed that the prevalence of polytherapy regimen was higher (p=0.02) and epilepsy duration was longer (p=0.03) in epilepsy patients with hypothyroidism (Table 3). Logistic regression analysis revealed that the only independent risk factor for hypothyroidism was being on a polytherapy regimen (p=0.02) (Table 4).

Table 1. The table shows list of antiseizure medications which were used by the epileptic patient group

Drug names	n (%)
Levetiracetam	261 (49.2%)
Valproate	134 (25.3%)
Lamotrigine	88 (16.6%)
Zonisamide	71 (13.4%)
Carbamazepine	90 (17.0%)
Clonazepam	21 (4.0%)
Lacosamide	55 (10.4%)
Oxcarbazepine	90 (17.0%)
Topiramate	29 (5.5%)
Clobazam	11 (2.1%)
Primidone	3 (0.6%)
Phenytoin	6 (1.1%)
Phenobarbital	3 (0.6%)

*151 (65.7%) of the patients were using 2 ASM drugs, 53 (23.0%) of the patients were using 3 ASM drugs, 23 (10.0%) of the patients were using 4 ASM drugs and 3 (1.3%) of the patients were using 5 ASM drugs.
ASM: Antiseizure medications

MAIN POINTS

- In this study, we characterized the relationship between thyroid dysfunction and antiseizure medicines (ASM) in an unselected adult patient population with epilepsy.
- According to our results, we suggest two main results; a) epilepsy is a risk factor for hypothyroidism, b) receiving any polytherapy regimen is a significant independent risk factor for hypothyroidism in patients with epilepsy.
- The routine evaluation for thyroid dysfunction should be considered part of routine medical care for patients receiving combination therapy and for those receiving any ASM for a long duration.

DISCUSSION

In this study, we found two major results, i) epilepsy is a risk factor for hypothyroidism; when compared with an age and gender-matched control group of patients without epilepsy, the percentage of hypothyroidism was significantly higher in patients with epilepsy, ii) independent of the ASM type, receiving any polytherapy regimen is a significant risk factor for hypothyroidism. In patients with hypothyroidism, the epilepsy duration was found to be longer. However, using binary logistic regression analysis, it was not found to be an independent risk factor for hypothyroidism.

In our study, 7.4% of epilepsy patients had a diagnosis of hypothyroidism and were receiving L-thyroxine treatment. This ratio was significantly higher than that of the control group (p=0.01).

Table 2. Frequency of hypothyroidism amongst patients with and without epilepsy

	Epilepsy patients (n=530)	Control group (n=110)	p value
Age (year±SD)	37.1±16.2	38.1±13.0	0.48
Female gender, n (%)	273 (51.5%)	61 (55.5%)	0.45
Hypothyroidism, n (%)	39 (7.4%)	1 (0.9%)	0.01

SD: Standard deviation

Table 3. Demographics regarding hypothyroidism amongst patients with epilepsy

	Hypothyroidism (+), (n=39)	Hypothyroidism (-), (n=491)	p value
Age (year±SD)	39.6±16.6	36.9±16.2	0.32
Duration of epilepsy (year±SD)	17.5±9.5	13.7±10.4	0.03
Female gender, n (%)	24 (61.5%)	249 (50.7%)	0.20
Other neurological disorders, n (%)	7 (17.9%)	113 (23.0%)	0.46
Polytherapy, n (%)	24 (61.5%)	206 (42.0%)	0.02

SD: Standard deviation

Table 4. Logistic regression analysis revealing the independent risk factor for hypothyroidism

	Odds ratio	Coefficient interval (95%)	p value
Age	1.01	0.99-1.04	0.20
Female gender	0.57	0.29-1.13	0.11
Polytherapy	2.36	1.17-4.76	0.02
Duration of epilepsy (years)	1.02	0.99-1.05	0.11

There is growing evidence regarding serious endocrinological comorbidities in epilepsy. Although the prevalence of thyroid dysfunction and evidence about the interrelation is conflictive, several investigations support the idea that hypothyroidism is more common in PWE than in the general population.[6] ASMs are the mainstay of treatment and postulation about the mechanisms differ, but ASMs affect the thyroid hormone levels.

Carbamazepine is one of the most investigated ASMs for its endocrinological adverse effects. Carbamazepine induces the P-450 enzyme system and increases the metabolism of thyroid hormones, which leads to low thyroid serum concentrations. Thyroid hormonal abnormalities were also reported with phenobarbital, phenytoin, valproate and oxcarbazepine, but not with lamotrigine, levetiracetam, topiramate, tiagabine and vigabatrin.[7]

Amongst several ASMs, significant correlations were reported between thyroid volume and thyroid hormonal abnormalities in adults, particularly those on valproate. The mechanism of valproate on thyroid homeostasis is unclear. One hypothesis suggests that an increase in TSH with valproate therapy results from g-aminobutyric acid-stimulating properties of valproate by inhibiting the release of somatostatin, which in turn inhibits TSH secretion. Another mechanism postulated for hypothyroidism is that valproate leads to zinc and selenium deficiency, which are important enzymes in thyroid hormone synthesis.

Oxcarbazepine, despite its structural resemblance to carbamazepine, does not induce enzyme activity. Even normalization of serum thyroid hormone levels induced by carbamazepine has been shown after replacement of carbamazepine with oxcarbazepine in adults.[8]

According to several studies, it appears that the effect of oxcarbazepine on thyroid function is short-term, transient, and less significant than the effects of carbamazepin. Phenytoin has also been investigated. Phenytoin induces the thyroid hormone metabolism and displaces thyroid hormones from serum-binding proteins, which in turn leads to low serum thyroid levels.

Phenobarbital was found to lower T3 and T4 levels only when it has been used for longer than six years. However, the changes on TSH concentrations were less marked than those in patients treated with valproate. A previous study has shown that the increased TSH concentrations returned to normal values after the withdrawal of phenobarbital. Thus, the effects of phenobarbital on thyroid function appear reversible.[9-11] However, transient TSH alterations leading to subclinical hypothyrodisim should also be regarded as a major health problem mainly in the adult patient population. In recent studies, it is emphasized that unstable TSH levels -even at the euthyroid level- are associated with a higher mortality rate.[12,13]

The second main finding of our study was that being on any polytherapy regimen was a major risk factor for hypothyroidism. The effects of polytherapy on thyroid functions have been investigated in five previous studies. In these studies being on polytherapy has also been proposed as a risk factor for hypothyroidism. The profound risk in patients receiving polytherapy might be explained by the fact that this particular group of patients are more likely to be exposed to a longer duration of ASM treatment and a higher seizure frequency. Higher seizure frequency may interfere with the hypothalamic axis and alter the TSH levels.[14-16]

Another finding of our study was that the duration of epilepsy was longer in epilepsy patients with hypothyroidism. However, according to the logistic regression analysis, this was not an independent risk factor for hypothyroidism. Further studies evaluating the relationship between the duration of treatment and hypothyroidism is warranted.

As a result, considering the current literature and our results, we might suggest that compared with an age and gender-matched population, hypothyroidism is more prevalent in epilepsy patients and should be regarded as a serious comorbidity. Being on a polytherapy regimen is an independent risk factor.

Study Limitations

Because of the retrospective design, there are several limitations of this study. First, baseline thyroid hormone levels were not availabl; therefore, we compared these parameters with an age and gender-matched control group to eliminate this bias.

The abscence of description of the comorbiditiesand other systemic and neurological disorders of the patients with epilepsy was another limitation. Our data regarding drugs other than ASMs were also lacking. Therefore, the potential negative endocrinological effects of these circumstances could not be clarified. Hence, the possible interaction of these parameters with the results of our study could not be eliminated.

Another limitation was the lack of body mass index of both the patient and the control group as obesity is closely related to altered serum thyroid levels; anthropometric values would add value to the findings of our study. To come over these limitations, we used multiple logistic regression analyses to correct these variables. Prospectively designed large-scaled studies are warranted.

CONCLUSION

In conclusion, epilepsy is a risk factor for hypothyroidism and irrespective from the ASM type, receiving a polytherapy regimen is an independent risk factor. Further studies are needed in this field, before a definite recommendation can be given, as hypothyroidism is a serious health problem that may result in increased cardiovascular morbidity and mortality.

Ethics

Ethics Committee Approval: The study was started with the permission of the Akdeniz University Faculty of Medicine Clinical Research Ethics Committee with the decision dated 17/02/2022 and numbered 7090450.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: E.A.D., Design: E.A.D., Data Collection or Processing: Y.Ş., Analysis or Interpretation: N.Ç.Ç.B., Y.Ş., Literature Search: N.Ç.Ç.B., E.A.D., Writing: N.Ç.Ç.B.

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COVID-19 Vaccine Take-up Rate, Safety and Tolerability in Patients with Epilepsy

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Abstract

Objective: Although vaccines are considered safe for most people, patients with some chronic diseases have been very hesitant to get vaccinated, especially at the initial stages of vaccination. We conducted a survey among patients with epilepsy (PWE) who are currently experiencing hesitations, aiming to investigate the vaccination rates against Coronavirus disease-2019 (COVID-19) and the side effects emerged in vaccinated patients.

Methods: Two hundred nineteen PWE were questioned during a routine outpatient follow-up through previously prepared questionnaires that contained questions about patients' demographic features, information about the vaccination status, and its adverse effects.

