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EDITORIAL



Dear Colleagues,

In this first issue of 2025, I want to express our gratitude to our journal's publisher, Galenos Publishing House for their effort to increase our journal's recognition.

We also thank to those who took the time to review our journal's manuscripts despite their daily workload. With the increasing number of submissions we will need them even more.

We also want to remind all our readers that Archives of Epilepsy is an open access journal. Thanks to our sponsor.

Best wishes,

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

A New Strategy in Epilepsy Therapy Through Attenuation of Phosphorylated Tau and Amyloid-beta

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Abstract

Epilepsy is a progressive disorder associated with cognitive decline and worsening of other neuropsychiatric comorbidities, as well as the development of drug resistance. Clinical and experimental evidence has shown a link between epilepsy and neurodegenerative pathways such as tau and amyloid-beta (A β) proteins. Increased phosphorylation of tau and A β is toxic to neurons and can lead to the destabilization of microtubules in the nervous system and axonal dysfunction, resulting in dendrite shrinkage, destabilization of synapses, and ultimately neuronal death. Inhibition or attenuation of tau and A β phosphorylation may provide neuroprotective effects and be beneficial in reducing seizures and neurodegeneration. Therefore, anti-amyloid antibodies represent a promising approach, though their use is accompanied by potential benefits and drawbacks. Additionally, anti-tau antibodies hold theoretical potential as an option in epilepsy therapy.

Keywords: Amyloid-beta peptides, epilepsy, neurology, seizure, tau protein

INTRODUCTION

A seizure is a sudden change in nerve function caused by an excessive discharge of neuronal impulses, or an imbalance in excitatory and inhibitory signals that are not well-coordinated in the brain. Epilepsy is a condition in which two or more seizures occur repeatedly without a trigger.¹ The World Health Organization states that epilepsy currently affects approximately 50 million people worldwide, making it one of the most common neurological disorders encountered globally.² Some cases of epilepsy that occur after brain injury [such as status epilepticus (SE), traumatic brain injury (TBI), or infection] are known as acquired or post-traumatic epilepsy. Typically, this form of epilepsy occurs after a lag time between the initial injury and seizures of at least 3 months, and sometimes several years.³ The International League Against Epilepsy (ILAE) classification includes aetiologies of epilepsy such as structural, genetic, infectious, metabolic, immune, and unknown causes. Additionally, The ILAE curriculum introduces another category, which include neurodegenerative.⁴ Neurodegeneration is a pathological sign in the brain associated with acquired epilepsy, and the process of neurodegeneration in epileptogenic areas triggers neuroinflammation, tissue reorganization, or molecular changes that can contribute to transforming an initially normal brain into an epileptic one.⁵ Ali et al.⁶ showed that epilepsy can be a progressive disorder associated with decreased cognitive function, increased neuropsychiatric comorbidities, and the development of drug resistance through pathological mechanisms often described in neurodegenerative conditions. Clinical and experimental studies have shown a correlation between epilepsy and neurodegenerative processes, such as increased levels of tau and amyloid-beta (A β) proteins in certain pathways.^{5,6} Therefore, this review will focus on the role of A β peptide accumulation and tau pathology in epilepsy, as well as explore the potential of anti-amyloid monoclonal antibodies and tau-centric treatments as novel strategies in the management of epilepsy.

Target Intervention in Epilepsy

Seizures are widely understood to result from either excessively enhanced excitatory processes in certain neuronal populations or insufficient neuronal inhibition. Traditionally, this mechanism was attributed to hyperactivity in glutamatergic transmission and a deficiency in γ -aminobutyric acid (GABA) receptor-mediated inhibition. However, emerging evidence highlights the complexity of GABA and glutamate interactions, revealing that both neurotransmitters can play excitatory and inhibitory roles within the central nervous system. In addition to synaptic N-methyl-D-aspartic acid (NMDA) and GABAA receptors, extra-synaptic receptors for these amino acid neurotransmitters have recently been implicated in seizure pathophysiology. Factors such as changes in gene expression, polymorphisms, loss or gain of

function mutations, and cellular energy imbalances can also disrupt the function of ligand- and voltage-dependent sodium, potassium, chloride, and calcium channels, further contributing to seizure activity. Thus, the primary goal of conventional anti-epileptic drugs is to decrease the frequency and severity of seizures by targeting voltage-dependent sodium, potassium, and calcium channels, GABA receptors, enzymes responsible for GABA metabolism, and GABA transporters.⁷

Despite this, acquired epilepsy exhibits diverse etiologies. A causative epileptogenic brain injury—such as stroke, SE, TBI, or infection—can be identified in a subset of patients. Growing evidence indicates that acquired epilepsy may be a progressive disorder, linked to cognitive decline, worsening neuropsychiatric comorbidities, and the development of pharmacoresistance. During epileptogenesis, a broad range of potentially pro-epileptogenic neurodegenerative changes occurs within limbic structures. These include mossy fiber sprouting, neuronal reorganization with synaptic remodeling, neurogenesis, blood-brain barrier disruption, alterations in GABA receptors and GABAergic neurons, changes in peptide, and brain-derived neurotrophic factor expression, neuroinflammation, ion channel modifications, and disruptions in axonal transport. Additionally, A β peptide accumulation, tau pathology, and protein phosphatase 2A (PP2A) dysfunction are observed, along with other cellular and functional changes. While these neuropathological changes are not specific to epilepsy, they closely resemble those found in neurodegenerative disorders such as Alzheimer's disease (AD).⁵ Novel therapies targeting neurodegenerative pathways, such as tau, A β , mammalian target of rapamycin (mTOR), and neuroinflammation, may hold the potential to serve as anti-epileptic and/or disease-modifying treatments for patients with acquired epilepsy.

Implication of Neurodegeneration-tau and A β Proteins in Epilepsy

Investigating the role of A β in the context of epilepsy is of critical importance, given several studies supporting a close association between AD and epileptic seizures, potentially sharing common underlying mechanisms. A β aggregation into oligomers and fibrils is established as the primary driver of neurotoxicity, with A β oligomers—rather than amyloid plaques—being strongly linked to neuronal loss. A β exists in two isoforms: A β 40, which is more abundant, and A β 42, which is more prone to aggregation and plays a greater role in the disease process.⁸ Studies using intracerebroventricular injection of A β 1-42 have demonstrated its ability to mediate neurodegeneration and induce an AD-like phenotype in animal models and non-human primates.⁹ The

mechanisms underlying A β 1-42-induced neurodegeneration include mitochondrial dysfunction, oxidative stress, degeneration of cholinergic neurons, and increased A β 1-42 deposition, ultimately leading to cell death. Additionally, A β regulates NMDA receptors (NMDARs) and disrupts the ionic balance between synaptic and extra-synaptic NMDAR signaling, contributing further to neuronal dysfunction and degeneration.⁸

The cascade of events in the development of seizures and tau pathology begins with endogenous tau having a facilitative role in the onset of seizure activity following disease or traumatic insult. This leads to network hyperexcitability, which, in turn, results in cognitive decline and the activation of cellular mechanisms involving mTOR and tau kinases and phosphatases. These mechanisms drive abnormal tau phosphorylation. Overactivation of these signaling pathways promotes pathological tau hyperphosphorylation and aggregation, increasing susceptibility to epilepsy. Furthermore, these pathological changes can contribute to the cognitive decline commonly associated with epilepsy.¹⁰

Tau and Beta-amyloid Interaction in Neuronal Death

Tau protein occurs naturally in the human brain and has several functions, including the assembly and stabilization of microtubules.¹¹ Tau has a significant influence on neuronal activity, and models with excessive tau expression show hyperexcitability, which can then induce seizures.¹² In neuronal cells, tau is concentrated in axons; however, a physiological role for tau in dendrites has been described.¹³ Tau plays an integral role in the hyperactivity observed in mouse models of SE. Loss of tau may also act as a neuroprotective mechanism, as it may result in impaired localization of postsynaptic fyn kinase, which is involved in cell growth, and reducing damage caused by neuronal overactivity.¹⁴

In addition to tau overload, patients with therapy-resistant chronic epilepsy show imaging characteristics of brain aging, increased A β burden, and accelerated ventricular expansion. Following seizures, surface receptors are activated, which in turn activate the mTOR pathway, causing increased endoplasmic reticulum (ER) and oxidative stress. Chronic activation of cellular stress pathways can result in neuronal death and cognitive impairment. ER stress activates pancreatic eIF2 kinase-like ER kinase (PERK), which then phosphorylates and activates eukaryotic translation initiation factor 2- α (eIF2 α); inhibiting protein synthesis and triggering neuronal cell death. At the same time, phosphorylated eIF2 α inhibits the translation of beta-site amyloid precursor protein (APP) cleaving enzyme 1 (BACE1) mRNA and enhances the amyloidogenic processing of APP. This processing by BACE1 β -secretase results in the release of soluble APP- β (sAPP β) and this processing by BACE1 γ -secretase generates the A β -42 peptide. In the same way, processing of non-amyloidogenic APP through the enzyme α -disintegrin and metalloproteinase 10 produces the peptides soluble APP- α (sAPP α) and peptide-3. In addition to increasing the expression of neprilysin, an enzyme that plays a role in the clearance of A β -42, A β -42 also induces mTOR activity, ER stress, and oxidative stress. Ribosomal protein kinase p70S6K, activated by mTOR, increases tau and BACE1 protein synthesis and phosphorylates tau. Cellular stress also activates pro-apoptotic jun N-terminal kinase (JNK) and inhibits the activity of PP2A, which is the major tau phosphatase, leading to decreased tau phosphorylation. In addition, JNK phosphorylates APP and tau

MAIN POINTS

- A large amount of phosphorylated tau was found in the sclerotic hippocampus, and its presence was statistically significant in relation to seizure frequency.
- Hyperphosphorylation of tau and resulting in microtubule destabilization resulting in axonal and synaptic dysfunction, as well as neurodegeneration.
- Accumulation of amyloid-beta (A β) can lead to cognitive dysfunction; abnormal tissue synchronization and resulting in epilepsy.
- Therapies that target the tau and A β pathways directly can be beneficial in reducing neurodegeneration and cognitive impairment and reducing seizure duration.

proteins, which can lead to neuronal death and further cognitive impairment (Figure 1).¹⁵ The ER stress response also increases their capacity for phagocytosis and the breakdown of tau.¹⁶ Polanco et al.¹⁷ showed that Aβ and tau interact in many neural compartments, including:

- In dendrites, Aβ facilitates the assembly of a postsynaptic excitotoxic signaling complex consisting of NMDARs and postsynaptic density protein 95 through several tau-dependent signaling cascades;
- Tau-mediated excitotoxicity and microtubule damage interact with the potential for long-term Aβ-induced disruption to cause synaptic damage;
- In addition, Aβ and tau interact synergistically to impair mitochondrial function and disrupt neuronal energy homeostasis.

Increased Phosphorylated Tau and Beta-amyloid in Epilepsy

Many recent clinical and experimental studies have shown evidence of an association between neurodegenerative markers such as the accumulation of phosphorylated tau¹⁸ and beta amyloid¹⁹ and mesial temporal lobe epilepsy (TLE),^{20,21} drug-resistant epilepsy,²² TLE,²³ drug-resistant TLE,¹⁵ and generalized SE.²¹ In a study conducted by Toscano et al.,²⁰ a large amount of phosphorylated tau was found in the sclerotic hippocampus, with this finding being statistically significant in its association with seizure frequency. However, in a study conducted by Aroor et al.,²² there was no statistically significant correlation between p-tau and/or Aβ pathology and full-scale intelligence quotient and epilepsy duration despite there being an increase in phosphorylated tau associated with neutrophil threads, neurofibrillary tangles (NFT) and Aβ accumulation. Gourmaud et al.¹⁵ showed that tau and amyloid found in drug-resistant TLE are associated with neurodegeneration, which

is the basis of cognitive impairment in patients with epilepsy. Therefore, therapies that target the tau and Aβ pathways directly can be beneficial in reducing neurodegeneration and cognitive impairment,¹³ and reducing seizure duration.¹⁵

Role of Phosphorylated Tau in Epilepsy

Under normal physiological conditions, the tau protein exists in a balance between binding and unbinding from the microtubules. This balance is regulated by the level of partial phosphorylation of tau, which is controlled by kinases and phosphatases that maintain microtubule stability. However, in pathological states, this balance is disrupted, causing hyperphosphorylation of tau and resulting in microtubule destabilization. An abnormal increase in tau phosphorylation can reduce its binding to microtubules, resulting in the destabilization of the cytoskeleton in the central nervous system. Pathologically, phosphorylated tau detaches from microtubules and forms aggregates called NFTs, which accumulate within neurons, astrocytes, and oligodendroglia, resulting in axonal and synaptic dysfunction, as well as neurodegeneration. A tau phosphatase enzyme, PP2A, supports tau-mediated microtubule stabilization and prevents NFT formation and aggregation of phosphorylated tau. Sodium selenate (Na₂SeO₄) increases PP2A activity. Treatment with sodium selenate for three months significantly reduces the phosphorylation levels of tau at the AT180 site and total tau in the hippocampus and amygdala of the model group compared to the control group. Treatment with sodium selenate significantly reduces the frequency and duration of seizures in animal models of epilepsy.³

Role of Amyloid-beta in Epilepsy

Aβ results from the breakdown of the APP by a group of enzymes, including α-secretase, β-secretase, and γ-secretase. Aβ then assembles into dense fibrillary plaques along with neurofibrils.

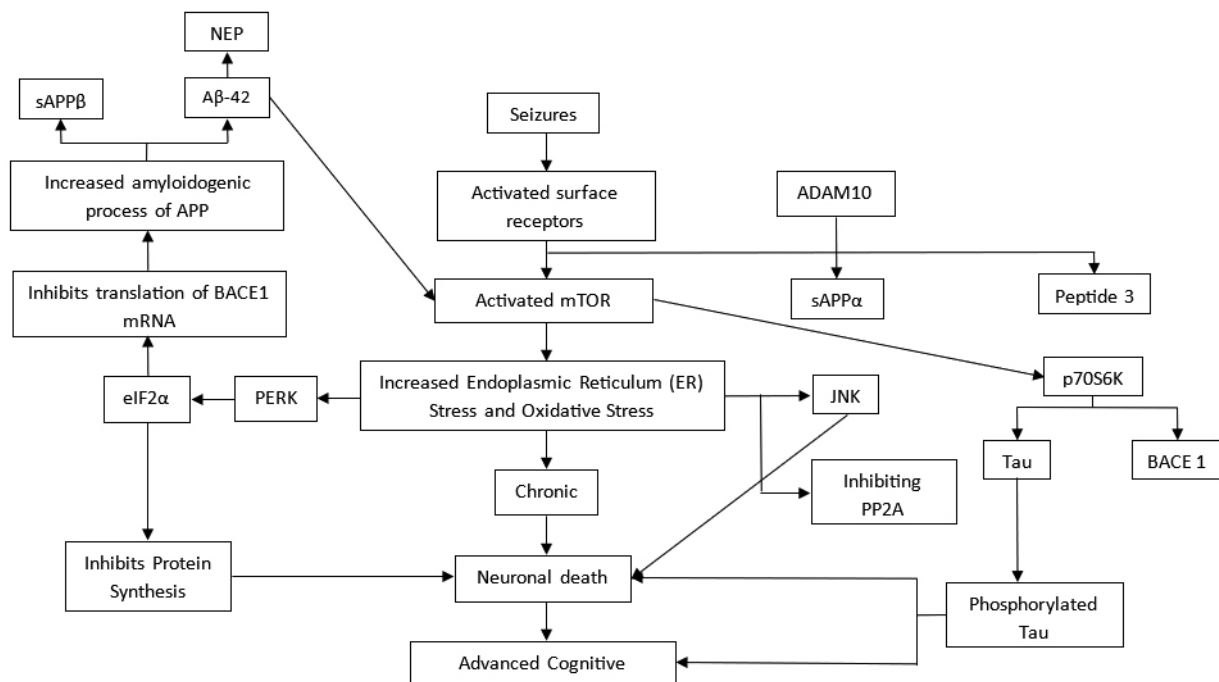


Figure 1. Role of tau and beta-amyloid in neuronal death
 JNK: Jun N-terminal kinase, PERK: Pancreatic eIF2 kinase-like ER kinase, BACE1: Beta-site amyloid precursor protein (APP) cleaving enzyme 1

These neurofibrils consist of phosphorylated tau protein deposits in the cytoplasm. This is a typical histopathological finding of AD. The buildup of neuritic plaques and NFT can have toxic effects on neurons, causing dendrite shrinkage, synapse changes, and ultimately neuronal death.²⁴ Research using post-mortem analysis has shown that A β pathology spreads from the basal-frontal and temporal lobes to the hippocampus, limbic system, and finally to the entire neocortex. A β accumulation increases and amplifies the burden of tau pathology, triggering its spread beyond the temporal lobe and leading to neurodegeneration manifested as A β -facilitated tauopathy. The relationship between A β and epilepsy has also been investigated in clinical studies in patients with refractory epilepsy (RE) who underwent resection of the temporal lobe or part of the hippocampus. The study results showed increased expression of the A β precursor protein (β -APP) in patients with RE compared to the control group. Immunostaining also confirmed the localization of β -APP mainly in the neuronal cytoplasm and axons of patients with RE. These findings indicate that increased expression of β -APP may play an important role in the pathological mechanisms underlying RE.²⁵ In patients with TLE who are drug unresponsive, and undergo temporal lobe resection, several molecular changes resemble those seen in patients with AD, including upregulation of APP expression and increased amyloidogenic processing of APP as indicated by increased expression of phosphorylated APP, A β 42, and A β 56 in the hippocampus and temporal lobe cortex. Accumulation of A β 42 can lead to cognitive dysfunction and abnormal tissue synchronization, resulting in epilepsy.¹⁵

Inhibition of Phosphorylated Tau and Beta-amyloid as a Novel Therapeutic Strategy in Epilepsy

Martin and Leeman-Markowski²⁶ showed that to prevent cells from undergoing apoptosis and restore cellular homeostasis, it is necessary to decrease caspase activity and pathways involving adenosine triphosphate (ATP), and increase tumor necrosis factor- α expression, along with the induction of tau phosphorylation and activation of the ER stress-induced PERK pathway. The decrease in the activity of caspase, which is an apoptotic effector protein, reduces the likelihood of further neurotoxic depolarization and cell death while promoting the restoration of cellular homeostasis. Induction of tau phosphorylation through caspase-6 cleavage indirectly reduces apoptotic signaling while maintaining cellular integrity and activates microglia, which are responsible for the degradation of tau into non-toxic components. Both caspase-3 and caspase-6 cleave tau at various sites, increasing its susceptibility to phosphorylation. However, increased tau phosphorylation reduces caspase-3 activation via a negative feedback loop. Unbalanced ER stress responses may induce atypical tau phosphorylation but have minimal acute effects. Tau oligomers (o-tau) and their aggregates activate microglia to phagocytose tau and convert it into nontoxic components. The ER stress response also upregulates Ca²⁺-ATPases in microglia, thereby increasing the phagocytic capacity and the breakdown of tau. Tau clearance is essential for restoring cellular homeostasis and rebalancing the ER stress response after shock or injury. In addition, there is a neuroprotective response involving A β to restore cells to programmed apoptotic signaling and rebalance signaling dynamics between apoptosis and necrosis. In response to recurrent ER stress and unbalanced signaling dynamics between apoptosis-necrosis and atypical tau phosphorylation, A β activation induces ER stress responses and increases caspase-3 cleavage of A β precursor proteins. Nonetheless, A β also recruits

microglia and reactive astrocytes in response to excitotoxic signals and increased tau concentration. The breakdown by microglia and reactive astrocytes of toxic tau and A β aggregates, reduces the effects of seeding and spreading of tau associated with A β . However, as increased microglial activity is indirectly induced by the presence of A β , this mechanism also has detrimental effects because it is linked to apolipoprotein E, amyloidosis, microglial transcriptional pathways, and ongoing neuroinflammation. Along with inflammation and microglial activation, reactive astrocytes are upregulated and recruited to clear toxic tau and A β , and subsequently drive cells towards apoptotic signaling. Ultimately, the reduction of inflammatory signals, as well as the phosphorylation of tau and beta-amyloid, are required once the signaling dynamics between apoptosis and necrosis are balanced to prevent the transition to irreversible degenerative pathways.²⁶ Owing to its negative impact leading to apoptosis, A β involvement is referred to as the final step in neuroprotection.

Emerging research indicates that AD and epilepsy share common neuropathological characteristics. Both conditions exhibit significantly reduced levels of A β 42 in comparison to healthy age-matched controls. This reduction in cerebrospinal fluid A β 42 is believed to result from the aggregation of A β 42 into amyloid plaques within the brain. Aducanumab and lecanemab are anti-amyloid antibodies that have received United States Food and Drug Administration (FDA) approval for the treatment of AD.²⁷ Anti-amyloid monoclonal antibodies, which significantly reduce A β plaques, are linked to an adverse event known as amyloid-related imaging abnormalities (ARIA). This can manifest with oedema (ARIA-E), microhaemorrhages, or superficial siderosis (ARIA-H). Meta-analyses of clinical trials involving 9,429 patients treated with anti-A β immunotherapy reported overall incidences of ARIA-E and ARIA-H at 6.5% and 7.8%, respectively, with 80.4% of ARIA cases being asymptomatic.²⁸ ARIA is thought to result from a temporary increase in vascular permeability caused by enhanced trafficking of parenchymal A β to the perivascular space and/or blood vessel leakage following vascular A β clearance. However, with continued antibody-mediated amyloid clearance, the structural integrity of the vessels may recover, and the incidence of ARIA typically declines after 6 to 9 months of treatment.²⁹

Alongside amyloid pathology, tau deposition also plays a role in the link between neurodegenerative disorders and epilepsy.²⁶ Tau-centric treatments can be an option for treating epilepsy. Suvorexant, an FDA-approved medication for insomnia, has been shown to reduce tau phosphorylation at specific sites and lower A β concentrations compared to a placebo. A 20 mg dose of suvorexant decreases tau phosphorylation and A β levels over time, demonstrating its efficacy. Suvorexant 20 mg, Approved by the FDA for treating insomnia, including in patients with mild-to-moderate AD, has a strong safety record. However, the 10 mg dose does not exhibit the same effects on A β or phosphorylated tau as the 20 mg dose.³⁰ Moreover, clinical studies suggest that, in hypertensive epilepsy patients, inhibiting the renin-angiotensin-aldosterone system may decrease epilepsy incidence over time. While these findings do not establish a causal relationship, they highlight the potential role of anti-hypertensive drugs, particularly angiotensin 2 receptor blockers, in preventing hypertension-related secondary complications like epilepsy. This approach could represent a novel therapeutic avenue for epilepsy through renin-angiotensin-aldosterone system inhibition.³¹ The development

of numerous innovative antiseizure medications with diverse mechanisms of action has significantly broadened the range of available therapeutic options. Anti-amyloid antibodies represent a promising approach; however, their use is accompanied by potential benefits and side effects, resulting in both advantages and disadvantages. Additionally, anti-tau antibodies hold theoretical potential as an option in epilepsy therapy.

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Evaluation of the Antioxidative and Protective Effects of Thymoquinone in a Pentylentetrazole-induced Epilepsy Model

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Abstract

Objective: Epilepsy is a common neurological disorder that leads to neuronal excitability and provokes various forms of cellular reorganization in the brain. We investigated the antioxidative and protective effects of thymoquinone (TQ) from the perspective of biomarkers in serum samples of rats using a pentylentetrazol (PTZ)-induced epilepsy model.

Methods: Twenty-one adult, male Wistar albino rats were randomly assigned to three groups. (1) Control (n=6); 0.5 mL saline (i.p.). (2) PTZ (n=7); 35 mg/kg PTZ (i.p.). (3) TQ+PTZ (n=8); 20 mg/kg TQ orally (p.o.)+ 35 mg/kg PTZ (i.p.). To induce kindling, PTZ was injected at a subconvulsive dose (35 mg/kg, i.p.) every other day for 24 days. Then, on the 26th day of the study, a single loading dose of PTZ (75 mg/kg) was injected into the animals. Seizure severity was evaluated with the Racine scale. Blood samples were taken from rats under anesthesia by the cardiac puncture method. The serum levels of myeloperoxidase (MPO), ischemia-modified albumin, total oxidant status (TOS), total antioxidant status (TAS), advanced oxidation protein products (AOPP), total sulfhydryl (T. sulfhydryl), and paraoxonase-1 (PON-1) were evaluated colorimetrically by the ELISA method, using a spectrophotometer.

Results: A significant relationship was found between PTZ and TQ+PTZ groups for TAS (p=0.020), TOS (p=0.006), AOPP (p=0.015), and T. sulfhydryl (p=0.009). MPO and PON-1 were not significant (p>0.05).

Conclusion: TQ may be used as an adjuvant agent in the regulation of epileptic seizures with its antioxidative and protective functions in the PTZ-induced epilepsy model. At the same time, serum parameters can potentially be diagnostic tools for the effective managing of treatment.