Results: We included 219 PWE in the study of which 112 (51.1%) were female and 107 (48.8%) were male. One hundred eighty patients (82.1%) had been vaccinated at least once, 75% of the patients preferred two doses of BNT162b2 mRNA COVID-19 vaccine, 9.4% of the patients preferred two doses of Sinovac's inactivated vaccine, 6.1% of the patients preferred three doses of Sinovac, and 9.4% of the patients preferred Sinovac and BNT162b2 vaccines. Seventy-seven (42.7%) patients reported that they experienced side effects after vaccination whereas ten patients (5.5%) reported worsening of their seizures after vaccination; one person stated that she/he was hospitalized in the intensive care unit due to status epilepticus.

Conclusion: Generally, the tolerance of COVID-19 vaccines has progressed with mild side effects in most cases, which is consistent with previous studies in the general population, similarly no serious and previously unreported side effects were found in our study. Our study showed that COVID-19 vaccines are well-tolerated and safe for seizures in PWE.

Keywords: Epilepsy, COVID-19 vaccination, Pfizer BioNTech, Sinovac-CoronaVac, side effect

INTRODUCTION

Due to the Coronavirus disease-2019 (COVID-19), which has more than 400 million cases to date, approximately 6 million deaths have occurred around the worldwide and approximately 100 thousand deaths in Turkey.[1] This disease, which causes a socioeconomic burden as well as serious health problems, has massively impacted global public health, and vaccination studies have started rapidly since the first day of the pandemic to prevent COVID-19, particularly severe disease. As of December 2022, 13 trillion vaccinations have achieved all over the worldwide and 139 million in Turkey, and vaccination started with Sinovac vaccine in Turkey, then continued with Pfizer BioNTech and finally Turkovac vaccine.[1] Owing to the vaccines developed at an extremely rapid pace, there was a reduction in the symptoms of COVID-19-related diseases and a decrease in hospitalizations and intensive care unit admissions.[2,3] Although the vaccine is considered safe for most people, patients with some chronic diseases have been very hesitant to get vaccinated, especially in the early stages of vaccination. Patients with epilepsy (PWE), one of the disease groups highly affected by the pandemic, were also the most hesitated group. The International League Against Epilepsy (ILAE) stated that there is no evidence associated with a high risk of side effects due to the COVID-19 vaccine in PWE, but in some countries having uncontrolled epilepsy is listed as a contraindication.[4] Especially at the beginning of vaccination in our country, in some centers, there were opinions that if patients had epilepsy, they should not be vaccinated. We conducted a survey among PWE who were currently experiencing hesitations, aiming to investigate the vaccination rates against COVID-19, the side effects emerged in vaccinated patients, the effect of the vaccine on epileptic attacks, and the reasons why unvaccinated PWE did not get vaccinated.

METHODS

This cross-sectional study was conducted in the Antalya Training and Research Hospital, which is a tertiary center in Turkey. Between November and December 2021, 219 PWE over the age of 18 who were diagnosed with epilepsy according to the ILAE guideline, and followed up in the epilepsy outpatient clinic of Antalya Training and Research Hospital were included in the study.

Patients with severe mental retardation who cannot express themselves, who do not have regular outpatient follow-up, and whose epilepsy diagnosis is unclear were excluded.

Patients were asked questions through previously prepared questionnaires during routine outpatient follow-up. The survey questions of 3 groups:

1. In addition to questions about demographic data such as age-gender-occupation of the patients, seizure types, seizure frequencies, and drugs they used were questioned. The seizure types of the patients were categorized according to the ILAE epilepsy classification 2017 guidelines.

2. The vaccination status of the patients was questioned and the reason for not being vaccinated and whether they were considering vaccination were also noted.

3. The status of vaccinated patients with COVID-19 infection before vaccination was recorded. Additionally, the frequency of vaccination, the type of vaccine, the local and systemic side effects experienced after each vaccine, as well as serious side effects that may cause hospitalization or disability were questioned. If there were any changes in the seizures of patients after vaccination were also questioned. Based on the seizure diaries kept by the patients, an increase of more than 50% in the frequency of seizures after vaccination compared to pre-vaccination, the emergence of new seizure types after vaccination, or the prolongation of seizure durations by more than 50% compared to the past or the presence of status epilepticus were recorded as an increase in the frequency of seizures.

The Ethics Committee of Antalya Training and Research Hospital (approval number: 16/13, date: 14/10/2021) approved this cross-sectional study, and written informed consent forms were obtained from all patients.

Statistical Analysis

All statistical analyses were performed using Statistical Package for the Social Sciences 22.0. Categorical variables were described as percentages, and continuous variables were described using mean±standard deviation. Means for continuous variables were compared using independent group t-tests when the data were normally distributed. Categorical variables analyzed by chi-square or Fisher's exact tests and p value of 0.05 or below were treated as significant.

RESULTS

The mean age of 219 PWE included in the study was 37.9±13.5 years, of which 112 (51.1%) were female and 107 (48.8%) were male. Eight (3.6%) patients were illiterate, 109 (49.9%) were primary school graduates, 59 (26.9%) were high school graduates, and 43 (19.6%) were university graduates. One hundred and five (47.9%) patients were employed, and 114 (52.1%) patients were unemployed at the time of the survey.

Of the patients, 157 (71.6%) were in focal epilepsy, 38 (17.3%) were in generalized epilepsy, 24 (10.9%) were in the unclassified group, and 116 of these patients were followed up without seizure. One hundred thirty (59.3%) patients have been receiving monotherapy, and 89 (40.6%) patients have been on polytherapy. Demographic data for all patients are presented in Table 1.

In total, 180 patients (82.1%) had been vaccinated at least once. At the time of our study, only Pfizer BioNTech (BNT162b2) and Sinovac-CoronaVac (Sinovac) vaccines were available in Turkey. In this context, when evaluated in terms of the vaccine types preferred by the patients, 75% of the patients preferred 2 doses of BNT162b2, 9.4% of the patients preferred 2 doses of Sinovac, 6.1% of the patients preferred 3 doses of Sinovac, and 9.4% of the patients preferred both Sinovac and BNT162b2 vaccines (Table 2).

The reasons for unvaccinated patients not being vaccinated at the time of the survey were questioned. 35.8% of the patients stated that they would never be vaccinated, 32% were undecided, and 32% stated that they had a vaccine appointment. When the reasons of the patients who decided not to get vaccinated were examined and 10.2% reported that they were scared of the interaction of the vaccine they used with anti-seizure medication (ASM), 12.8% were afraid of the side effects that the vaccine could cause, 12.8%

Table 1. Demographic characteristics of the study group

Features	n	Percent (%)
Gender		
Male	107	48.8
Female	112	51.2
Marital status		
Married	120	54.7
Single	99	45.3
Education		
Illiterate	8	3.6
Primary education	109	49.9
High school	59	26.9
University	43	19.6
Job		
Working	105	47.9
Not working	114	52.1
Epilepsy type		
Focal epilepsy	157	71.6
Generalized epilepsy	38	17.3
Unknown	24	10.9
Epilepsy surgery		
Yes	3	1.3
No	216	98.6
Comorbidity		
Yes	54	24.6
No	165	75.3

MAIN POINTS

- No previously undescribed side effects were observed in patients with epilepsy (PWE) vaccinated with Coronavirus disease-2019 (COVID-19) vaccines.
- Our study showed that COVID-19 vaccines are well-tolerated.
- Our study showed that COVID-19 vaccines are safe in terms of not increasing the frequency of seizures in PWE.

did not feel the need to be vaccinated because they experienced COVID-19, 30.7% were afraid of triggering seizures after vaccination, and 33.3% reported that they would not be vaccinated for other reasons (Table 2).

When we analyzed the demographic data of vaccinated and unvaccinated PWE, the average age of unvaccinated patients was 32.1±11.3 years, and 22.3% of female patients and 13% of male patients were not vaccinated. According to the analysis, a statistically significant relationship was found between age and those who were vaccinated, and the vaccination rate increased as the age increased (p=0.003). Additionally, the relationship between vaccination and comorbidity was examined, and no statistically significant difference was observed (p=0.50). Demographic data of vaccinated and unvaccinated patients are given in Table 3.

Considering the side-effect rates of the vaccinated patients, 77 (42.7%) patients reported that they experienced side effects after vaccination. The most common side effects were pain and tenderness at the vaccination site (39.4%); others were; swelling at the injection site (1.6%), redness at the vaccination site (0.5%), post-vaccine fatigue (12.7%), myalgia (6.1%), fever (6.6%), arthralgia (1.6%), runny nose (0.5%), diarrhea (0.5%), and sore throat (1.1%). Side effects were most frequently observed in patients who received 2 doses of BNT162b2. The mean duration of the observed side effects was 1.8±2.72 days. While 10 patients (5.5%) reported worsening of their seizures after vaccination, 1 person stated that she/he was hospitalized in the intensive care unit due to status epilepticus Although the patient describing status epilepticus was approximately twelve h after vaccination, the exact time interval for patients reporting worsening seizures is unknown.

Of the 10 patients describing worsening of seizures, 7 received 2 doses of BNT162b2, 1 received Sinovac + BNT162b2, 1 received 2 doses of Sinovac, and 1 received 3 doses of Sinovac vaccine (Table 4).

Table 2. Vaccination characteristics of the patients included in the study

Features	n	Percent (%)
COVID-19 history		
Yes	192	87.6
No	27	12.3
Vaccination		
Yes	180	82.1
No	39	17.8
Vaccine type		
BNT162b2 2 doses	135	75
Sinovac 2 doses	17	9.4
Sinovac 3 doses	17	9.4
Sinovac + BNT162b2	11	6.1
Reason for not vaccinating		
Afraid of triggering seizures after vaccination	12	30.7
Had COVID-19 before	5	12.8
Afraid of the side effects	5	12.8
Afraid of the interaction with anti-seizure medication	4	10.2
Other	13	33.3

BNT162b2: BioNTech, COVID-19: Coronavirus disease-2019

No patients described serious side effects.