Keywords: Pentylentetrazole (PTZ)-kindling model, thymoquinone, antioxidative effect, protective effect

INTRODUCTION

Epilepsy is a multifactorial disease that causes recurrent epileptic seizures, which are characterized by abnormal neuronal activities.¹ It can result from a range of acquired and genetic causes, including traumatic brain injury, stroke, tumors, central nervous system infection, and various medical conditions. In some cases, it may also be linked to specific gene mutations.² Seizures are caused by inhibiting γ -aminobutyric acid (GABA) receptors and the excitation of glutamate receptors.¹ Many researchers are working on epilepsy, which includes a kindling model. Kindling is commonly used in modeling epilepsy and its seizures. Experimental animal kindling models are advantageous for investigating seizures, which are the dominant phenotype of the disease.³ The most common agent used for this purpose is pentylentetrazol (PTZ). PTZ functions by interacting with the receptor⁴ of the GABA type A (GABAA) chloride ionophore complex. Repeated doses of PTZ (20-35 mg/kg) trigger seizures by causing increased excitatory activity or decreased inhibitory effects.⁵ PTZ causes changes in GABAergic and glutamatergic systems, leading to receptor blockade by binding to GABAA receptors. Thus, neurons become depolarized.⁶ Additionally, PTZ increases the density and sensitivity of receptors for glutamate, an excitatory neurotransmitter.⁶

Natural agents, which are among the options in the treatment of epilepsy, although their efficacy has not yet been fully established, are preferred because they have low side effects and are mostly non-toxic compared to other chemical agents. However, while searching for the action mechanisms of these agents in deep metabolic pathways, their positive or negative effects on known, easily sampled parameters that can be used by almost every service provider are ignored. The use of natural compounds to treat various neurological diseases has recently been an important area of research. Thymoquinone (TQ), the active component of *Nigella sativa* (NS), is a substance with antioxidant, antihyperlipidemic, antidiabetic, anti-inflammatory, gastroprotective, hepatoprotective, antihypercholesterolemic, anticarcinogenic, anxiolytic, antidepressant, antipsychotic, and analgesic properties.⁷ TQ has been shown to have anticonvulsant activity in rats by causing an increase in GABAergic tone via an opioid receptor.⁸ In a study, TQ pretreatment (10 mg/kg) reduced oxidative stress (OS) indices such as malondialdehyde and nitrate in hippocampal tissue. Additionally, it decreased severe seizure activity in a rat model of temporal lobe epilepsy (TLE) induced by intrahippocampal injection. Additionally, it has been shown that TQ can reduce hippocampal neuron loss, astrogliosis, and lipid peroxidation in the cornu ammonis-1 (CA-1), CA-3, and hilar regions.⁹ The treatment of mice with TQ (5, 10, and 20 mg/kg i.p.) and a subconvulsive PTZ dose on alternate days provided dose-dependent protection against PTZ-induced exacerbation, as well as learning and memory impairments. Additionally, treatment of mice with TQ (20 mg/kg) inhibited PTZ-induced biochemical changes in the brain and increased the brain glutamate level. These results suggest that glutamate and subsequent OS and excess NO production via inducible NO synthase play an important role in the pathophysiology of PTZ-induced kindling and cognitive impairments in mice. TQ may provide dose-dependent protection against PTZ-induced inflammation and cognitive impairment. The inhibition of PTZ-induced brain OS and NO overproduction, alongside an increase in the expression and activity of inducible NO synthase, may play a significant role in the protective effect of TQ against brain injury.¹⁰

During seizure activity, the antioxidant defense mechanism in the brain decreases, and the amount of free radicals increases. This situation triggers OS.¹¹ Reactive oxygen species (ROS) are produced during cellular metabolism. Excessive production of ROS causes OS.¹¹ Total oxidative status (TOS) and total antioxidant status (TAS) are OS parameters.¹² Advanced oxidation protein products (AOPPs) are novel markers of OS. AOPP occurs during OS and performs various biological activities, such as the induction of proinflammatory cytokines and adhesive molecules.¹³ The sulfhydryl group (SH) is a thiol group that reliably reflects OS. Thiol groups are oxidized by ROS.¹⁴ Paraoxonase (PON) is a 43-45 kDa glycoprotein mainly synthesized by the liver. PON-1 is a Ca²⁺-dependent enzyme transported by circulating high-density

lipoproteins (HDLs).¹⁵ The antioxidant action of PON-1 and PON-3 protects HDL and low-density lipoproteins from oxidation.¹⁵ The activation of antioxidant activity depends on the hydrolysis of phospholipids or lipid peroxide products.¹⁵ Ischemia in cerebral tissue has been identified as a potential factor influencing the development of epilepsy.¹⁶ Albumin is converted to ischemia-modified albumin (IMA) during ischemic events. IMA has a low binding capacity for metals such as copper, nickel, and cobalt.¹⁷ Increasing evidence points to the role of inflammation during epileptic activity.¹⁸ Gene array studies have demonstrated that immune response-related genes are upregulated during epileptic activity.¹⁹ Leukocytes play a pivotal role during epileptic activity, and depletion of neutrophils in animal models prevents both seizure induction and epilepsy development.²⁰ Myeloperoxidase (MPO) is found in the azurophilic granules of neutrophils and macrophages. It is released when neutrophils and macrophages are activated. MPO leads to the destabilization of atherosclerotic plaques by activating metalloproteinases.²¹

To evaluate the antioxidant and protective effects of TQ, we measured MPO, IMA, TOS, TAS, AOPP, total sulfhydryl (T. sulfhydryl), and PON-1 serum levels in the epilepsy model induced by PTZ. In this study, we searched for descriptive evidence of the therapeutic nature of TQ in the serum parameters of TQ-treated epilepsy animals.

Additionally, we demonstrated for the first time the antioxidative and protective properties of different doses of TQ in the PTZ-induced epilepsy model. Therefore, TQ may be usable as an adjuvant agent in epilepsy treatment.

METHODS

Animal Treatment

Twenty-one male Wistar albino rats were used. Animal numbers were determined by power analysis (G*Power). Rats were housed with ad libitum access to food and water on a 12-h light/12-h dark cycle at a temperature of 25±2 °C. Rats were randomly divided into 3 groups: (1) The control group (n=6) was administered 0.5 ml of saline (i.p.); (2) The PTZ group (n=7) was administered 35 mg/kg PTZ injection (i.p.). (3) The TQ+PTZ group (n=8) was administered 20 mg/kg TQ orally (p.o.) 2 hours before each PTZ (35 mg/kg) injection. The PTZ (35 mg/kg) injection was administered to the PTZ and TQ+PTZ groups on days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, and 24 of the study. Consequently, the kindling model was generated. Following the generation of the kindling model, a convulsive final dose of PTZ (75 mg/kg) was administered (i.p.) to induce seizures.²² In addition, TQ was not administered before the administration of the final dose of PTZ (75 mg/kg).

In addition to 6 animals per group calculated by power analysis, +2 animals were considered in the PTZ and TQ+PTZ groups for experimental losses. One animal was lost in the PTZ group at the beginning of the experiment. Following all injections, rats were observed in standard cages of 35x35x35 cm for 30 minutes to assess seizure scores. The seizure behaviors of the rats were scored according to the Racine criteria. These criteria included no change in behavior "0", myoclonic jerks characterized by sudden and repetitive head and neck movements, "1", unilateral or incomplete clonic seizure, "2", clonic seizure with forelimb clonus and

MAIN POINTS

- Evaluation of the anti-oxidative effect of thymoquinone (TQ).
- Demonstration of the neuroprotective effect of TQ.
- Evaluation of the usability of TQ as an adjuvant agent in the treatment of epilepsy.
- Demonstration of its preventive effect on cognitive impairment caused by seizures.

rearing, “3”, tonic-clonic seizure, “4”, tonic-clonic seizure with full extension of all four limbs, and “5”, falling.²³ Additionally, seizure severity and seizure number were used to evaluate epileptic activity. Seizure severity was considered entering stage 4 or 5, while the number of seizures was considered as three consecutive occurrences at stage 4 or 5.

The latency of a seizure is the time that elapses between the administration of the PTZ dose and the onset of the first clonic jerk or sudden twitch.

Biochemical Analysis

We evaluated the minimum doses in this reference in 4 animals before starting the study. After these doses, to determine whether the animals entered anesthesia, the rats were rolled onto their sides once every minute, starting 1 minute after the injection, to check for loss of righting reflex. Then, toe pinch was applied to each rat to determine whether the withdrawal reflex was present. In the toe pinch response test, a pinch was applied to the metatarsal or metacarpal regions with forceps without causing any damage. In addition, reflexes were measured by pinching one hind leg and one forelimb once every minute. Turning and withdrawal reflexes were not observed in the animals after approximately 5 minutes.²⁴ Therefore, it was decided that ketamine/xylazine anesthesia was appropriate doses (60/6 mg/kg) (i.p).

Blood samples were taken from rats under anaesthesia by cardiac puncture. We used a needle to draw blood externally, without opening the chest. The needle was inserted into the base of the sternum, inclined upward into the chest cavity at an angle of 15-20 degrees to the left of the midline, and then slowly aspirated. Once the blood started to flow into the syringe, aspiration was continued with constant and equal pressure. Blood samples were taken in EDTA tubes and were centrifuged at 3,000 rpm for 10 min and then serum samples were separated. The serum samples were stored at -20 °C until biochemical analysis was performed.

MPO activity has been measured by spectrophotometry. Then, 290 μ L (50 mM, pH: 6) of phosphate buffer, 3 μ L (20 mg/mL) of O-dianisidine hydrochloride substrate solution, and 3 μ L of hydrogen peroxide (H_2O_2 , 20 mM) were added to the 96-well plate. 10 μ L of samples were added to each well of the microplate and absorbance was measured at 450 nm. MPO activity was evaluated as the degradation of 1 μ mol H_2O_2 per liter per second (U/L) at 25 °C.²⁵

The cobalt albumin binding test was used to measure the serum IMA level. A total of 95 μ L of serum was mixed with 5 μ L of cobalt chloride and then incubated. The IMA concentration was measured spectrophotometrically at 500 nm. IMA levels are shown on the calibration curve with absorbance values in the range of 5-180 U/mL.²⁶

Measurements of TAS and TOS were carried out using the spectrophotometric method developed by Erel.^{27,28} TAS levels are expressed as millimolar Trolox equivalents per gram (mmol Trolox equivalents). TOS levels are expressed in micromolar hydrogen peroxide equivalents (μ mol H_2O_2 equivalents) per liter.

AOPP levels were measured using a spectrophotometric method.²⁹ The values are expressed as μ mol/g protein.

T. sulfhydryl levels were measured via a spectrophotometric method using 5,50-dithiobis-2-nitrobenzoic acid (DTNB). In this method, a thiol-disulfide exchange reaction between DTNB and thiol groups was utilized.³⁰

PON activity was measured spectrophotometrically at a wavelength of 412 nm by the method developed by Eckerson et al.³¹

This study was approved by the Bezmialem Vakıf University Experimental Animals Local Ethics Committee (no: 2021/236, date: 21.09.2021).

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) 24.0 software package was used for statistical analyses. Normality analyses were performed with Kolmogorov-Smirnov, and Shapiro-Wilk tests. ANOVA was used to compare groups and within groups, and the Mann-Whitney U test was used to analyze the differences between them. We identified significant differences using a one-way ANOVA with Bonferroni correction for multiple comparisons at a significance level of $\alpha=0.05$. $P<0.05$ was considered to indicate statistical significance. Results are presented as mean differences \pm standard error. The data were analyzed using the statistical package SPSS (release 22.0, SPSS Inc, Chicago, IL, USA) for Windows.

RESULTS

Evaluation of the Effect of TQ on Latency and Seizure Duration

In our study, the effects of TQ on the latency period and seizure duration were evaluated. The latent period was longer in the TQ+PTZ group than in the PTZ group (70.6 \pm 6.4 and 54.5 \pm 2.6), and the seizure duration was shorter in the TQ+PTZ group than in the PTZ group (10.1 \pm 0.7 and 11.5 \pm 0.9) ($p<0.05$) (Table 1).

The values are presented as the mean \pm SE of the mean. A comparison was conducted between the PTZ group and the TQ+PTZ group concerning seizure duration and latency ($p<0.05$).

Biochemical Analysis

One-way ANOVA was used to analyze mean differences in the analysis of data within groups. Multiple comparative tests and Bonferroni correction were used in the analysis of differences between groups. One-way ANOVA results; among the TQ+PTZ group, the MPO activity (563 \pm 591.256 and 1160.493 \pm 510.359 U/mL, $p=0.0002$), total TOS (18.811 \pm 3.763 and 32.354 \pm 13.510 μ mol/L, $p=0.0001$), and AOPP (14.714 \pm 7.305 and 43.000 \pm 30.640 μ mol/L, $p=0.0022$) levels were significantly lower than those in the PTZ. In addition, when the TQ+PTZ group was compared with the PTZ group, the TAS (1.398 \pm 0.523 and 1.893 \pm 0.0.192 mmol/L;

Table 1. The effects of TQ on seizures

Groups	Latency (sec)	Duration (sec)	p value
PTZ	54.5 \pm 2.6	11.5 \pm 0.9	0.0003
TQ+PTZ	70.6 \pm 6.4	10.1 \pm 0.7	

TQ: Thymoquinone, PTZ: Pentylentetrazol

p=0.0004), T. sulfhydryl (1159.245±868.631 and 344.264±90.840 nmol/mg protein; p=0.0013), and PON-1 (1470.601±287.250 and 792.171±211.731 U/L; p=0.0001) levels were significantly greater. The IMA level decreased in the TQ+PTZ group compared to that in the PTZ group, with levels of 23.482±15.654 ng/mL and 28.314±14.928 ng/mL, respectively (p=0.0591). However, this decrease was not statistically significant. Data from multiple comparative analyses expressing the significance between groups are given in Table 2.

DISCUSSION

In our study, we used biochemical analyses to demonstrate that TQ has antioxidative and seizure-protective effects on a PTZ-induced epilepsy model. The results obtained showed that the parameters measured here changed during epileptic seizures. Therefore, the change in parameters other than MPO and PON-1 after TQ treatment, suggests that it may be effective before the seizure.