The clinical characteristics of the patients who experienced side effects were also examine; no statistically significant difference was observed between age, type of seizure, and number of anti-seizure drugs used due to comorbidity and having had COVID-19. In terms of gender, side effects were more common in females (p=0.0004). Demographic information of patients describing worsening of seizures is given in Table 4 and Table 5.

There was no statistical significance between age, vaccine type, seizure classification, and seizure frequency among patients who described and did not describe worsening in seizures, and again there was a statistically significant seizure frequency rate in female gender (p=0.02) (Table 5).

DISCUSSION

The COVID-19 vaccine started to be administered in our country on January 13, 2021, and serious indecisiveness was observed in society during the first days of vaccination. PWE also experienced hesitancy about getting vaccinated due to reasons such as; interaction with the ASM they use and fear of triggering seizures. Additionally, in some health centers where vaccination was administered at the beginning of the vaccination period, health workers had the same hesitations about PWE for an unknown reason and tended to refer patients to neurologists before vaccination. Due to these hesitations, the Turkish Epilepsy Society published a statement stating that there was no evidence of a high risk of side effects to the COVID-19 vaccines in individuals with epilepsy.[5] Additionally,

Table 3. Demographic comparison between vaccinated and unvaccinated group

Features	Vaccinated (n)	Unvaccinated (n)	p value
Age	39.1±13.6	32.1±11.3	0.003
Gender			0.07
Male	93 (86.9%)	14 (13.1%)	
Female	87 (77.6%)	25 (22.3%)	
Marital status			0.62
Single	100	20	
Married	80	19	
Education			0.18
Illiterate	7	1	
Primary education	93	26	
High school	43	16	
University	37	6	
Job			0.91
Working	86	19	
Not working	94	20	
Epilepsy type			0.08
Focal epilepsy	129	28	
Generalized epilepsy	28	10	
Unknown	23	1	
Comorbidity			0.50
Yes	46	8	
No	134	31	

Table 4. Features of ten patients who describe worsening of seizures

Patient	1	2	3	4	5	6	7	8	9	10
Age	39	43	57	39	38	43	23	36	24	55
Gender	M	F	F	F	F	F	F	M	F	F
Epilepsy duration	22	29	43	29	15	15	12	11	16	54
Number of anti-seizure medication	1	3	3	1	2	3	3	6	2	4
Seizure type	Focal	Focal	Focal	G	G	Focal	Focal	Focal	G	Focal
Seizure frequency	None	1/ 3 3 month	4-5/month	1/ 3 3 month	4-5/month	4-5/month	4-5/month	4-5/month	1/ 3 3 month	None
Comorbidity	No	No	No	No	No	DM	Mild MR	Intracranial mass	Mild MR	No
Had COVID-19 before	No	No	No	Yes	Yes	No	No	No	No	No
Vaccine type	2 dose B	2 dose S	2 dose B	S + B	2 dose B	2 dose B	2 dose B	3 dose S	2 dose B	2 dose B
Side effects	P, A	P, Fa, A	P, A	P, Fa, A	P, Fa, A, So	P, Fe, A, So	A	A	A	Fa, A, HA

M: Male, F: Female, Epilepsy duration: Year, FIAS: Focal impaired, Focal: Focal epilepsy, G: Generalized epilepsy, DM: Diabetes mellitus, MR: Mental retardation, B: BNT162b2, S: Sinovac, P: Pain, A: Arthralgia, Fa: Fatigue, So: Sore throat, Fe: Fever, HA: Headache, COVID-19: Coronavirus disease-2019

Table 5. Comparison of patients who described worsening/not worsening in their seizures

Features	Patients not describing worsening in seizures n=169	Patients describing worsening in seizures n=10	p value
Age	39.1±13.8	39.7±11.0	0.91
Gender			0.04
Male	90	2	
Female	79	8	
Marital status			0.35
Married	93	7	
Single	76	5	
Education			0.02
Illiterate	5	2	
Primary education	88	5	
High school	39	3	
University	37	0	
Job			0.62
Working	81	4	
Not working	88	6	
Epilepsy type			0.25
Focal epilepsy	121	7	
Generalized epilepsy	25	3	
Unknown	23	0	
Comorbidity			0.07
Yes	41	5	
No	128	5	
Vaccine type			0.96
BioNTech 2 doses	127	7	
Sinovac 2 doses	16	1	
Sinovac 3 doses	10	1	
Sinovac + BioNTech	16	1	

ILAE's view was that the risk of COVID-19 infection could be much more harmful than the risk of adverse effects from vaccines.[6]

In our hospital, which is a tertiary epilepsy center in Turkey, we presented real-life data including the reasons for vaccine hesitancy, side effects of vaccines, and the effects of vaccines on seizures of PWE.

At the time of our study, at least 2 dose vaccination rates in Turkey were around 83%, while this rate was around 79% in Antalya, and the vaccination rates of our patients were similar to the general population.[7] Generally, the tolerance of COVID-19 vaccines has progressed with mild side effects in most cases, which is consistent with the previous studies in the general population,[8,9] and no serious and previously unreported side effects were found in our study. When the mean duration of all vaccine-related systemic and local side effects was considered, it was observed as 1.8±2.7 days in our study, and similar durations were observed in the clinical trials of vaccines and in the literature.[9,10]

The most common side effect was pain/tenderness on the vaccinated arm (39.4%), which was observed more frequently after the BNT162b2 vaccine. Compared to the side effect rates observed in the clinical trials of both vaccine studies, it was found to be low.[8,10] Additionally, in a meta-analysis published by Lin et al.,[11] wide local side-effect rates were observed in vaccine studies conducted in PWE in various countries, and a similar rate of side effects was observed as in a study by Özdemir et al.[12] in Turkey (36%). This may be an ethnic difference, or, it may be because the patients cannot remember or can forget the side effects since our study was conducted retrospectively. This is a limitation of our study. Although the frequency of local side effects after BNT162b2 vaccine was higher in our study, in a study including 111 PWE vaccinated with Sinovac and BNT162b2 vaccines in Germany, side effect profiles and side effect frequencies of vaccines were compared and similar results were observed in both comparisons. Additionally, in that study, it was argued that the risk of worsening seizures after vaccination was minimal.[13] In our study, when the side effects and clinical features were compared, no correlation was observed with any factor other than female gender, including comorbidity. In a previous study conducted in a tertiary epilepsy

center in Germany, a significant difference between vaccine side effects and female gender, age, and early age of onset was observed. As in our study, no relationship could be found between the number of ASMs and vaccine side effects, and it has been argued that this might be because patients using a high number of ASMs attributed less value to side effects.[14]

There were 10 (5.5%) patients who described increased seizures after vaccination. One of these patients was a patient hospitalized in the intensive care unit due to status epilepticus. Since the same patient had non-epileptic seizures in addition to epileptic seizures, it was not possible to distinguish whether the seizures she/he described as an increase was non-epileptic or epileptic. Although it was previously reported that vaccines would not increase seizures, a slight increase in risk was reported only in childhood encephalopathies such as Dravet's syndrome.[15] However, although studies with new vaccines (mRNA) are limited, due to our experience, we think that the COVID-19 vaccine has no effect on seizures in PWE and there is no difference in the side-effect profile compared with the normal population, as stated in many studies. According to the literature, post-vaccine status epilepticus is not an expected side effect, but it is thought that the increase in seizures after vaccination is mostly coincidental or related to the natural course of the disease.[16] This rate was found to be slightly higher in female gender in patients with vaccine hesitancy, and when the relationship between the causes of hesitancy and comorbidities was examined, no statistically significant relationship was found. In a population-based study conducted in Brazil in 2022 to investigate COVID-19 vaccine hesitations and related factors by gender, vaccination rates were found to be slightly higher in males, in line with our study. Unlike our study, a correlation was observed between having comorbidity in the male gender group and having a high education level in the female gender, and hesitation about vaccination.[17] As one of the main findings of our study, it was determined that the indecision to get vaccinated decreased with age. We think that the possible reason for this may have been influenced by the fact that the COVID-19 epidemic has been more severe in the elderly and in the presence of comorbidities since the beginning of the epidemic. In a multicenter study conducted on patients who were not previously diagnosed with epilepsy, similar to our study, it was found that vaccine hesitancy decreased as age increased, and attention was drawn to the fact that elderly people were more likely to volunteer to be vaccinated due to fear of death.[18]

Study Limitations

Our study has some limitations. The number of PWEs included in the study was relatively small and no comparison could be made because there was no healthy control group. This leads to limitations in the comparison of side effects. Larger studies are needed to evaluate vaccine types, side effect profile, and tolerability in PWE.

CONCLUSION

In conclusion, our study showed that COVID-19 vaccines are well tolerated and safe for seizures in PWE.

Ethics

Ethics Committee Approval: The Ethics Committee of Antalya Training and Research Hospital, approval number: 16/13, the date: 14/10/2021.

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

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Original Article

Retrospective Analysis of Patients Undergoing Video-EEG Monitoring

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Abstract

Objective: Video-electroencephalography (EEG) monitoring (VEM) is an essential tool in diagnosing and treating epilepsy as it enables real-time monitoring and recording of electrical activity in the brain. We investigated the role of VEM in the diagnosis and treatment of epilepsy and recurrent paroxysmal events.