Table 2. Multiple comparisons analysis of serum parameters and groups

Dependent variable	Groups	Groups	Mean difference	SE	95% CI	p value
Myeloperoxidase (U/mL)	Control	PTZ	-507.822	193.352	-1005.441-(-10.203)	0.044*
		TQ+PTZ	-913.752	185.563	-1391.324-(-436.179)	0.0001*
	PTZ	Control	507.822	193.352	10.203-1005.441	0.044*
		TQ+PTZ	-405.930	210.409	-947.446-135.587	0.197
	TQ+PTZ	Control	913.752	185.563	436.179-1391.324	0.0001*
		PTZ	405.930	210.409	-135.587-947.446	0.197
TOS (ng/mL)	Control	PTZ	-2.440	3.606	-11.721-6.842	1.000
		TQ+PTZ	-15.982	3.461	-24.890-7.074	0.0001*
	PTZ	Control	2.440	3.606	-6.842-11.721	1.000
		TQ+PTZ	-13.542	3.924	-23.643-(-3.442)	0.006*
	TQ+PTZ	Control	15.982	3.461	7.074-24.890	0.0002*
		PTZ	13.542	3.924	3.442-23.643	0.006*
TAS (mmol/L)	Control	PTZ	0.188	0.153	-0.205-0.581	0.694
		TQ+PTZ	0.683	0.147	0.306-1.060	0.0002*
	PTZ	Control	-0.188	0.153	-0.581-0.205	0.694
		TQ+PTZ	0.495	0.166	0.067-0.923	0.020*
	TQ+PTZ	Control	-0.683	0.147	-1.060-(-0.306)	0.0002*
		PTZ	-0.495	0.166	-0.923-(-0.067)	0.020*
AOPP (mmol/L)	Control	PTZ	-1.989	0.153	-23.698-19.719	1.000
		TQ+PTZ	-30.275	0.147	-51.109-(-9.441)	0.003*
	PTZ	Control	1.990	0.153	-19.719-23.698	1.000
		TQ+PTZ	-28.286	0.167	-51.909-(-4.662)	0.015*
	TQ+PTZ	Control	30.275	0.147	9.441-51.109	0.003*
		PTZ	28.286	0.166	4.662-51.909	0.015*
Total sulphhydryl (nmol/mg protein)	Control	PTZ	-48.282	225.884	-629.628-533.064	1.000
		TQ+PTZ	-863.262	216.785	-1421.189-(-305.336)	0.002*
	PTZ	Control	48.282	225.884	-533.064-629.628	1.000
		TQ+PTZ	-814.981	245.811	-1447.610-(-182.352)	0.009*
	TQ+PTZ	Control	863.262	216.785	305.336-1421.189	0.002*
		PTZ	814.981	245.810	182.352-1447.610	0.009*
PON-1 (U/L)	Control	PTZ	-456.159	112.561	-745.851-166.467	0.001*
		TQ+PTZ	-678.430	108.027	-956.452-(-400.409)	0.0001*
	PTZ	Control	456.159	112.561	166.467-745.851	0.001*
		TQ+PTZ	-222.271	122.491	-537.518-92.976	0.246
	TQ+PTZ	Control	678.430	108.027	400.409-956.976	0.0001*
		PTZ	222.271	122.491	-92.976-537.518	0.246

*P<0.05 is significant. Multiple comparison analyses were performed with the Bonferroni post-hoc test. SE: Standard error, CI: Confidence interval, PTZ: Pentylene tetrazol, TQ: Thymoquinone

In a study evaluating the toxicological effects of TQ, intraperitoneal doses of TQ higher than 50 mg/kg body weight were lethal to mice, the LD50 being 90.3 mg/kg i.p.³² This study also showed that i.p. injection of 4, 8, 12.5, 25, and 50 mg/kg TQ into mice did not cause any changes in biochemical indices such as serum alanine transaminase and lactate dehydrogenase.³² Several toxicological studies indicated that oral administration of TQ in the range of 10-100 mg/kg has no toxic or lethal effects in mice.³³⁻³⁷ In another study, the maximum tolerated dose of TQ when injected ip was 22.5 mg/kg in male rats and 15 mg/kg in female rats, while the dose was 250 mg/kg, after oral administration in both male and female rats.³⁸ In our study, oral administration of TQ (20 mg/kg) dose is compatible with the literature.

TQ has been shown in several studies to reduce OS and increase antioxidant defense. TLE is a type of epilepsy characterized by neuronal loss, reactive astrogliosis, and increased OS. In a rat model of TLE, TQ treatment was shown to have a protective effect on hippocampal areas. It has been stated that TQ reduces OS and seizure activity.⁹ TQ can reduce the OS caused by PTZ. In our study, TQ decreased the TOS level and increased the TAS level. The antioxidant effects of NS and TQ have been suggested.^{39,40} Hosseinzadeh et al.⁴¹ found that NS oil and TQ have antioxidant effects during cerebral ischemia-reperfusion injury in the rat hippocampus. The antioxidant effects of NS in other animal models of nervous system disorders have also been reported, which sometimes have been confirmed by human studies.^{17,42-44} These findings are compatible with ours. TQ decreased the AOPP levels in our study. Aksu et al.⁴⁵ showed that AOPP levels increased in children with generalized-type epilepsy. Additionally, it has been stated that the number of seizures increases with an increase in AOPP. According to these results, TQ can reduce the formation of oxidized protein products. Additionally, in our study, TQ also increased the T. sulfhydryl level. In the PTZ epilepsy model, it was stated that NS extracts administered at 200 mg/kg and 400 mg/kg increased the total thiol amount.⁴⁶ Therefore, TQ can increase antioxidant capacity by increasing sulfhydryl levels. we demonstrated that TQ increased the level of PON-1. A study has shown that brain PON-1 activity decreases after PTZ injections. PON-1 has a significant role in neurodegenerative disorders because it has antioxidative and anti-inflammatory properties.⁴⁷ OS inactivates PON-1,⁴⁸ and the decreased activity of this enzyme increases ROS. This decrease in PON-1 activity will further increase the cell's sensitivity to OS, causing neurodegeneration. This study showed that treatment with Brilliant Blue decreased PON-1 activity. This decrease in activity may be related to either lower levels of OS or a neuroprotective effect.⁴⁹ Another study showed that the activity of PON-1 decreases in epilepsy patients, as referenced in citation.⁵⁰ Our research results show that TQ may cause an increase in PON-1 activity. Additionally, TQ reduced the serum IMA concentration in our study. However, this decrease was not statistically significant. It was observed that serum IMA levels were significantly greater in epileptic patients than in healthy controls.¹⁷ These findings are compatible with ours. In our study, we demonstrated that TQ decreased the MPO level. In a study investigating the relationship between MPO and seizures in a pilocarpine-induced epilepsy model, MPO activity increased both in the hippocampal regions and in the plasma. Also, this study has shown that an increase in the MPO is associated with epileptogenesis.⁵¹ It was stated that the MPO level increased in a

PTZ-induced kindling model in mice.⁵² Şimşek et al.⁵³ showed that serum MPO levels decreased in epilepsy patients using antiepileptic drugs. They suggest that antiepileptics have MPO-inhibiting properties. We suggest that TQ can reduce the level of MPO.

Landucci et al.⁵⁴ were the first to demonstrate that TQ has neuroprotective properties in a Kainic acid-induced TLE model. They found that TQ increased the basal level of the key plasticity protein PSD95 and could regulate the endoplasmic reticulum stress pathway. Various studies have shown that TQ has protective effects on brain damage. One of these studies showed that in the status epilepticus model, which causes the production of ROS, TQ treatment attenuates brain injury by modulating the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway. This study demonstrated that TQ treatment can activate the antioxidant defense system.⁵⁵ The severity of seizures was significantly lower in the TQ group. The results of the behavioral experiments performed in this study showed that TQ also positively affects learning and memory. Additionally, TQ has been shown to increase the expression of the Nrf2 and HO-1 proteins, and SOD in the hippocampus.⁵⁵ In a lithium-pilocarpine-induced epilepsy model, TQ was shown to prevent epilepsy by reducing the expression of nuclear factor kappa B, which mediates inflammatory reactions.⁵⁶ It has been shown that TQ improves electroencephalography profiles, reduces the severity of seizures, and improves learning and memory functions.⁵⁶

In the PTZ-induced epilepsy model, it has been shown that TQ administration causes a prolongation of the latency period and a decrease in the duration of seizures in mice.⁵⁷ In our study, we also showed that TQ treatment prolonged the latency period and shortened the seizure duration. Additionally, our findings revealed for the first time, that TQ exerts a protective effect in a model of PTZ-induced epilepsy. These results are in agreement with the literature.

Study Limitations

One limitation of this study is that these results need to be confirmed in humans. Thus, the effectiveness of TQ in the treatment of epilepsy may come to the fore.

CONCLUSION

In conclusion, we evaluated the effect of TQ on MPO, IMA, TOS, TAS, AOPP, T. sulfhydryl, and PON-1 levels in the PTZ-induced epilepsy model. TQ causes antioxidative and protective changes based on these measured parameters. Additionally, TQ prolonged the latency period and shortened the seizure duration. Although experimental studies indicated the beneficial effects of TQ against nervous system problems, better-designed clinical trials in humans are needed to confirm these effects. TQ is considered for use as an adjuvant agent in epilepsy treatment. Additionally, TQ has therapeutic potential against cognitive impairment caused by seizures. As a result, the values of serum biomarkers obtained in the epilepsy model indicate that TQ treatment results in improvements reflected in the serum data, which in turn enhances the related metabolic pathways. Serum biochemistry analyses can measure the effectiveness of treatments in human diseases. They show the effectiveness of TQ treatment in the epilepsy model, and the markers investigated in this study should be evaluated within routine epilepsy screenings.

Ethics

Ethics Committee Approval: This study was approved by the Bezmialem Vakıf University Experimental Animals Local Ethics Committee (no: 2021/236, date: 21.09.2021).

Informed Consent: Animal experiment.

Footnotes

Authorship Contributions

Biochemical Analyses: S.Ö., İ.Ö.K., Surgical and Medical Practices: M.P., Concept: M.P., Design: M.P., Data Collection or Processing: M.P., N.P.A., Analysis or Interpretation: M.P., F.H., İ.Ö.K., S.Ö., Ş.G.Y., Literature Search: M.P., Writing: M.P., İ.M., N.P.A., Ş.G.Y.

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

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Positive Bias in the Prolonged QT Interval in Epilepsy is Related to the Calculation Method Rather Than Specific Anti-seizure Medications

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Abstract

Objective: Previous studies have shown conflicting results regarding the significantly prolonged QT interval in epilepsy, which could be attributed to the method of calculating the corrected QT (QTc). This study aimed to investigate the impact of the method on the calculation of QTc by determining the agreement between these methods using the Bland-Altman plot.

Methods: This cross-sectional study included 86 patients of both sexes aged <18 years. The patients were categorized into group 1 (new cases, untreated epilepsy); group 2 (sodium valproate treatment); and group 3 (levetiracetam treatment). The QTc interval of each participant was calculated using 10 different methods. Bias was assessed using Bland-Altman plot analysis.

Results: The mean±standard error of QTc was within the normal range and did not show significant differences between groups 2, 3, and 1, despite the detection of significant prolonged QTc in the number of patients in each group. Bland-Altman analysis showed significant disagreement between methods with positive mean bias when using Bazett's formula compared with other formulas.

Conclusion: Prolonged QTc interval was negligible in treated or untreated epileptic patients, and the overestimation of prolonged QTc was related to the calculation method used for overestimation of QTc, and a positive bias was related to the use of Bazett's formula compared with others.

Keywords: Epilepsy, anti-seizure medicines, QT-interval, Bland-Altman analysis

INTRODUCTION

Variable effects of epilepsy or its therapeutic agents showed variable effects on the heart. Epileptic patients, particularly those using carbamazepine and sodium valproate, were at risk of developing cardiac arrhythmias.¹ Evidence of ventricular repolarization, as shown by the prolongation of the QT period in the electrocardiogram (ECG) record, was observed during the interictal period in epilepsy patients.² QT interval, which is corrected QT (QTc) by using Bazett's formula, has been reported to be prolonged with carbamazepine, sodium valproate, and levetiracetam in epileptic patients.³ Lamotrigine in different doses produced a non-significant decrease in the QTc interval estimated by using the Framingham equation.⁴ In healthy subjects, gabapentin enalapril at higher doses did not produce a significant effect on the QTc interval estimated by using Fridericia's equation,⁵ as did topiramate, carbamazepine, or sodium valproate as monotherapy, which did not produce effects on the QTc interval calculated by Fridericia's equation in epileptic children.⁶ The variability in the effects of anti-seizure medicines (ASMs) may be related to the different methods of calculating the QTc interval. Several methods are used to calculate the QTc interval, including Bazett's, Fridericia's, Hodges', Framingham's, and other equations. In addition, the accuracy of the QT-nomogram is varied with each formula, as it has been found that the application of Rautaharju's formula [which used a cutoff value of 477 milliseconds (ms)] is superior to Bazett's or Fridericia's formulas.^{7,8} Another study proposed a new formula derived from Bazett's, Hodges's, Fridericia's, and Framingham's formulas for calculating the QTc interval at a heart rate between 40 and 140 beats per minute, which showed agreement with Hodges's but not with other formulas by using Bland-Altman analysis.⁹ Therefore, it is necessary to include the specifications of each formula in the assessment of the cardiac effects of ASMs, as the estimation of QTc by one method could be within normal limits, while using the other method will be significantly prolonged. This study aimed to detect the negative or positive bias by applying Bland-Altman analysis in calculating the QTc interval in epileptic patients treated with sodium valproate or levetiracetam compared with non-treated patients by applying different methods of calculation.