Methods: We retrospectively examined patients monitored in our VEM unit between 2008-2016. We registered demographic and clinical information from the patients' files. The VEM was performed until at least three typical seizures were recorded or the predetermined recording period ended. An experienced neurologist reviewed and interpreted all video-EEG recordings and compared them to the initial diagnoses. Any changes in the diagnoses and treatment plans were recorded.

Results: A total of 252 patients were included in this study. VEM was performed for pre-surgical planning or vagal nerve stimulation in 170 (67.46%), diagnosis/differantial diagnosis in 54 (21.42%), seizure classification in 18 (7.14%), and treatment follow-up in 10 patients (3.96%). A total of 187 patients (74.2%) had seizures [11 of whom had both epileptic seizures and psychogenic non-epileptic seizures (PNES)], 14 (5.55%) had only PNES, and one (0.39%) had a sleep attack due to idiopathic hypersomnia. VEM provided an additional contribution in diagnosis in 197 patients (78.17%). Diagnosis and management were changed in 26 (10.31%) and 175 patients (69.16%), respectively, following VEM.

Conclusion: VEM plays a crucial role in the diagnosis and management of epilepsy, particularly when used in presurgical planning. In additionally, VEM, the gold standard in diagnosing PNES, may change the diagnosis, especially in patients with PNES or PNES plus epilepsy.

Keywords: Epilepsy, diagnosis, video-electroencephalography, video-EEG monitoring

INTRODUCTION

Video-electroencephalography (EEG) monitoring (VEM) is an indispensable part of daily epilepsy practice, as it allows for real-time monitoring and recording of electrical activity in the brain. VEM can be used to distinguish between epilepsy and other paroxysmal events, such as psychogenic non-epileptic seizures (PNES), and to define the seizure type and determine the seizure onset zone before epilepsy surgery.[1,2] Furthermore, VEM can provide long-term investigation of continuous spike-wave discharges in Landau-Kleffner syndrome and electrical status epilepticus during sleep.[1]

Continuous VEM can also show the duration and frequency of ictal activity, making it a useful tool for the treatment follow-up. In some cases, VEM may even reveal different seizure types than those determined by anamnesis and interictal EEG, potentially changing diagnosis.[3]

In this study, we investigate the contribution of VEM in the diagnosis and treatment of patients with epilepsy, along with its ability to change the primary diagnosis before VEM and the treatment approach.

METHODS

Patient Population

We retrospectively investigated the patients who were monitorized in the Cerrahpaşa Faculty of Medicine Faculty, Department of Neurology, VEM unit between 2008-2016. The İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Institutional Ethical

Committee approved the study (no: A-18, date: 07.03.2017), and the need for informed consent was waived by the ethics committee. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. We registered relevant information from patient files: Demographic features, clinical semiology, age of seizure onset, seizure frequency, anti-seizure drugs (ASD), neurological examination findings, a history of febrile seizures or other disorders, history of familial epilepsy, prior EEG, brain magnetic resonance imaging (MRI), and ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) findings.

Seizure types of patients were classified according to the International League Against Epilepsy (ILAE) classification in 2017.[4]

Video-EEG Monitoring Procedure

The VEM recordings were performed using scalp electrodes following the international 10-20 electrode montage system.[5] Scalp electrodes were placed using a collodion, and sphenoidal or anterior temporal electrodes were placed if necessary. The data were digitally recorded using 16-32 channel referential, longitudinal, and transversal bipolar montages. Additionally, a continuous high-resolution video recording was performed during the VEM. Spikes, sharp waves, spike and wave complexes, and temporal intermittent rhythmic delta activity were considered epileptiform activity, and continuous focal slow wave activity was also determined.[6]

To confirm that the seizures or attacks detected during the recording were similar to habitual ones, and to report behavioral changes and seizures during the patient hospitalization, a companion accompanied the patients and pressed the alarm button when necessary.

As activation methods, intermittent photic stimulation and hyperventilation were performed in all patients. ASDs were reduced or discontinued to facilitate the onset of seizures, and were continued at the same doses after the proper seizure recording. VEM was continued until at least three habitual seizures of the patient were recorded or until the planned duration of recording ended. EEG technicians constantly monitored patients for possible status epilepticus, and all necessary equipment for intervention was kept in an easily accessible area.

All EEG recordings were reviewed and interpreted by an experienced neurologist, and the results were compared with the clinical presentation and previous EEG findings. The VEM recording time, number of seizures observed, ictal and interictal EEG findings, and both the preliminary and final diagnoses were noted.

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences software (version 24.0), and the data were presented as mean±standard deviation or percentage. A p value less than 0.05 was considered statistically significant.

RESULTS

Patient Characteristics

A total of 252 patients were included in this study. There were 130 females (51.58%) and 122 males (48.41%). While the mean age of the patients was 32.75±10.1 years (ranging from 13-65 years), mean age of seizure onset was 13.1±9.93 years (ranging from 1 month-59 years). Mean VEM duration was 3.2±1.8 days (ranging from 1-9 days). Five patients (1.98%) had daily, 121 patients (48.01%) had weekly, 61 patients (24.2%) had monthly, and 11 patients (4.36%) had annually seizures, and 54 (21.42%) patients did not have recurrent seizures at the time of the recording.

The reason for VEM was as follows: i) evaluation of drug-resistant epilepsy before epilepsy surgery or vagal nerve stimulation (VNS) in 170 (67.46%), ii) for diagnosis or differential diagnosis in 54 (21.42%), iii) seizure classification in 18 (7.14%), and iv) treatment follow-up in 10 (3.96%).

Various neurological examination findings were detected in 36 patients (14.28%). Additionally, intellegence was normal in 192 (76.19%), there was mental retardation in 55 (21.82%), and there were no data regarding intellegence in 5 (1.98%).

While 225 patients (89.28%) had more than 2 or more ASDs and 23 patiens (9.12%) had one ASD, the remaining 4 patients (1.58%) were drug-free. Six patients (2.38%) had prior epilepsy surgery, and three (1.19%) had VNS. Fifty-nine patients (23.41%) had a psychopathology and 54 received (21.42%) antipsychotic drugs.

Past history revealed that 167 patients (66.26%) had a history of febrile convulsions and 10 patients (4.36%) had a history of CNS operation due to abscess, tumor or cavernoma. A total of 180 patients (71.42%) had a family epilepsy history.

Cranial MRI findings are given in Table 1. ^{18}F-FDG PET was performed in 141 patients (56.34%). Focal hypometabolism was

Table 1. Cranial MRI findings

Cranial MRI findings	Patients, n (%)
Mesial temporal sclerosis	98 (38.88)
- Mesial temporal sclerosis	71 (28.17)
- Probable mesial temporal sclerosis	19 (7.53)
- Dual pathology	8 (3.17)
Gliosis	39 (15.47)
Focal cortical dysplasia	13 (5.15)
Other malformations of cortical development	10 (3.96)
- Polymicrogyria	3 (1.19)
- Heterotopia	3 (1.19)
- Schizencephaly	1 (0.39)
- More than one malformations of cortical development	3 (1.19)
Tumour	6 (2.38)
- Dysembryoplastic neuroepithelial tumor	2 (0.79)
- Ganglioglioma	1 (0.39)
- Other	3 (1.19)
Other pathologies	26 (10.31)
Normal	60 (23.8)
Total	252 (100)

MRI: Magnetic resonance imaging

detected in 123 of 142 patients (86.61%) who underwent interictal PET examination, whereas PET examination was normal in 19 of them (13.38%).

Interictal EEG findings before VEM are given in Table 2 in detail.

Interictal and Ictal Findings of Video-EEG Monitoring

Interictal EEG was normal in 43 patients (17.06%). There was a focal epileptiform activity in 186 (73.8%), slowing of background activity in 15 (5.95%), and generalized epileptiform activity in 8 (3.17%).

A total of 187 patients (74.2%) had a seizure recording during VEM. When patients who had an ictal record were evaluated all together, seizures could be localized in 90 (48.12%), and lateralized in 34 patients (18.18%). The rest of 63 patients (33.68%) were as follows: 57 (30.48%) non localised/lateralized/no ictal activity, 6 patients (3.2%) generalized onset epilepsy/epileptic encephalopathy.

Among epilepsy surgery candidates (n=170), 160 had seizures during VEM. Ictal activity was localized in 78 (48.75%) and lateralized in 29 (18.12%). In the remaining 53 patients (33.12), ictal EEG was normal/non-localized or there was a generalized onset ictal pattern.

Seizure Characteristics on Video-EEG Monitoring

Among 252 patients, 187 patients (74.2%) had seizures. While forty-two patients (22.45%) had one seizure, 145 (77.54%) had two or more seizures. Seizure types are given in Table 3. Additionally, 14 patients (5.55%) had only PNES, 11 (4.36%) had both epileptic seizures and PNES, and one patient (0.39%) had sleep attack (idiopathic hypersomnia). None of the patients experienced serious adverse events such as severe injury or status epilepticus.

What Changed After Video-EEG Monitoring

Before VEM, there were 67 patients with normal EEG findings and 42 patients with only slowing of background activity in interictal EEG. Among these 109 patients, 43 (39.44%) showed interictal epileptiform findings on VEM.

MAIN POINTS

- Video-electroencephalography (EEG) monitoring (VEM) plays a crucial role in the diagnosis and management of epilepsy.
- The contribution of VEM in diagnosis and treatment is higher in presurgical planning compared to other indications.
- Video-EEG might change the diagnosis, especially in patients with psychogenic non-epileptic seizures.

Table 2. Interictal EEG findings before video-EEG monitoring

Interictal EEG findings	Patients, n (%)
Normal	67 (26.58)
Background slowing	42 (16.66)
Epileptiform activity	143 (56.74)
- Focal	124 (49.2)
- Generalized	19 (7.53)
Total	252 (100)

EEG: Electroencephalography

During VEM, out of all patients, 187 patients (74.2%) had seizures (11 of whom had both epileptic seizures and PNES), 14 (5.55%) had only PNES, and one (0.39%) had a sleep attack due to idiopathic hypersomnia. In five patients with seizures, it was impossible to make a judgment about the origin or type of seizures. The remaining 50 patients (19.84%) did not experience any attack. Therefore, overall, VEM provided an additional contribution to 197 patients (78.17%). Interestingly, two patients with a diagnosis of drug-resistant focal epilepsy were diagnosed with generalized onset epilepsy after VEM. Among all patients, the diagnosis was changed in 26 (10.31%) after VEM.

In the epilepsy surgery group, there were 170 patients. Their mean age at seizure onset was 11.8±6.5 years (ranging from one month to 59 years) and the mean VEM duration was 3.53±1.7 days (ranging from one day to one week). Although 160 patients experienced at least one seizure, the seizure-onset zone remained undiagnosed in three of them. Overall, VEM made an additional contribution in handling 157 patients (92.35%) who were monitored for epilepsy surgery. Interestingly, the diagnosis changed from epilepsy to epilepsy plus PNES in one patient (0.58%) in this group. Overall, a desicion for resective surgery was made in 72 patients (28.57%), but 64 had surgery, eight patients refused. Fifty patients who underwent resective surgery achieved seizure-free status (78.12%). Further diagnostic tests (^{18}F-FDG PET, single-photon emission computed tomography, neuropsychological evaluation), and invasive monitoring were planned in 60 patients (23.8%). At the time of the study, nine patients underwent VNS, and in one of them (11.11%), the seizure frequency decreased by about 50%. Moreover, 17 patients underwent resective surgery following invasive monitoring, and five of them (29.41%) became seizure-free.

In the diagnosis/differential diagnosis group, there were 54 patients. Final diagnoses were as follows: PNES in 14 (25.92%), epilepsy in 12 (22.22%), epilepsy plus PNES in 10 (18.51%), and hypersomnia in one (1.85%). Fourteen patients (25.92%) did not experience any paroxysmal event, and 3 (5.55%) remained undiagnosed despite the recorded attacks. Overall, VEM provided a support to diagnose in 37 of 54 patients (68.51%). Additionally, the diagnosis changed

Table 3. Recorded seizure types in video-EEG monitoring

Seizure type	Patients, n (%)
Focal onset, impaired awareness	100 (53.47)
Focal to bilateral tonic clonic	38 (20.32)
Focal onset, preserved awareness	18 (9.62)
Focal onset, unknown awareness status	16 (8.55)
- Tonic	8 (4.27)
- Hypermotor	6 (3.2)
- Gelastic seizures	2 (1.06)
Generalized onset seizures	7 (3.74)
- Atypical absence	3 (1.6)
- Tonic-clonic	2 (1.06)
- Tonic	1 (0.53)
- Myoclonic	1 (0.53)
Focal and generalized onset seizures	5 (2.67)
Remained undiagnosed	3 (1.6)
Total	187 (100)

EEG: Electroencephalography

in 23 of 54 patients (42.59%), with the change being from epilepsy to purely PNES in 12 patients, from epilepsy to epilepsy plus PNES in 10 patients, and from epilepsy to hypersomnia in one patient. The mean diagnostic gap before the diagnosis of PNES was found to be 4.9±2.1 years. The mean duration of VEM in patients with PNES was 0.8±1.3 days, which was shorter compared to the total group. Twelve of the 14 patients (85.71%) with purely PNES had previously been diagnosed with epilepsy and had been prescribed at least one ASD before VEM. The ASDs used by these patients were discontinued and they were referred to psychiatry.

In the seizure classification group (n=18), the following diagnosis was made: focal onset epilepsy in 3 (16.66%), generalized onset epilepsy in 2 (11.11%), and epileptic encephalopathy in 4 (22.22%). The remaining 9 patients (50%) did not experience any paroxysmal event. Overall, VEM did an additional contribution to seizure classification in 50%. One patient (5.55%) underwent VNS, further diagnostic tests were planned in one (5.55%), and the management did not change in 16 (88.88%).

Out of the ten patients who were monitored for treatment follow-up, only two (20%) had seizures with a localized ictal pattern. There was no change in the diagnosis and treatment approach in this group of patients.

Ten patients (3.96%) were lost during follow-up, and management did not change in 67 patients (26.58%). Overall, the management changed after VEM in 175 patients (69.16%). Procedures performed after VEM are given in detail in Table 4.

DISCUSSION

The major findings of our study were: i) VEM provided an additional contribution to the diagnosis in 78% of patients, ii) VEM changed diagnosis in 10% of patients, and, iii) the treatment changed in 69% of patients after VEM. It is worth noting that previous studies have mainly examined the short-term outcomes of patients who were monitored in VEM units, ranging from six months to six years.[3,7-16] Our study provided long-term results of VEM as it included patients who were monitored for a period of 8 years. Additionally, our study mainly included patients who were evaluated for presurgical evaluation, and it evaluated the contribution of VEM for treating drug-resistant epilepsy, which is different from the focus of existing studies in this field.[7,10,12,14,15,17]

Table 4. Procedures performed after video-EEG monitoring

Procedure	Patients, n (%)
Desicion for resective surgery	72 (28.57)
- Surgery performed	64 (25.39)
- Refusing the surgery	8 (3.17)
No change in management	67 (26.58)
Invasive monitoring	35 (13.88)
Referral to psychiatry	30 (11.9)
Additional tests needed/not yet finalised at the time of this study	25 (9.92)
Vagus nerve stimulation	11 (4.36)
Lost to follow-up	10 (3.96)
Corpus callosotomy	2 (0.79)
Total	252 (100)

EEG: Electroencephalography

VEM provides essential information in patients with recurrent paroxysmal events via a simultaneous recording of brain bioelectrical activity and video recording.[1,15] VEM can be used for various purposes, such as diagnosing epilepsy, seizures classification, planning surgery for refractory epilepsy, identifying non-epileptic paroxysmal events, and monitoring treatment for epilepsy.[1,7,10,15] The diagnostic contribution of VEM ranges from 61% to 88%.[3,12,14,18] Consistently, VEM contributed to the diagnosis of 78% of the patients in our study. The duration of VEM in our study was 3.2±1.8 days, which is concordant with previous reports.[15,17] Since approximately 3-4 days of recording can provide solutions to many unanswered questions in a particular patient, any patient with intractable, recurrent paroxysmal events should be given the chance for VEM.

The use of VEM was found to be more effective in the diagnosis and treatment of epilepsy surgery cases, as opposed to its use in cases of diagnosis/differential diagnosis, seizure classification, and treatment follow-up. Although there is a lack of data comparing the effectiveness of VEM in different medical indications, Alving and Beniczky[10] found that VEM is more beneficial in pre-surgery cases than in cases involving diagnosis or seizure classification.

Previous studies have shown that the utility of VEM in changing the diagnosis ranges from 6% to 60%, and in changing treatment ranges from 19% to 73%.[3,7,12,13,17] In our study, the diagnosis was changed in around 10% of patients. The most common change was from epilepsy to pure PNES or epilepsy to epilepsy plus PNES, as reported in literature.[3,7,13]

Additionally, different studies have reported that the ratio of pure PNES diagnosis after VEM ranged from 4% to 30%.[3,8,13,15,18,19] Benbadis et al.[20] found that roughly one-quarter of patients diagnosed refractory epilepsy and sent for VEM had PNES, not epilepsy. Our diagnostic change ratio and pure PNES ratio were lower than in studies that excluded patients who were monitored for epilepsy surgery.[3,15,19] This is because patients who are candidates for epilepsy surgery undergo extensive investigation before VEM, which reduces the likelihood of diagnostic change. Additionally, we have an additional video EEG monitoring unit in our department, which is used for shorter recordings within the limits of a working day and which is mostly preserved for patients with probable PNES. Patients with PNES need a shorter monitorization period, as shown in this study and in some others, so such a daily unit may be sufficient for most of these patients.[3,14,15,19]

ILAE considers that the diagnostic delay of PNES is around three years.[21] However, Volbers et al.[22] showed that this time could be around seven years. In our study population, the mean diagnostic gap was 4.9 years. The diagnostic gap can be shortened after the widespread use of VEM in patients with PNES. Collaboration with psychiatry during VEM may be another benefit of VEM because psychiatrists worldwide, who stay away from patients with PNES, seem to contribute to wrong epilepsy diagnosis in this patient population.[23] This situation could lead to severe consequences, such as misdiagnosis of refractory epilepsy, prescription of unnecessary medications, and even invasive procedures, all of

which can impede the timely initiation of appropriate psychiatric treatment.[21,24] VEM is the gold standard for diagnosing PNES and avoiding such situations.[19,21]

In our study, the treatment plan for 69% of patients changed after VEM, which is consistent with previous research.[7,13] As expected, most of these changes occurred in the group of patients undergoing epilepsy surgery. Resective surgery was performed in 64 patients (25.39%), and 78% of them remained seizure-free. Unfortunately, in some regions, few patients with drug-resistant epilepsy who could benefit from VEM may not have access to it due to a limited number of VEM units.[25] It is important to not only increase the availability of VEM units, but also to raise awareness of drug-resistant epilepsy and ensure that patients with this condition are referred for VEM in a timely manner. This can help improve the diagnosis and treatment options for these patients.