METHODS

Study Design

This cross-sectional study was conducted at the University of Diyala Faculty of Medicine, in 2023. The Institutional Scientific Committee of the University of Diyala Faculty of Medicine, approved this study according to the Helsinki guidelines (decision no: 243, date: 21.05.2024). The participants or their proxy were informed that the study would not interfere with their management, and they requested ECGs to document the effects of ASMs on the heart, specifically on ventricular repolarization represented by measuring the duration of the QT interval in ms.

Data Collection

Epileptic patients were recruited from public health centers who attended the medical centers for management or follow-up. Eligible patients included both sexes that were 18 years old. The criteria for inclusion were newly diagnosed epileptic patients (at the time of entry, they were not using treatment) and those treated with sodium valproate or levetiracetam for at least 3 months as part of a monotherapy schedule. Patients with cardiovascular diseases, pregnant women, and those using antiarrhythmic drugs or drugs that could potentially affect the heart rate or the conduction of impulses treated with more than one ASM were excluded. A total of 86 participants were recruited, and they were divided into the following groups:

Group 1: Newly diagnosed epilepsy (n=22; 10 females and 12 males),

Group 2: Epilepsy patients treated with a variable dosage schedule of sodium valproate (n=40; 13 females and 27 males),

Group 3: Epileptic patients treated with a variable dosage schedule of levetiracetam (n=24; 14 females and 10 males).

Definition of Pathological Conditions

The heart rate, P-R period, R-R interval, and QTm were measured manually by two independent physicians. A 12-lead standard ECG record was adjusted to 10 mm/mV, and the record speed was 25 mm/min. An ECG record strip with sinus rhythm was included in the study; abnormal rhythms were excluded from the study. The ECG strips were then scanned, and the scanned image was magnified using a PC windows photo viewer to zoom. The durations of small and large squares in the ECG records is 40 ms and 200 ms, respectively. The heart rate (which is equal to 300 divided by the number of large squares between two consecutive R waves), PR interval (which was measured from the beginning of the P-wave

to the beginning of the QRS complex wave), and QTm (which is measured from the beginning of the QRS complex wave to the end of the T-wave; the average of 5 measurements were considered).

The QTc interval was calculated using 10 different formulas as follows;

$$QTc = QT / \sqrt{RR} \text{ (Bazett)}.^{10}$$

$$QTc = QT / RR^{1/3} \text{ (Fridericia)}.^{11}$$

$$QTc = QT + 0.154 \times (1 - RR) \text{ (Framingham)}.^{12}$$

$$QTc = QT + 0.00175 \times (HR - 60) \text{ (Hodges)}.^{13}$$

$$QTc = QT + 0.24251 - 0.434 \times e^{-0.0097 \times HR} \text{ [Rautaharju (1)]}.^{14}$$

$$QTc = QT \times (120 + HR) / 180 \text{ (Rautaharju-2)}.^7$$

$$QT + 0.205 \times (1 - RR) \text{ (Schlamowitz)}.^{15}$$

$$QTc = QT / RR^{0.413} \text{ (Dmitrienko)}.^{16}$$

$$QTc = QT - 0.04462 + 0.664 \times e^{-2.7 \times RR} \text{ (Sarma)}.^{17}$$

$$QTc = QT / \log_{10}[10 \times (RR + 0.07)] \times \log_{10}(10.7) \text{ (Ashman)}.^{18}$$

The cutoff values of QTc as a pathologically prolonged interval in children and adolescents are 455 ms (female) and 440 ms (male).¹⁹

Statistical Analysis

The results are expressed as a number, percentage, minimum-maximum value, median (25th-75th percentiles), 95% confidence interval, and mean±standard error. The results were analyzed using the Statistical Package for Social Sciences (version 24, IBM-compatible cooperation, USA). The data on the participants' characteristics were analyzed using Fisher's exact probability test (sex, residency, family history of epilepsy) and the independent Kruskal-Wallis test (age and duration of epilepsy). A two-paired one-way analysis of variance followed by the lysergic acid diethylamide test was used to determine significant differences between treated groups and new cases (the untreated group) of epilepsy. The positive and negative bias in the calculation of QTc using different formulas was assessed by using Bland-Altman analysis with one sample t-test applied to measure the difference in the QTc value and 95% confidence interval between each formula and other formulas. Statistical analysis was not applicable to no-observation data (zero-value) in the characteristics of the participants. A p value of less than 0.05 indicates the lower limit of significance.

RESULTS

The characteristics of the participants are displayed in Table 1. The distribution of sexes (p=350), age (p=0.222), residence (p=0.343), family history of epilepsy (p=0.578), and duration of epilepsy (p=0.776 between groups 1 and 3) were not significantly different. Of the participants, 19.1% (19 out of 86) had a positive family history, whereas 4.7% (4 out of 86) had a history of head injuries.

Figure 1 shows a positive correlation between QTm and R-R interval, and one participant in group 2 had a QTm of 640 ms.

MAIN POINTS

- Anti-seizure medicines (ASMs) are safe and have minimal effects on ventricular repolarization.
- There are many methods for calculating the corrected QT (QTc) interval, but these methods did not show an agreement.
- The use of one method will show that one ASM significantly prolongs the QTc, while another method will show no significant effects.
- It is necessary to use the same calculation method for QTc when reporting the effects of ASMs on QTc.

The correlation coefficients were 0.559 ($p=0.007$), 0.469 ($p=0.002$), and 0.309 ($p=0.142$) for groups 1, 2, and 3, respectively. The correlation coefficient tended to decline in treated patients compared with untreated patients. The nomogram showed that the QTm of the participants with respect to their heart rate was within the normal limit, except for one participant in group 2, who was above the border line of the nomogram (Figure 2). This result indicates that QTm interval measurements were within normal limits for both untreated and treated patients of whatever medicines. Table 2 shows that there were non-significant differences between groups 1 and 2 or 3 in heart rate, P-R period, R-R interval, and QTm measurements. Furthermore, the QTc interval determined using the 10 formulas was not significantly different between the groups. The mean value of QTc calculated using Bazett's formula was higher than the corresponding values of QTc determined using other formulas in each group. Table 3 shows that significantly prolonged QTc using Bazett's formula was observed in 3 participants in group 1 and 6 participants in group 2. Furthermore, the detection

of a significantly prolonged QTc interval varied according to the calculation formula used. Accordingly, the significantly prolonged QTc in each studied group was related to the method for calculating the QTc interval.

As shown in Table 4, the Bland-Altman analysis showed significant bias (disagreement) in the value of QTc when calculated using different formulas. Disagreements between Bazett and other methods were observed in all groups. The application of the Fridericia method was in agreement with other methods, including the Framingham, Hodges, and Rautanarju-2 methods only in untreated patients (group 1) and with the Hodges method in group 3. The Framingham method agreed with Hodges and Rautanarju-2 in calculating QTc for groups 1 and 3. The Hodges method agreed with the Dmitrienko method in group 3. Agreement in calculating the QTc interval was observed in the interplay comparison between the Rautaharju (1), Schlamowitz, Dmitrienko, Sarma, and Ashman methods. These findings indicate that there is no reliable method for calculating the QTc interval in epileptic patients.

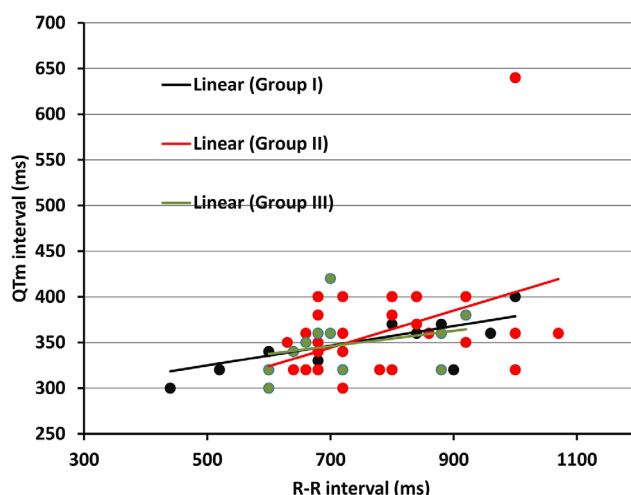


Figure 1. Relationship between R-R interval and measured QT interval (QTm) in epileptic patients Group 1: new cases; group 2: treated with sodium valproate; group 3: treated with levetiracetam ms: Milliseconds

Table 1. The characteristics of the participants

Variables	Group 1	Group 2	Group 3	p value
Sex (male:female)	12:10	27:13	10:14	0.350
Age	14 (9, 15.5)	12 (8.3, 15.8)	14 (9, 18.8)	0.222
Residency				
Urban	18	33	22	0.343
Rural	4	7	2	
Family history of epilepsy	4	9	6	0.578
History of head injury	1	3	0	NA
The type of epilepsy				
Idiopathic generalized epilepsy	16	35	20	
Absence (petit mal) seizures	2	5	2	NA
Focal epilepsy	4	0	2	
Duration of epilepsy	-	2.5 (2, 3)	2.5 (1, 5.3)	0.776
History of status epilepticus	0	4	0	NA
Oral dosage regimen of antiepileptic (mg/day)	-	400 (400, 400)	1000 (500, 1000)	NA

The results are expressed as numbers and medians (25th-75th percentiles). The p value was calculated using an independent-samples Kruskal-Wallis test for age (between groups 1, 2, and 3) and duration of epilepsy (between groups 1 and 2) and by Fisher's exact probability test for other variables. NA: Not applicable because there are no observation data (zero value). The differences between groups 1 and 2 were not statistically analyzed because of the difference in the strength of antiepileptics

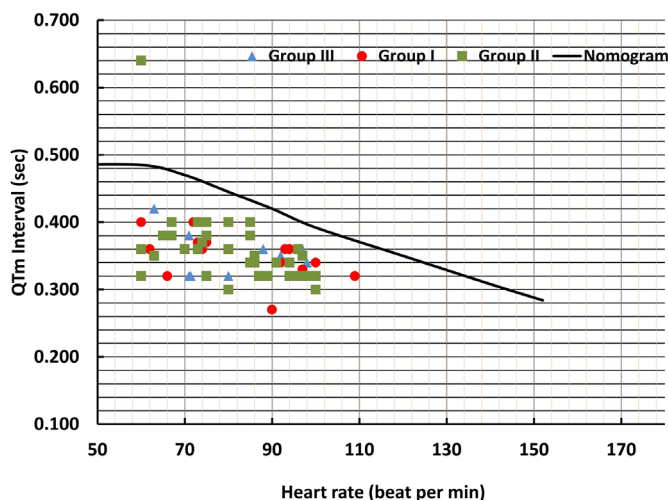


Figure 2. Nomogram of the relationship between heart rate and measured QT interval (QTm) in patients with epilepsy. Group 1: new cases; group 2: treated with sodium valproate; group 3: treated with levetiracetam

Table 2. Calculated QT interval ms using different formulas in patients with epilepsy

Variable	Group 1	Group 2	Group 3	p value
RR-interval ms	746±31 (440-1000)	768±20 (600-1070)	738±24 (600-920)	*0.537; †0.833
Heart rate bpm	83±3 (60-109)	82±2 (60-100)	84±3 (63-100)	*0.769; †0.802
QTm	351±6 (300-400)	358±9 (300-640)	349±6 (300-420)	*0.567; †0.865
Bazett-QTc	411±7 (337-485)	410±8 (320-640)	409±8 (341-502)	*0.966; †0.890
Fridericia, QTc	389±6 (331-445)	392±8 (320-640)	388±7 (334-473)	*0.836; †0.883
Framingham-QTc	390±5 (335-449)	394±8 (320-640)	389±6 (338-466)	*0.743; †0.927
Hodges-QTc	392±6 (331-435)	396±8 (320-640)	391±5 (339-425)	*0.640; †0.955
Rautaharju (1)-QTc	398±6 (334-443)	403±7 (320-640)	398±5 (345-433)	*0.643; †0.981
Rautaharju (2)-QTc	395±6 (331-444)	399±8 (320-640)	394±6 (340-434)	*0.674; †0.940
Schlamowitz-QTc	404±6 (341-466)	406±8 (320-640)	403±7 (345-482)	*0.841; †0.963
Dmitrienko, QTc	399±6 (334-469)	400±8 (320-640)	398±7 (337-487)	*0.929; †0.888
Sarma, QTc	402±7 (334-461)	402±8 (320-640)	399±7 (337-476)	*0.976; †0.818
Ashman, QTc	401±4 (334-471)	401±8 (320-640)	399±8 (337-488)	*0.984; †0.855