Study Limitations

This study has some limitations that should be taken into consideration. First, since it is a single-center study, the findings may not be representative of other centers' clinical practices. Second, the retrospective design of the study may have led to a selection bias as patients with insufficient medical records were excluded. Third, since most of our patients were monitored for presurgical planning, and all of them underwent extensive investigation before VEM, the rate of diagnostic changes and new diagnoses could be lower than it actually is, which may limit the generalizability of the results.

CONCLUSION

VEM has a significant impact on the diagnosis and management of patients with recurrent paroxysmal events. The contribution of VEM in diagnosis and treatment is higher in presurgical planning compared to other indications. In our study, VEM changed diagnosis for 10% of patients and a change in treatment in 69% of patients. In addition, more than 75% of patients who underwent resective surgery following VEM remain seizure-free. Furthermore, VEM, the gold standard in diagnosing PNES, might change the diagnosis, especially in patients with PNES or PNES plus epilepsy.

Ethics

Ethics Committee Approval: The İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Institutional Ethical Committee approved the study (no: A-18, date: 07.03.2017).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: A.M., C.A., Ş.D., T.T., S.N.Y., Design: A.M., C.A., Ş.D., T.T., S.N.Y., Data Collection or Processing: A.M., C.A., Ş.D., T.T., S.N.Y., Analysis or Interpretation: A.M., C.A., Ş.D., T.T., S.N.Y., Literature Search: A.M., C.A., Writing: A.M., C.A., Ş.D., S.N.Y.

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Epileptic "Paroxysmal Arousal" in the Differential Diagnosis of NREM Parasomnia "Confusional Arousal"

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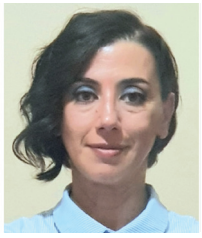

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Presented in: The case (Patient 1) was previously presented as an oral presentation at the 21st National Sleep Medicine Congress, held online from November 5-7, 2021. The authors of the presentation were Yılmaz Öz B, Ser MH, Benbir Şenel G, and Karadeniz D, and the topic was the differential diagnosis between epileptic "paroxysmal arousal" and NREM parasomnia "confusional arousal" in the context of a case.

The case (Patient 2) was previously presented as a poster at the Clinical Neurophysiology EEG-EMG Congress held from 26 to 30 October 2022 in Bodrum-Muğla. The poster, titled "Presentation of Two Patients Diagnosed with Epileptic Paroxysmal Arousal and Its Differential Diagnosis with Confusional Arousal" (Poster Presentation - P026), was authored by Çalışkan B, Karadeniz D, and Benbir Şenel G.

Abstract

Sleep-related hypermotor epilepsy (SHE) should be differentiated from NREM parasomnias in terms of a similar clinical presentation. The lack of ictal and/or interictal epileptic encephalographic (EEG) features in SHE complicates the differential diagnosis. Moreover, epileptic paroxysmal arousal (PA) does not present with associated hyperkinetic motor events typical of SHE, and this should be carefully evaluated from confusional arousal (CA), a type of NREM parasomnia. In this term, this paper aims to present three patients referred to the Sleep and Disorders Unit with the prediagnosis of CA but diagnosed as epileptic PA following video-polysomnography (PSG) with multichannel EEG recordings; and aims to discuss the clinical, EEG, and PSG characteristics of these patients on the basis of literature data.

Keywords: Sleep-related hypermotor epilepsy, epileptic paroxysmal arousal, NREM parasomnias, confusional arousal

INTRODUCTION

Patients with walking and searching behaviors that occur episodically during sleep at night were first described by Pedley and Guilleminault in 1977.[1] Despite the absence of any accompanying epileptic electroencephalographic (EEG) findings, these attacks were found to be of epileptic origin due to a positive response to antiseizure medication (ASM). This condition was later termed "epileptic nocturnal wandering" (ENW). Afterward, similar cases were reported to occur during the non-rapid eye movement (NREM) sleep phase at night, characterized by dystonic-ballistic complex motor movements, resembling somnambulism attacks, and defined as hypnagogic or nocturnal paroxysmal dystonia (NPD).[2] The idea that NPD is epileptic in origin, even in the absence of epileptic EEG abnormalities, has gained widespread acceptance owing to the brief duration and stereotypic nature of the attacks, as well as the response to ASM. In 1986, Peled and Lavie[3] reported on a series of patients who exhibited frequent paroxysmal awakenings during the NREM sleep stage and suggested that these episodes were of epileptic origin. In the follow-up, Montagna et al. published cases similar to Peled and Lavie's patients, which were characterized by stereotypical recurrent nighttime awakenings, some of these cases also showed EEG anomalies, they used the term "paroxysmal awakening" [paroxysmal arousal (PA)].[3,4] Episodic occurrences of ENW, NPD, and PA during nocturnal sleep have been identified as components of nocturnal frontal lobe epilepsy.[4,5] In subsequent years, the designation "Sleep-related hypermotor epilepsy" (SHE) has been increasingly recognized as an appropriate term, given the identification of epileptic foci beyond the frontal lobe through invasive recordings in affected patients.[6-8]

Although the diagnosis of SHE is more likely in the presence of major attacks characterized by excessive, unusual, and high-amplitude motor movements, it can be challenging to differentiate between NREM parasomnias in the presence of minor attacks with calmer

and less pronounced features such as paroxysmal awakening. According to the International Classification of Sleep Disorders, confusional arousal (CA) are defined by confusion, disorientation, meaningless speech, and impaired responsiveness, particularly in the first half of the night and during deep NREM sleep.[9] Although simple and purposeful motor movements are commonly observed in CA, sometimes more complex and violent movements can accompany these NREM parasomnia attacks. Both CA and epileptic paroxysmal awakenings can have a familial tendency, and parasomnias can also be observed in family members of patients with epilepsy. Furthermore, epilepsy and NREM parasomnias can coexist in the same individual, leading to diagnostic challenges.[10,11] This article aims to discuss the differential diagnosis of two types of nocturnal arousal disorders, confusional awakening and paroxysmal awakening, by presenting three cases. The patients were initially diagnosed with confusional awakening but were later found to have epileptic PA.

CASE PRESENTATIONS

Patient 1

A 10-year-old female patient with unknown developmental delays was referred to our sleep laboratory due to complaints of nocturnal snoring, respiratory pauses, sweating, and abnormal movements during sleep. Additionally, she reported experiencing episodes of sudden awakening, standing up, and staring blankly, which occurred exclusively during sleep, and recurred 2-3 times per night, almost every night since she was 7 years old. According to the patient's mother, these episodes included convulsive movements that started in both arms and spread to the entire body. The duration of episodes was short, lasted minutes, occurring at any time during the night, but were more frequent during the first half of the night. Rarely, the patient reported feeling nauseous or experiencing chest heaviness before the episodes. While some episodes were associated with the urge to urinate, the patient did not actually void during the episodes. The patient reported receiving treatment with valproic acid and levetiracetam, but there was no improvement in her symptoms. The patient scored 2 points on the Frontal Lobe Epilepsy and Parasomnias (FLEP) scale, suggesting epilepsy.

In her medical history, the patient was the fourth child out of five siblings. It was revealed that the mother had an uncomplicated pregnancy and delivery and had no history of febrile convulsions or head trauma. Developmental milestones were reached properly. There was a first degree consanguinity between the patient's parents. Febrile convulsions were reported in her uncle's children.

The patient's previous medical history was unremarkable, with a normal EEG both at wakefulness and during the short sleep period during the daytime. Cranial magnetic resonance imaging (MRI) revealed no obvious pathology. Polysomnography (PSG) and EEG recordings conducted in the sleep laboratory did not reveal any sleep-related respiratory or movement disorders. Pre- and morning awakening EEG recordings showed synchronous and symmetrical tonic and phasic elements of sleep in both hemispheres. During the same night, six episodes occurring in NREM sleep stages were observed. All episodes began with eye opening, and one episode was accompanied by standing up in bed. During the episodes, rapid activity on the left, especially localized in the P3 electrode, was noted, but a typical ictal pattern was not observed. The final episode, which occurred in the morning, started with a very stereotypical pattern characterized by eye opening and rising in bed (Figure 1) and progressed to a bilateral tonic-clonic seizure (Video 1). Similar to the other episodes, rhythmic evolution was observed in rapid activities that can be localized especially on the P3 electrode. No interictal epileptic activity was detected during the entire examination. Brain positron emission tomography revealed the hypometabolism in the left prominent bilateral lateral temporal cortex and the left inferior parietal cortex. With these findings, the patient was diagnosed with epileptic PA and started on carbamazepine treatment. The patient was referred to the epilepsy unit for further evaluation.

Patient 2

A 28-year-old female patient with a prior diagnosis of Joubert syndromepresented to our sleep laboratory with complaints of snoring and respiratory arrest during sleep; and feeling tired upon waking up in the morning. The patient had been experiencing episodes of falling asleep after headaches, accompanied by sensations of shapes and spinning bananas since the age of twelve, leading to a diagnosis of epilepsy and subsequent treatment with carbamazepine. The patient had also previously experienced bilateral tonic-clonic seizures before undergoing tooth extraction. After being treated with ASM, the patient reported that the shape fluctuations largely disappeared. The patient's mother reported incidents of the patient waking up at night and looking around, staring blankly, and then returning to sleep, as well as other sleep-related episodes, such as talking, kicking, moving her legs back and forth, and picking up objects with her hand, for approximately one year. These episodes could occur 1-2 times per night at any time of the night and lasted for a brief duration of less than 1 min. Based on the FLEP scale assessment, the patient scored 0 points, which suggests parasomnia as the likely diagnosis.

According to the patient's medical history, she was the second-born of two siblings. The mother's pregnancy was uneventful, and the patient was delivered at term via cesarean section due to cord entanglement. There was no history of febrile convulsions or head trauma. The patient was noted to be hypotonic at birth and achieved sitting, walking, and sentence-level speech at the ages of one, 3.5, and six years, respectively. The parents were second-degree relatives, and there was a history of epilepsy in the patient's cousin's children.

The patient's previous EEG at wakefulness and short sleep periods during daytime yielded normal results. Cranial MRI findings were consistent with Joubert syndrome. PSG examination, conducted in conjunction with a 16-channel EEG at our sleep and disorders laboratory, revealed no sleep-related breathing or movement

MAIN POINTS

- In the differential diagnosis of sleep-related hypermotor epilepsy, it is important to consider non-rapid eye movement (NREM) parasomnias and more rarely REM parasomnias.
- In the differentiation of these disorders, detailed clinical evaluation, video examinations to examine whether the episodes show stereotypic features , and evaluation with polysomnographic examination including 16-channel electroencephalographic are recommended.
- However, it should be remembered that these two conditions can be seen together.

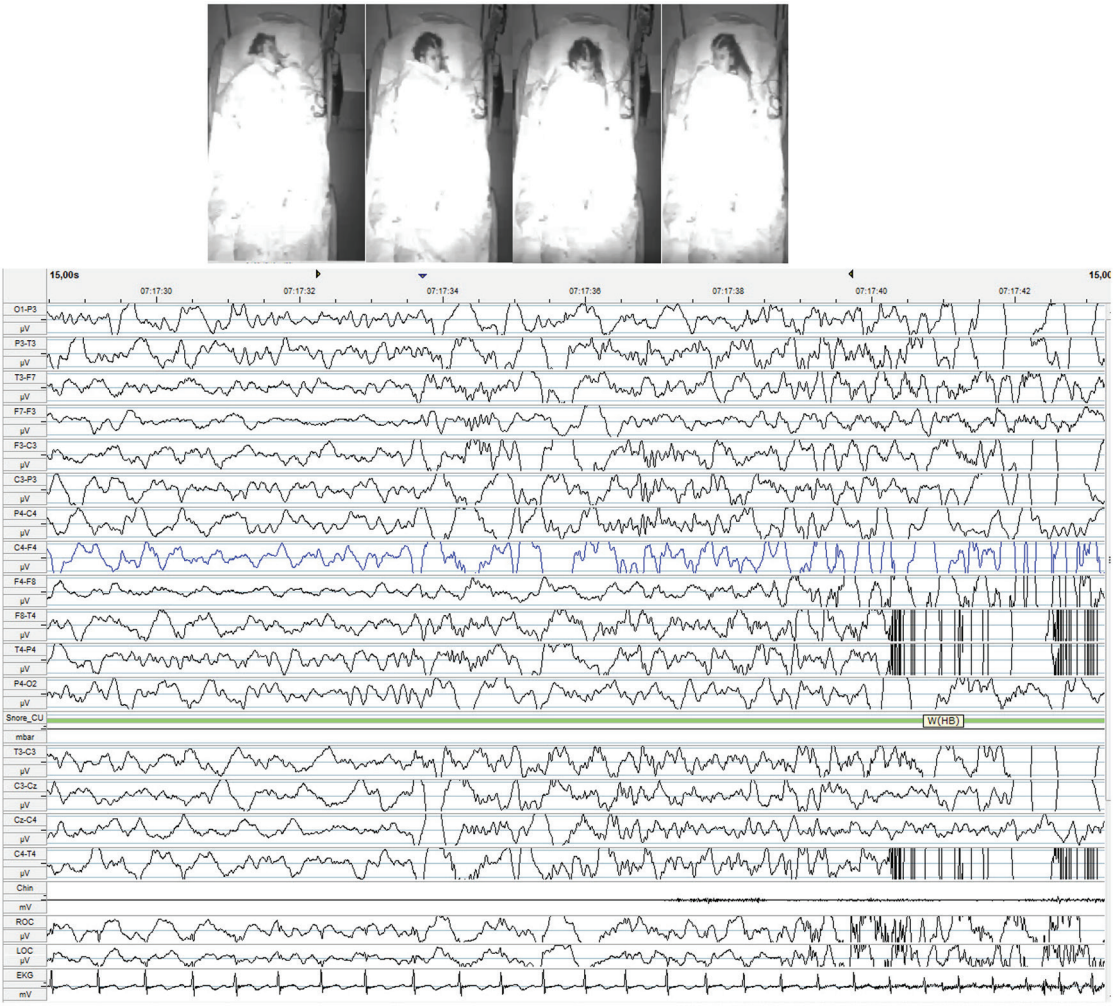

Figure 1. EEG image of Patient 1 at the onset of the epileptic PA episode that evolved into bilateral tonic-clonic seizures
EEG: Electroencephalography, PA: Paroxysmal arousal

disorders. Pre- and morning wakefulness EEG recordings demonstrated a basic bioelectrical activity based on 7-8 Hz alpha rhythm. The tonic and phasic components of sleep were observed simultaneously and symmetrically in both hemispheres, and sleep phases could be easily distinguished. During the study, eight episodes occurring in the N3 sleep stage were observed on the same night. In these fairly stereotypical episodes, following a generalized delta paroxysm on EEG, movements in the patient's right hand and slight deviation of the head to the right were observed. The prominent sharp wave activities in the left frontocentral regions during superficial NREM sleep stages showed an evolution during attacks (Figure 2). The patient was diagnosed with epileptic PA. As the episodes during sleep were electrophysiologically consistent with epileptic seizures, the dosage of the patient's ASM was increased, and the patient was monitored in the epilepsy unit.

Patient 3

A 20-year-old male patient presented with complaints of opening eyes, looking frightened, and making movements as if shaking something while sleeping at night, which had been present since the age of 7 years. The patient experienced episodes of shouting and, in rare cases, getting up and running. The attacks were observed almost every night, particularly in the first half of the night and early morning and recurred 1-4 times per night. The patient reported that the attacks never resolved spontaneously despite receiving various treatments, including different antiseizure and tricyclic antidepressant medications. Although initial treatment provided relief, the attacks eventually resumed. The patient's FLEP scale was calculated as 0 to -1 point (in favor of parasomnia).

There was no significant feature in her past and family history, and no family members with similar complaints were present. The patient's previous waking EEG and cranial MRI were normal.

PSG examination performed using 16-channel EEG in our sleep and disorders unit showed normal baseline bioelectrical activity in the pre- and morning wakefulness EEG recordings. During the N3 sleep stage of the first half of the night, an attack characterized by eye-opening, fear expression, vocalization, and rapid transition to a semi-sitting position in bed was observed. In the second episode, also monitored in the first half of the night and during the N3 sleep stage, a hyperkinetic motor seizure was recorded, characterized as eye-opening, fear expression, and vocalization, followed by rapid, aimless, and high-amplitude limb movements (Video 2). During both attacks, on the background of non-lateralized or non-localized baseline fast activity, an asynchronous activity with high amplitude and sharp elements lasting 2-3 s followed by a suppression pattern

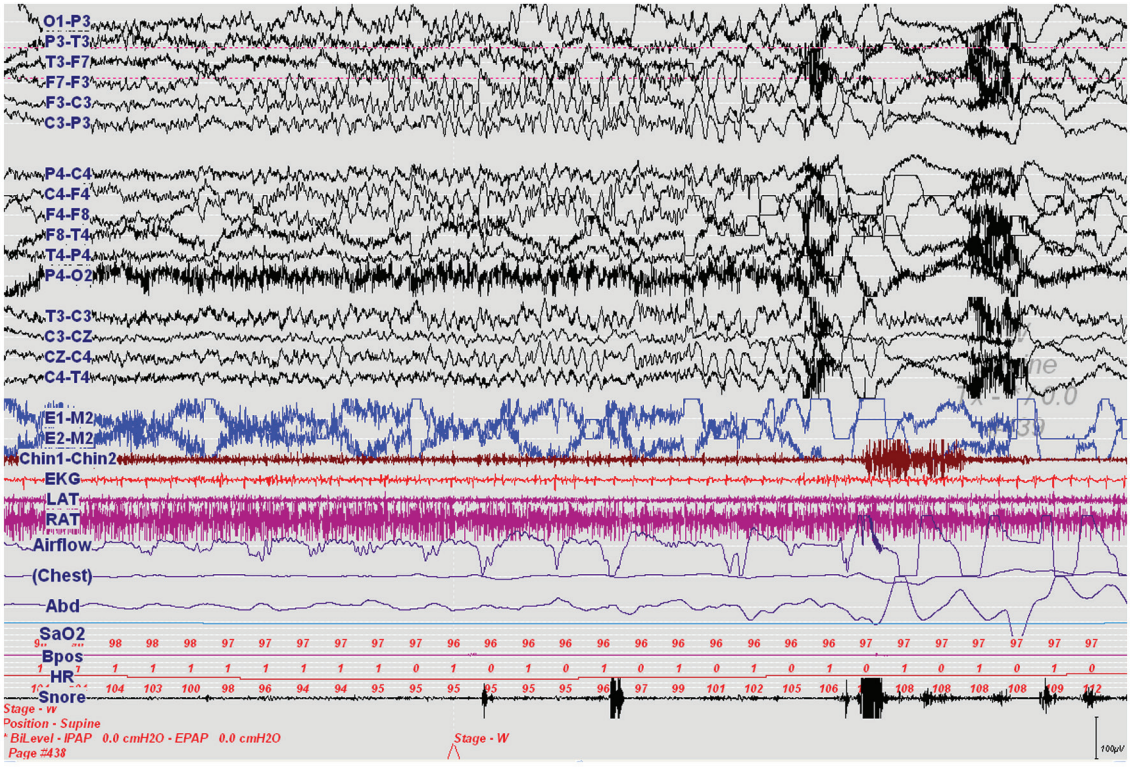

Figure 2. Temporal and spatial propagation of the sharp wave activity that started in the left fronto-central area during the attack in Patient 2