The results are presented as mean±SE (minimum-maximum). P values were calculated using a one-way, two-tailed analysis of variance with a post-hoc LSD test. *Compared between groups 1 and 2; †compared between groups 1 and 3. Group 1: New patients; group 2: patients treated with sodium valproate; group 3: patients treated with levetiracetam. ms: Milliseconds, bpm: Beats per minute, QTc: Corrected QT, LSD: Lysergic acid diethylamide, SE: Standard error

Table 3. Distribution of participants with QTc intervals (≥440 ms for males and ≥550 ms for females) in epileptic patients

Formulas	Group 1 (n=22)	Group 2 (n=40)	Group 3 (n=24)
Bazett	3 (13.6)	6 (15%)	2 (8.3)
Fridericia	0 (0.0)	3 (7.5)	2 (8.3)
Framingham	0 (0.0)	2 (5)	2 (8.3)
Hodges	0 (0.0)	2 (5)	0 (0.0)
Rautaharju (1)	0 (0.0)	2 (5)	0 (0.0)
Rautaharju (2)	0 (0.0)	3 (7.5)	0 (0.0)
Schlamowitz	1 (4.5)	5 (12.5)	2 (8.3)
Dmitrienko	1 (4.5)	3 (7.5)	2 (8.3)
Sarma	1 (4.5)	3 (7.5)	2 (8.3)
Ashman	1 (4.5)	3 (7.5)	2 (8.3)

Group 1: New patients; group 2: patients treated with sodium valproate; group 3: patients treated with levetiracetam. QTc: Corrected QT, ms: Milliseconds

Table 4. Bias in calculating the QTc interval by using Bland-Altman analysis for the agreement in between formulas in patients with epilepsy

Methods agreement	Group 1 (n=22)		Group 2 (n=40)		Group 3 (n=24)	
	Mean difference (95% CI)	p value	Mean difference (95% CI)	p value	Mean difference (95% CI)	p value
Bazett, Fridericia	21.3 (14.9, 27.7)	<0.001	18.5 (15.1, 22.0)	<0.001	21.3 (16.7, 25.8)	<0.001
Bazett-Framingham	20.3 (12.8, 27.8)	<0.001	16.5 (13.0, 19.9)	<0.001	19.5 (14.4, 24.6)	<0.001
Bazett-Hodges	19.1 (9.4, 28.9)	0.001	14.0 (10.1, 17.8)	<0.001	18.0 (9.2, 26.7)	<0.001
Bazett-Rautaharju (1)	12.7 (3.4, 22)	0.010	7.6 (4.1, 11.0)	<0.001	11.2 (2.1, 20.3)	0.018
Bazett-Rautaharju (2)	15.7 (5.7, 25.7)	0.004	10.9 (7.6, 14.2)	<0.001	14.8 (5.8, 23.7)	0.002
Bazett-Schlamowitz	7.4 (2.8, 11.9)	0.003	4.6 (2.8, 6.4)	<0.001	6.1 (3.1, 9.1)	<0.001
Bazett, Dmitrienko	11.3 (7.8-14.7)	<0.001	9.8 (8.0, 11.6)	<0.001	11.2 (8.8, 13.6)	<0.001
Bazett, Sarma	8.8 (6.1, 11.5)	<0.001	8.7 (6.8, 10.6)	<0.001	9.8 (7.0, 12.7)	<0.001
Bazett, Ashman	9.6 (7.4, 11.8)	<0.001	9.0 (7.5, 10.5)	<0.001	10.2 (8.5, 10.5)	<0.001
Fridericia, Framingham	-0.86 (-2.32, 0.59)	0.233	-2.0 (-3.0, -1.1)	<0.001	-1.6 (-3, -0.2)	0.006
Fridericia, Hodges	-2.1 (-7.7, 3.4)	0.430	-4.6 (-7.5, -1.6)	0.004	-3.3 (-10.3, 3.7)	0.221
Fridericia, Rautaharju (1)	-8.6 (-14.0, -3.0)	0.005	-7.7 (-10.3, -5.1)	<0.001	-10.3 (-17.9, -2.6)	0.002
Fridericia-Rautaharju (2)	-5.59 (-11.7, 0.5)	0.069	-10.9 (-14.3, -7.6)	<0.001	-6.5 (-13.8, 0.8)	0.026
Fridericia, Schlamowitz, Switzerland	-14.1 (-16.8, -11.4)	<0.001	-14.0 (-16.5, -11.4)	<0.001	-15.3 (18.0, -12.6)	<0.001
Fridericia, Dmitrienko	-10.0 (-13.0, -7.0)	<0.001	-8.72 (-10.4, -7.1)	<0.001	-10.0 (-12.2, -7.8)	<0.001
Fridericia, Sarma	-12.3 (-19.2, -5.5)	0.001	-9.8 (-12.8, -6.7)	<0.001	-11.4 (-15.8, -7.1)	<0.001
Fridericia-Ashman	-11.6 (-16.0, -7.1)	<0.001	-9.6 (-11.6, -7.5)	<0.001	-11.1 (-13.8, -8.3)	<0.001
Framingham-Hodges	-1.3 (-6.0, 3.4)	0.579	-2.5 (-5.0, -0.03)	0.047	-1.7 (-7.8, 4.3)	0.566
Framingham-Rautaharju (1)	-7.8 (-12.7,-2.9)	0.003	-8.9 (-11.7, -6.1)	<0.001	-8.7 (-15.3, -2.0)	0.013
Framingham-Rautaharju (2)	-4.7 (-10.08, 0.63)	0.080	-5.7 (-8.0, -3.4)	<0.001	-4.9 (-11.4, 1.6)	0.133
Framingham-Schramowitz	-13.2 -16.4, -10.0)	<0.001	-11.9 (-14.0, 9.8)	<0.001	-13.8 (-18.2, -11.3)	<0.001
Framingham, Dmitrienko	-9.1 (-13.2, -5.1)	<0.001	-6.7 (-8.5, -4.9)	<0.001	-8.4 (-11.3, -5.6)	<0.001
Framingham, Sarma	-11.5 (-19.3, -3.6)	0.006	-7.72 (-10.5, -5.0)	<0.001	-9.8 (-13.8, -5.8)	<0.001
Framingham, Ashman	-10.7 (-16.3, -5.2)	<0.001	-7.5 (-9.6, -5.4)	<0.001	-9.5 (-12.7, -6.3)	<0.001
Hodges-Rautaharju (1)	-6.5 (-7.5, -5.5)	<0.001	-6.4 (-7.2, -5.5)	<0.001	-7.0 (-7.8, -6.1)	<0.001
Hodges-Rautaharju (2)	-3.5 (-4.8, -2.1)	<0.001	-3.2 (-4.2, -2.1)	<0.001	-3.2 (-4.6, -1.9)	<0.001
Hodges-Schlamowitz	-12.0 (-17.9, -6.1)	<0.001	-9.4 (-12.1, -6.7)	<0.001	-12.0 (-18.6, -5.5)	0.001
Hodges, Dmitrienko	-7.9 (-14.9, -0.8)	0.030	-4.2 (-7.1, -1.2)	0.007	-6.7 (-14.3, 0.9)	0.079
Hodges-Sarma	-10.2 (-21.0, 0.2)	0.054	-5.2 (-7.9, -2.5)	<0.001	8.12 (14.9, 1.3)	0.021
Hodges-Ashman	-9.5 (-17.9, -1.1)	0.029	-5.0 (-8.0, -2.0)	0.002	-7.8 (-15.4, -0.1)	0.046
Rautaharju (1)-Rautaharju (2)	3.0 (1.8, 4.3)	<0.001	3.2 (2.0, 4.4)	<0.001	3.8 (2.4, 5.1)	< 0.001
Rautaharju (1)-Schlamowitz	-5.45 (-11.09, 0.18)	0.057	-3.0 (-5.4, -0.7)	0.013	-5.1 (-12.1, 1.9)	0.146
Rautaharju (1)-Dmitrienko	-1.4 (-8.2, 5.5)	0.683	2.2 (-0.7, 5.1)	0.135	0.3 (-7.8, 8.3)	0.950
Rautaharju (1)-Sarma	-3.7 (-13.9, 6.5)	0.462	1.2 (-1.3, 3.7)	0.344	-1.2 (-8.0, 6.0)	0.739
Rautaharju (1)-Ashman	-3.0 (-11.2, 5.2)	0.462	1.4 (-1.5, 4.3)	0.343	-0.8 (-9.0, 7.3)	0.835
Rautaharju (2)-Schlamowitz	-8.5 (-14.9, -2.1)	0.011	-6.2 (-8.6, -3.8)	<0.001	-8.8 (-15.8, -1.9)	0.015
Rautaharju (2)-Dmitrienko	-4.4 (-11.9, 3.05)	0.233	-1.0 (-3.4, 1.4)	0.404	-3.5 (-11.3, 4.3)	0.364
Rautaharju (2)-Sarma	-6.7 (-17.8, 4.3)	0.219	-2.0 (-4.7, 0.63)	0.132	-4.9 (-12.3, 2.4)	0.179
Rautaharju (2)-Ashman	-6.0 (-14.9, 2.9)	<0.001	-1.8 (-4.3, 0.7)	0.144	-4.6 (-12.5, 3.4)	0.245
Schlamowitz, Dmitrienko	4.1 (2.4, 5.8)	<0.001	5.2 (3.3, 7.1)	<0.001	5.3 (3.6, 7.1)	<0.001
Schlamowitz-Sarma	1.8 (-3.6, 7.1)	0.497	4.2 (2.2, 6.2)	<0.001	3.9 (2.0, 5.8)	<0.001
Schlamowitz, Ashman	2.5 (-0.5, 5.5)	0.497	4.4 (2.6, 6.2)	<0.001	4.3 (2.6, 5.9)	<0.001
Dmitrienko-Sarma	-2.1 (-6.6, 2.0)	0.277	-1.0 (-2.9, 0.9)	0.285	-1.1 (-4.4, 1.6)	0.342
Dmitrienko, Ashman	-1.6 (-3.2, 0.03)	0.054	-0.8 (-1.3, -0.4)	0.001	-1.1 (-1.8, -0.4)	0.003
Sarma-Ashman	0.7 (-2.1, 3.5)	0.597	0.2 (-1.4, 1.8)	0.800	0.3 (-2.2, 2.9)	0.727

The p values were calculated using a sample t-test. Group 1: new cases; group 2: patients treated with sodium valproate; group 3: patients treated with levetiracetam. The bold cell exhibited a non-significant difference, indicating agreement.
 QTc: Corrected QT, CI: Confidence interval

DISCUSSION

The results showed that significant disagreement between the methods used in calculating QTc interval was the cause of prolonged QTc interval detection in epilepsy patients without treatment or treated with sodium valproate or levetiracetam. The study findings are unaffected by the participant characteristics because no significant differences in the individuals' distinguishing characteristics. The results of this study showed that prolonged QTc intervals were observed between 0-13.6%, 5-15%, and 0-8.3% in groups 1, 2, and 3, respectively. The variability in these percentages is related to the methods of calculating the QTc interval. Bazett's method overestimated the QTc interval compared with the other methods. It has been found that a significantly prolonged QTc interval, which was calculated using Bazett's method, was 454 ms (mean) in epileptic children <2 years of age.²⁰ Therefore, using Fridericia's or Framingham's methods will result in a decrease in the mean value of QTc by 21.3 and 20.3 ms, respectively; i.e., the QTc interval is within the normal range.

In adults, the QTc interval calculated using Fridericia's formula was 441.2±56.6 ms in patients treated with levetiracetam, which is significantly higher than the cutoff value of QTc²¹, which is higher than the QTc interval calculated using Dmitrienko's, Sarma's, or Ashman's methods. Therefore, the calculation method is critical for identifying patients at risk of developing prolonged QTc intervals. Gervasi et al.²² showed a significant correlation between heart rate and QTc interval using Bazett's and Framingham's methods, but not Fridericia's method. Furthermore, there is a difference in the QTc values estimated by Bazett's (469 ms), Hodges's (361 ms), Framingham's (458 ms), and Fridericia's (451 ms) indices, which agrees with the findings of this study.²² Another study tested nine formulas by using Person's correlation test between two formulas of the following: Bazett's, Fridericia's, Hodges's, Sarma's, Lecocq's, Rautaharju's, Framingham's (Sagie's), Arrowood's, and Malik's formulas and found that the detection of prolonged QT intervals depended on the estimation method of calculation.²³ Another study reported significant errors in the assessment of drug-induced prolonged QTc interval, particularly with Bazett's and Fridericia's methods, but the study did not mention the magnitude of bias for these formulas.²⁴ The positive bias found using Bazett's method in this study is consistent with others who reported false positive results for prolonged QTc intervals calculated using Bazett's method in children, and those authors recommended using Fridericia's method.²⁵

The present study showed that the mean difference in QTc between Bazett's and Fridericia's methods was 21.3 ms, which indicates that this method is preferable for calculating QTc in children. The wide mean differences in the calculated QTc interval between Bazett's and Fridericia, Framingham, or Hodges's formulas allow these formulas to replace Bazett's formula in the calculation of the QTc interval.²⁶ The strength of this study is using the Bland-Altman plot analysis, which detects the magnitude of positive bias and an agreement between Fridericia's-Framingham's (+1 ms) and Fridericia's-Hodges's (+2.2 ms). Furthermore, this study revealed that epilepsy per se is not associated with prolonged QTc interval, whereas sodium valproate and levetiracetam significantly prolonged QTc interval in epileptic patients by up to 7.5% and 8.3%, respectively.

Study Limitations

One important limitation of this study is the small sample size, which is difficult to overcome because the study was conducted on specific patients aged 18 years.

CONCLUSION

This study highlights the need to use a proper formula for calculating the QTc interval, particularly for the assessment of drugs in epilepsy, by using Bland-Altman plot analysis. Fridericia, Framingham, and Hodges formulas showed agreement regarding QTc, and ASMs induced significant prolonged QTc in a small percentage.

Ethics

Ethics Committee Approval: This cross-sectional study was conducted at the University of Diyala Faculty of Medicine, in 2023. The Institutional Scientific Committee of the University of Diyala Faculty of Medicine, approved this study according to the Helsinki guidelines (decision no: 243, date: 21.05.2024).

Informed Consent: It is verbal. Written consent not applicable.

Footnotes

Authorship Contributions

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

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






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Factors Associated with Internalized Stigma in People with Epilepsy: A Hospital-based Study in Medan, Indonesia

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Abstract

Objective: Stigma toward epilepsy is associated with a negative self-concept and has a negative impact on people with epilepsy (PWE) and their families, especially in low-to middle-income countries in which the majority of PWE live. This study aimed to assess and identify factors associated with internalized stigma in PWE.

Methods: A cross-sectional study was conducted among patients with epilepsy at two university teaching hospitals in Medan, North Sumatra, Indonesia, from December 2022 to May 2023. Participants (n=81) with generalized or focal epilepsy, aged >18 years, literate in Bahasa Indonesia, and without psychiatric comorbidities were included. We used Internalized Stigma of Epilepsy (ISEP), which was validated in Bahasa Indonesia, to measure stigma across five subscales.

Results: The mean age was 34.7±14.5 years with an approximately equal gender distribution. Most participants (79%) demonstrated moderate internalized stigma, with a mean ISEP score of 57.96±9.90. Males exhibited higher ISEP scores than females [62.5 (36.0-71.0) vs. 59.0 (36.0-79.0)]. A statistically significant difference in stigma scores was noted between males and females (p=0.039, p<0.05). Additionally, patients with generalized tonic-clonic seizures displayed lower stigma scores than those with absence seizures [59.5 (36.0-71.0) vs. 71.0 (65.0-79.0)].

Conclusion: This study highlights the need to improve knowledge and raise awareness regarding epilepsy to decrease the stigma associated with the condition.

Keywords: Epilepsy, stigma, Indonesia

INTRODUCTION

Epilepsy is a neurological disorder that can affect individuals of diverse ages, races, social backgrounds, and geographical locations.¹ The disease exerts a significant impact on the global disease burden, with approximately 50 million people worldwide experiencing epilepsy. Annually, approximately 5 million new cases are diagnosed, and an estimated 4-10 out of a thousand individuals live with persistent epilepsy, necessitating ongoing therapy. Notably, the prevalence of epilepsy is highest in low- and middle-income countries, accounting for approximately 80% of cases, particularly affecting 12.7 out of 1000 people in developing countries.^{2,3} In Indonesia, a developing country with a population of around 260 million, the incidence of epilepsy ranges from 1.1 to 1.8 million individuals. Research conducted in 15 Indonesian cities in 2013 identified 2,288 cases of epilepsy, including 487 new cases.^{3,4}

Epilepsy is a neurological disorder characterized by either two or more unprovoked or reflex seizures occurring more than 24 hours apart, a single unprovoked or reflex seizure in an individual with a 60% risk of another seizure within the next 10 years, or an epilepsy syndrome.⁵ Epileptic seizures often induce anxiety and fear in individuals and those around them, leading to social exclusion. Consequently, individuals with epilepsy frequently encounter challenges in education, at home, and in the workplace.⁶

Stigma encompasses societal perceptions marked by labeling, stereotyping, and discrimination that arises from discrediting differences. It is typically categorized into “enacted stigma”, involving real instances of discrimination by the public, and “self-stigma”, representing internalized stigma experienced by individuals with feelings of inferiority, shame, secrecy, or withdrawal.^{4,7,8} Self-stigma significantly impacts the treatment of epilepsy patients, influencing treatment adherence and potentially delaying diagnosis, leading to heightened risks of uncontrolled seizures. Stigma is also a risk factor for somatic disorders and mental health issues in patients with epilepsy, influencing therapy outcomes, prognosis, and quality of life. Several studies have identified factors contributing to stigma in patients with epilepsy,

including age, gender, seizure frequency and type, knowledge about epilepsy, treatment received, and perceptions of those around them. According to the International League Against Epilepsy Task Force on Stigma in Epilepsy (2022), stigma arises from inadequate information about epilepsy, low educational levels, economic disparities, residing in underdeveloped environments, and biased beliefs.⁹⁻¹¹ The Internalized Stigma of Epilepsy (ISEP) serves as a scale to quantify stigma in patients with epilepsy. Adapted from the Internalized Stigma of Mental Illness,¹² ISEP has undergone various studies and validations in multiple countries, including Indonesia. The instrument is recognized as valid and reliable for assessing stigma perceptions, making it applicable for use in the context of epilepsy in Indonesia.⁴

METHODS

Study Design and Participants

This observational analytical cross-sectional study was conducted at the neurology outpatient clinic of two university teaching hospitals in Medan North Sumatra Indonesia, Adam Malik General Hospital and Universitas Sumatera Utara Hospital, from December 2022 until May 2023. Using a non-random consecutive sampling method, we recruited literate people with epilepsy (PWE) with epilepsy older than 18 years who were able to communicate fluently in Bahasa Indonesia and who had no psychiatric comorbidities. Informed consent was obtained from each patient.

Procedures

We collected demographic data, including age, sex, occupation, and education level. The ISEP was assessed using the ISEP validated in Bahasa Indonesia. The ISEP comprises 29 items on perceived stigma. It consists of five subscales measuring “Alienation” with 6 items, “Stereotype Endorsement” with 7 items, “Discrimination Experience” with 5 items, “Social Withdrawal” with 6 items, and “Stigma Resistance” with 5 items. Each item has four response options scored using Likert scale from 1 to 4. The “Alienation” subscale measures the subjective experience of being less than a full member of society. The “Stereotype Endorsement” subscale measures the degree to which respondents agreed with common stereotypes regarding PWE. The “Discrimination Experience” subscale is composed of five items intended to capture respondents’ perception of how they are being treated by others. The “Social Withdrawal” subscale consists of statements like “I don’t talk about myself much because I don’t want to burden others with my epilepsy”. The “Stigma Resistance” subscale measures the degree of resistance toward being stigmatized or remain unaffected by internalized stigma. The maximum score is 116 and the minimum score is 29. Based on these scores, the perception of stigma was

classified as low (<50.75), medium (50.75-94.25), and high (>94.25).^{4,12}

Statistical Analysis

Data were coded and entered Statistical Package for Social Sciences windows version 25 for analysis. Descriptive statistics were used for the sociodemographic and clinical variables. Data are presented as mean value±standard deviation for normally distributed continuous variables, median (minimum-maximum) for continuous variables with non-normal distribution, or frequency (%) for categorical variables. We used Mann-Whitney and Kruskal-Wallis tests to compare the mean stigma score with demographic variables. The significance level was set at $p < 0.05$.

RESULTS

The study involved 81 patients with epilepsy, with a mean age of 34.7 ± 14.5 years and an almost equal gender distribution. Most patients had university education (51.9%) and were college students (32.1%). The majority of subjects experienced generalized tonic-clonic seizures (96.3%), whereas 3.7% experienced absence seizures. Although we initially intended to include patients with both focal and generalized epilepsy, we ultimately did not identify any individuals with focal seizures. The mean seizure duration was 94.2 ± 101.5 months. In terms of treatment, most subjects used antiepileptic drug (AED) monotherapy (63%), whereas the remaining 37% used polytherapy. The subject characteristics are presented in Table 1.

The majority of subjects exhibited a moderate level of internalized stigma (79%), whereas 21% displayed a low level of internalized stigma. The mean ISEP score was 57.96 ± 9.90 . The breakdowns of scores by subscale were as follows: Alienation subscale, 3.7 ± 3.1 ; Stereotype Endorsement subscale, 13.3 ± 2.7 ; Discrimination Experience subscale, 9.4 ± 2.8 ; Social Withdrawal subscale, 12.1 ± 3.1 ; and Stigma Resistance subscale, 9.4 ± 2.7 . The detailed responses to the questionnaire items are presented in Tables 2 and 3.

In this study, we observed that males exhibited higher ISEP scores than females [62.5 (36.0-71.0) vs. 59.0 (36.0-79.0)]. A statistically significant difference in stigma scores was noted between males and females ($p = 0.039$, $p < 0.05$). Additionally, patients with generalized tonic-clonic seizures displayed lower stigma scores than those with absence seizures [59.5 (36.0-71.0) vs. 71.0 (65.0-79.0)], with a significant difference in stigma scores between those two types ($p = 0.012$). However, there were no significant differences in stigma scores according to education level, occupation, and the use of AEDs (Table 4).

DISCUSSION

This study aimed to assess stigma and identify factors associated with internalized stigma in individuals with epilepsy. The study involved 81 patients from neurology outpatient clinics at two university teaching hospitals in Medan, Indonesia. The mean age of the patients was 34.7 ± 14.5 years, with an approximately equal gender distribution. Age is related to epilepsy prevalence and incidence, with a lower prevalence in children, increasing prevalence in adolescents and young adults, and decreasing prevalence after 30 years.^{13,14} Older age at epilepsy diagnosis is

MAIN POINTS

- This study assessed the internalized stigma among individuals with epilepsy in Medan using the Internalized Stigma of Epilepsy scale.
- Gender and type of seizures influenced stigma levels; men experienced higher stigma than women, and those with absence seizures reported more stigma than those with generalized tonic-clonic seizures.
- The findings of this study suggest increased educational efforts and support to mitigate internalized stigma and improve the quality of life of people with epilepsy.

correlated with a poorer quality of life, potentially due to better emotional control when diagnosed at a younger age.¹⁵ Studies have reported a peak prevalence of epilepsy around 30-34 years, reinforcing the notion that epilepsy is generally a disease of the young.¹⁶ Previous research indicates a slightly higher prevalence in men than in women, which is attributed to differences in brain development and social effects.^{17,18}

Biftu et al.¹⁹ (2015) found that among the 408 patients examined, 71.8% experienced seizure frequencies of 1-11 times per year. Most participants (76%) received monotherapy, and 67.2% had a history of non-adherence to AEDs. Another study in Sudan reported that generalized tonic-clonic seizures were the most prevalent type, accounting for 68% of cases, followed by focal seizures at 11%.²⁰ Another study involving 431 patients with epilepsy showed that 25.3% had generalized seizures and 8.9% had focal seizures. Discrepancies in seizure type classification may

Table 1. Subject characteristics

Characteristics	n (81)	%
Sex		
- Male	40	49.4
- Female	41	50.6
Age, years	Mean=34.7±14.5; Median=31.0 (18.0-73.0)	
Level of education		
- Primary	2	2.5
- Middle school	4	4.9
- High school	33	40.7
- University	42	51.9
Occupation		
- College students	26	32.1
- Civil servant	21	25.9
- Entrepreneur	13	16.0
Unemployed	11	13.6
- Housewife	7	8.6
- Retired	3	3.7
Type		
- Generalized tonic-clonic	78	96.3
- Absence	3	3.7
Duration of epilepsy	Mean=94.2±101.5; Median=60.0 (1.0-480.0)	
Antiepileptic drug		
- Monotherapy	51	63.0
- Polytherapy	30	37.0

Table 2. ISEP score

Characteristics	n (81)	%
Level of internalized stigma		
- Low (<50.75)	17	21.0
- Moderate (50.75-94.25)	64	79.0
- Severe (>94.25)	0	0
Mean ISEP scores		
- Alienation	Mean=13.7±3.1; Median=13.0 (9.0-20.0)	
- Stereotype	Mean=13.3±2.7; Median=14.0 (8.0-20.0)	
- Discrimination	Mean=9.4±2.8; Median=10.0 (5.0-15.0)	
- Social withdrawal	Mean=12.1±3.1; Median=13.0 (6.0-19.0)	
- Stigma resistance	Mean=9.4±2.7; Median=10.0 (5.0-18.0)	
- Total score	Mean=57.9±9.9; Median=60.0 (36.0-79.0)	

ISEP: Internalized Stigma of Epilepsy

result from early misidentification of focal-onset symptoms during generalized seizures, leading to a higher prevalence.²¹⁻²³ Our study is consistent with these findings, indicating that the majority of patients received monotherapy (63%), experienced generalized tonic-clonic seizures (96.3%), and had a mean seizure duration of 94.2±101.5 months.^{21,24} In our study, we initially aimed to include patients with both focal and generalized epilepsy. However, due to recruitment challenges, the final sample consisted exclusively of patients with generalized epilepsy.