Table 1. Differential diagnosis of SHE, NREM parasomnias and REM sleep behaviour disorder

Features	SHE	NREM parasomnias	REM sleep behavior disorder
Symptom onset (age)	<30 years	<10 years	>50 years
Sleep stage	N1, N2, sleep stage transitions	N3	R
Time of attacks	Any time	First half of the night	Second half of the night
Duration of attacks	5-60 seconds	2-30 minutes	seconds-2 minutes
Frequency of attacks	Clusters in the night	Sporadic, rarely clusters in the night	Sporadic, rarely clusters in the night
Onset-end	Sudden, with arousal reaction	Slow, with N2 sleep stage	Sudden
Semiology	Highly stereotypic, hypermotor, asymmetric, tonic/dystonic	Complex, variable, similar but not stereotypical, eyes are open	Partly stereotypical, eyes are closed, dream recall
Consciousness	Variable	Confusion	Normal after attack
Risk of causing damage	Low	High	Middle
PSG	>50% normal	Rhythmic, hypersynchronous delta activity	REM sleep without atonia

SHE: Sleep-related hypermotor epilepsy, NREM: Non-REM, REM: Rapid eye movement, PSG: Polysomnography

lasting 1 s was observed; there was no ictal epileptic activity except for muscle artifact subsequently. No sleep-related respiratory or movement disorder was detected. After carbamazepine was started, the patient was referred to the epilepsy unit for further investigations.

DISCUSSION

Differential diagnosis is challenging in nocturnal motor events without any epileptiform activity on ictal and interictal EEGs. Although clinical clues can be helpful in some cases (Table 1), this distinction is not always clear in our clinical practice. NREM parasomnias typically manifest at a younger age and commonly follow a benign course, resolving spontaneously before the age of 18 years.[12-14] Compared to epilepsies, the frequency of attacks in NREM parasomnias is lower, with incidence ranging from 1 to 4 per month. In contrast, epilepsy exhibit recurrent attacks and may even relapse during the night. The presence of stereotypic, extrapyramidal system-related findings such as dystonic posture, ballistic movements, and chorea-athetosis as well as violent and agitated motor behaviors indicate epilepsy. In PA, the absence of hyperkinetic motor behavior is a challenging factor in the diagnosis.

Although all three patients were referred to our sleep and disorders unit with suspicion of CA, the occurrence of recurrent stereotypic attacks throughout the night led us to evaluate them further in detail and reach the diagnosis of PA. The diagnosis of PA was also supported by the fact that the attacks starting in a similar manner

evolved into bilateral tonic-clonic seizures. FLEP scale used in the differential diagnosis of NREM parasomnias and SHE in our patients showed that FLEP score of PA attacks that were not accompanied by hyperkinetic motor movements or did not become bilateral tonic-clonic were mostly in accordance with NREM parasomnias, with one supporting epilepsy, but none in accordance with epilepsy.[15] It is therefore important to note that this could result in patients being misdiagnosed with CA as NREM parasomnia. In this term, it is essential for the diagnosis and differential diagnosis that all episodes, rather than a single episode, are considered in clinical evaluation and PSG recording with multiple EEG channels throughout the night.

Ictal EEG findings that accompany epileptic PA are infrequently detected in scalp EEG recordings. However, the presence of ictal EEG findings during PA episodes recorded during stereo-EEG has been demonstrated in patients in whom epilepsy surgery is planned.[16] The stereo-EEG method, which has increased usage in recent years, enables the "*in vivo*" neurophysiological evaluation of epilepsy. This method allows for assessing the physiological and pathological activity in cortical and subcortical areas during wakefulness and sleep, and intracerebral activity during epileptic seizures. In another study, the presence of a functional interaction between different superficial EEG electrodes during nocturnal seizures was recorded and defined as synchronization probability and suggested to be used in the differential diagnosis of CA and PA.[17,18] During NREM parasomnias and CA episodes, the typical EEG pattern is usually characterized by the presence of stage N1-like theta and/or intermittent alpha rhythm following delta activity.[10] In a detailed video-PSG evaluation of patients with definite NREM parasomnia and SHE, major and minor events were analyzed according to sleep stages, and the total number of motor events was found to be significantly higher in SHE patients.[19] In both groups, it was observed that the episodes occurred mostly in the N2 and N3 sleep stages, but it was reported that major episodes occurring out of the N3 sleep stage favored SHE and minor episodes occurring in the N3 sleep stage favored NREM parasomnia.

Video-PSG findings, including 16-channel EEG, of the three patients showed that epileptic EEG features were seen in only one patient. The remaining two patients did not exhibit any ictal or interictal epileptic abnormalities. In the first patient presented (Patient 1), some episodes were preceded by delta-alpha paroxysms supporting NREM parasomnias. In fact, video recordings of the last presented case (Patient 3) showed that (Video 2), the fast theta-alpha frequency rhythms mixed with hypersynchronous delta activity at the onset of the attack are similar to those seen in NREM parasomnias. Although there is a possibility of comorbidity between NREM parasomnia and epilepsy, or less commonly, an epileptic attack triggered by an arousal reaction associated with NREM parasomnia, it was concluded following multidisciplinary evaluations that all three patients exhibited stereotypical and similar attacks of the same nature. Therefore, a diagnosis of epileptic PA was made for all three patients.

Abnormal thalamocortical loops are believed to be the underlying pathophysiological mechanism between NREM parasomnias and frontotemporal seizures.[20,21] A hypothesis suggests that NREM parasomnias are caused by increased cyclic alternating patterns resulting from increased sleep instability and arousal oscillations. This pattern creates a milder stimulus in specific brain regions.[12,22,23] Conversely, epileptic seizures are believed to be triggered by the activation of a more intense stimulus within larger brain regions.[22-24] Although this article focuses on the differential diagnosis between SHE and NREM parasomnias in the context of CA and PA, REM sleep behavior disorder is also included in the differential diagnosis of more agitated and violent attacks (Table 1).[24] In addition to the conditions discussed in this article, the differential diagnosis of epileptic seizures should also include nocturnal panic attacks, nightmare disorders, and paroxysmal hyperkinetic movement disorders.[25,26] Rarely, SHE attacks may occur during the REM sleep stage, and it has been suggested that the transition from REM sleep, which has an antiseizure effect, to the waking phase may trigger the seizure. This is because spontaneous wakefulness reactions are more frequent and the wake threshold is lower during the REM sleep stage.[27]

CONCLUSION

The differential diagnosis of CA, NREM parasomnia, and epileptic PA can still be challenging, as shared by the patients presented in the video examples, despite the use of video-EEG and PSG examinations. In addition to detailed clinical evaluation, demonstration of stereotypic features of attacks with multiple attack recordings in video-PSG recordings including multichannel EEG, careful examination of EEG patterns, and multidisciplinary approaches of neurologists specialized in sleep disorders and epilepsy will ensure the correct diagnosis and an appropriate treatment plan.

Ethics

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: G.B.Ş., S.N.Y., D.K., Design: G.B.Ş., Ö.U., S.N.Y., D.K., Data Collection or Processing: G.B.Ş., R.U., S.N.Y., D.K., Analysis or Interpretation: G.B.Ş., S.N.Y., D.K., Literature Search: G.B.Ş., R.U., Ö.U., S.N.Y., D.K., Writing: G.B.Ş., R.U., Ö.U., S.N.Y., D.K.

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Video 1. Two episodes of Patient 1 in the same night: the first of the five stereotypically recurrent epileptic PA characterized by eye opening and sitting up in bed; and the last episode starting similar to epileptic PA but evolving into bilateral tonic-clonic seizure
PA: Paroxysmal arousal
http://dx.doi.org/10.4274/ArchEpilepsy.2023.2023.231085.video1

Video 2. Epileptic PA in Patient 3 characterized with eye opening, fear expression, vocalization and rapid transition to semi-sitting position on the bed, followed by SHE episode with similar onset but accompanied by hyperkinetic motor movements
PA: Paroxysmal arousal, SHE: Sleep-related hypermotor epilepsy
http://dx.doi.org/10.4274/ArchEpilepsy.2023.2023.231085.video2

Erratum

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The mistake has been made inadvertently by the author.

'Author names' and 'Cite this article as' section on page 16 of the related article has been corrected by the author stated below:

Incorrect Author names:

Elif Ayık[1], Aynur Fevzioğlu[2], Gizem Baki Kaşıkçı[2], Cengizhan Kaşıkçı[2], İpek Midi[1]

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