Epilepsy is often stigmatized, with a study in Sudan reporting depression (28%), anxiety (18%), and social problems (37%) among patients with epilepsy. In the present study, 79% of patients experienced moderate self-stigma. While most subjects disagreed with items related to alienation, stereotype endorsement, discrimination experience, and social withdrawal, certain items, particularly those related to embarrassment, feelings of inferiority, and negative stereotypes, revealed persistent negative stigmas toward epilepsy.^{21,24}

In general, in our study, the patient's answers to the alienation, stereotype endorsement, discrimination experience, and social withdrawal subscales, the majority of subjects answered disagree, which describes a positive thing where the stigma experienced by the subjects in this component was relatively minimal. However, several items included questions number 4 (I feel embarrassed because I suffer from epilepsy) and number 6 (I feel inferior to other people who do not suffer from epilepsy), which are part of the alienation subscale, as well as question number 7 (because I suffer from epilepsy, the stereotype of "wrong assumptions" about epilepsy applies to me) part of stereotype endorsement subscale. Most of the subjects answered in the affirmative, which illustrates that there is still a negative stigma toward PWE. Likewise, in question number 25 (I feel comfortable appearing in public with someone who is known to suffer from epilepsy), the majority of subjects still answered "disagree," which also illustrates the negative stigma toward patients with epilepsy.^{4,12}

Stigma in patients with epilepsy may be linked to low health score coping. The low score of coping is found in one in five patients with epilepsy. Having seizures more than three times per month lowers the score of patients with epilepsy.^{21,24} In our study, higher stigma scores (indicating more negative perceptions) were found in male patients, those with at least an elementary school education, unemployed individuals, those with absence seizures, and those using monotherapy. Sex and type of epilepsy had a statistically significant influence on stigma formation. However, there were no significant differences in stigma scores based on education level, occupation, and AED use, contrary to some previous studies. The results in this study are certainly not in line with several studies that state that epilepsy patients with an education level less than high school or who do not work are reported to be significantly more susceptible to experiencing stigma.²⁵

Mao et al.²⁶ found a significant negative correlation between self-confidence and stigma among patients with epilepsy and a significant positive correlation between self-confidence and knowledge. This indicates that proper knowledge about epilepsy can increase the self-confidence of patients with epilepsy and can decrease the stigma associated with epilepsy. Low education level, long seizure duration, and young age at first onset have an impact on the formation of stigma. However, no relationship was found

Table 3. Prevalence of internalized stigma in percentages

Item	Strongly disagree [n (%)]	Disagree [n (%)]	Agree [n (%)]	Strongly agree [n (%)]
Alienation				
I feel out of place in the world because I have epilepsy.	15 (18.5)	41 (50.6)	20 (24.7)	5 (6.2)
Having epilepsy has spoiled my life.	11 (13.6)	51 (63.0)	15 (18.5)	4 (4.9)
People without epilepsy could not understand me.	9 (11.1)	47 (58.0)	21 (25.9)	4 (4.9)
I am embarrassed or ashamed that I have epilepsy.	11 (13.6)	34 (42.0)	32 (39.5)	4 (4.9)
I am disappointed in myself for having epilepsy.	12 (14.8)	43 (53.1)	21 (25.9)	5 (6.2)
I feel inferior to others without epilepsy.	10 (12.3)	29 (35.8)	30 (37.0)	12 (14.8)
Stereotype endorsement				
Stereotypes about epilepsy apply to me.	21 (25.9)	31 (38.3)	29 (25.8)	0 (0.0)
People can tell that I have epilepsy by the way I look.	18 (22.2)	54 (66.7)	9 (11.1)	0 (0.0)
Individuals with epilepsy tend to be violent.	27 (33.3)	54 (66.7)	0 (0.0)	0 (0.0)
Because I have epilepsy, I need others to make decisions for me.	9 (11.1)	36 (44.4)	23 (28.4)	13 (16.0)
People with epilepsy cannot enjoy a fulfilling life.	31 (38.3)	39 (48.1)	10 (12.3)	1 (1.2)
Persons with epilepsy should not marry.	38 (46.9)	35 (43.2)	7 (8.6)	1 (1.2)
I cannot contribute anything to society because I have epilepsy.	26 (32.1)	51 (63.0)	3 (3.7)	1 (1.2)
Discrimination experience				
People discriminate against me because I have epilepsy.	23 (28.4)	50 (61.7)	6 (7.4)	2 (2.5)
Others think that I can't achieve much in life because I have epilepsy.	24 (29.6)	48 (59.3)	5 (6.2)	4 (4.9)
People ignore or take me less seriously because I have epilepsy.	29 (35.8)	33 (40.7)	16 (19.80)	3 (3.7)
People often patronize me or treat me like a child just because I have epilepsy.	26 (32.7)	31 (38.3)	24 (29.6)	0 (0.0)
Nobody would be interested in getting close to me because I have epilepsy.	26 (32.1)	44 (54.3)	9 (11.1)	2 (2.5)
Social withdrawal				
I do not talk about myself because I do not want to burden others with my epilepsy.	14 (17.3)	39 (48.1)	25 (30.9)	3 (3.7)
I do not socialize as much as I used to because my epilepsy might make me look or behave "weird".	14 (17.3)	51 (63.0)	16 (19.8)	0 (0.0)
Negative stereotypes about epilepsy keep me isolated from the "normal" world.	14 (17.3)	49 (60.5)	17 (21.0)	1 (1.2)
I stay away from social situations to protect my family or friends from embarrassment.	21 (25.9)	39 (48.1)	20 (24.7)	1 (1.2)
Being around people who do not have epilepsy makes me feel out of place or inadequate.	23 (28.4)	50 (61.7)	6 (7.4)	2 (2.5)
To avoid rejection, I avoid getting close to people who do not have epilepsy.	16 (19.8)	54 (66.7)	11 (13.6)	0 (0.0)
Stigma resistance				
I feel comfortable being seen in public with a person known to have epilepsy.	3 (3.7)	29 (35.8)	28 (34.6)	21 (25.9)
In general, I can live my life the way I want to.	0 (0.0)	7 (8.6)	43 (53.1)	31 (38.3)
I can have a good, fulfilling life despite my epilepsy.	2 (2.5)	4 (4.9)	45 (55.6)	30 (37.0)
Individuals with epilepsy make important contributions to society.	2 (2.5)	3 (3.7)	62 (76.5)	14 (17.3)
Living with epilepsy has made me a tough survivor.	2 (2.5)	11 (13.6)	46 (56.8)	22 (27.2)

between stigma and age, gender, wealth, and type/frequency of seizures.²⁶ A study found that many PWE experiencing internalized stigma tend to have lower education levels and limited access to quality healthcare services. These patients often received misleading information about epilepsy from unreliable sources. Most PWE acknowledge epilepsy as a neurological disorder, and those who understand its cause tend to have less fear, more positive attitudes, and greater confidence in managing or treating their condition than those who lack this understanding.²⁷ Stigma in patients with epilepsy was also positively correlated with the severity of seizures ($p=0.034$), number of epilepsy medications ($p=0.035$), depression score ($p<0.0001$), and quality of life ($p<0.0001$). However, stigma was negatively correlated with health literacy ($p=0.0001$), self-efficacy ($p<0.0001$), social support ($p<0.0001$), and functional

status ($p<0.0001$ for mental component, $p=0.0005$ for functional component).²⁸

One study found that patients with a disease duration of 2-5 years are four times more likely to experience self-stigma than those with less than 1 year of illness. This heightened perception may arise from the chronic nature of the disease, inadequate coping strategies, and difficulty in resisting stigma, which can worsen cultural and social challenges. Likewise, individuals with 6-10 years and 11 or more years of illness also exhibit a fourfold increase in stigma perceptions compared to those with shorter durations. Differences from previous studies may be attributed to variations in health systems, research methods, and stigma measurement scales.²⁵

Table 4. ISEP score based on subject characteristics

Characteristics	Stigma score [median (min-max)]	p
Sex		0.039
- Male	62.5 (36.0-71.0)	
- Female	59.0 (36.0-79.0)	
Level of education		0.267
- Primary	66.5 (63.0-70.0)	
- Middle school	61.5 (55.0-70.0)	
- High school	61.0 (36.0-79.0)	
- University	59.0 (36.0-70.0)	
Occupation		0.904
- College students	59.5 (36.0-71.0)	
- Unemployment	62.0 (50.0-70.0)	
- Housewife	59.0 (36.0-71.0)	
- Entrepreneur	59.0 (36.0-79.0)	
- Civil servant	61.0 (36.0-70.0)	
- Retired	59.0 (59.0-63.0)	
Type		0.012
- Generalized tonic-clonic seizure	59.5 (36.0-71.0)	
- Absence	71.0 (65.0-79.0)	
Antiepileptic drug		0.875
- Monotherapy	61.0 (36.0-79.0)	
- Polytherapy	59.5 (36.0-70.0)	

*Mann-Whitney and Kruskal-Wallis test.
min-max: Minimum-maximum, ISEP: Internalized Stigma of Epilepsy

Study Limitations

The current study has several limitations, including a small sample size consisting of only patients with generalized epilepsy and a lack of exploration into the relationship between seizure duration and self-stigma. The knowledge levels of epilepsy and seizure causes were not extensively examined.

CONCLUSION

Our study identified various factors influencing internalized stigma in epilepsy, highlighting the role of gender. However, it is important to note that we initially aimed to include patients with both focal and generalized epilepsy. Due to recruitment challenges, the final sample consisted of patients with generalized epilepsy. This limitation may have affected the generalizability of our conclusions, but we believe our findings still provide valuable insights into this specific group. In conclusion, our study underscores the need for raising awareness and enhancing knowledge to reduce epilepsy-related stigma.

Ethics

Ethics Committee Approval: This study was approved by the Research Ethics Committee of the Faculty of Medicine, Universitas Sumatera Utara (number: 2/KEPK/USU/2023, date: 20.03.2023).

Informed Consent: A written informed consent form was obtained from each patient.

Presented in: The study has been presented as a virtual poster presentation at the International League Against Epilepsy Congress 2023.

Footnotes

Authorship Contributions

Surgical and Medical Practices: F.I.F., A.N.Z.N., Concept: F.I.F, A.F., A.K., Design: F.I.F., A.F., A.N.Z.N., Data Collection or Processing: A.N.Z.N., O.A.D., Analysis or Interpretation: F.I.F., O.A.D., Literature Search: F.I.F., A.F., A.N.Z.N., O.A.D., Writing: F.I.F., A.K., O.A.D.

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Evaluation of Patients Monitored in Long-term Video-electroencephalography: Clinical and Demographical Specificities with Management Implications

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Abstract

Objective: Long-term video-electroencephalography monitoring (LTVEM) is an invaluable technique to assess patients with epilepsy, specifically for differential diagnosis and managing drug-resistant epilepsy. LTVEM plays a crucial role in the surgical management of epilepsy. We aimed to determine the clinical and demographic specificity of patients monitored at the LTVEM unit and the optimal length of hospitalization to decide on management.

Methods: Demographic data, electrophysiological findings, seizure types, duration, latencies, length of stay, and treatment of 96 consecutive adult patients who were monitored at the LTVEM unit between August 2023 and February 2024 were retrospectively evaluated.

Results: We identified 49 (51%) epileptic patients, 34 (35.4%) non-epileptic patients, and 9 (9.4%) patients with coexistence of epilepsy and psychogenic non-epileptic seizure (PNES). The latency of the first PNES attack was shorter than that of the first epileptic attack. The mean seizure duration of patients diagnosed with PNES was longer than that of patients diagnosed with epilepsy. The mean latency time to first interictal epileptiform discharge (IED) in patients with generalized epilepsy was shorter than the mean latency time to first IED in patients with focal epilepsy. The mean length of stay of patients with focal epilepsy was significantly longer than that of patients with generalized epilepsy ($p < 0.001$).

Conclusion: One-third of the patients monitored in our LTVEM unit were diagnosed with PNES. The latency of the first seizures of patients diagnosed with PNES was shorter than that of patients diagnosed with epilepsy, whereas the seizure duration of PNES was longer. It has been revealed that the first IED latency in patients with focal-onset seizures, and probably related to this, the length of hospital stay is longer than that in patients with generalized epilepsy. We believe that the current study may be helpful in planning the LTVEM unit hospitalization period and appointments for different types of seizure.

Keywords: Epilepsy, epilepsy surgery, long-term video electroencephalography, psychogenic non-epileptic seizures

INTRODUCTION

Although epilepsy is one of the oldest diseases of humans, it remains a challenging disease in terms of differential diagnosis.¹ Almost a century ago, the invention of electroencephalography (EEG) made it easier to determine whether a patient has epilepsy. Still, a much more important cornerstone was the invention of video recording and its use with EEG.¹

Seizures are transient events rarely observed in the clinic or recorded on routine outpatient EEG; therefore, video recordings of events are a powerful extension of anamnesis because they may answer the questions in physicians' minds.¹ In addition, developing technologies, such as long-term video EEG monitoring (LTVEM), may be more helpful in differentiating epilepsy, determining the epileptogenic zone in the brain, and evaluating surgical aspects of epilepsy management.²

Although the number of LTVEM units has been increasing daily, there are still some difficulties and uncertainties in patient management, appointment protocols, and evaluation of patients' clinical and electrophysiological findings.³

In this study, we aimed to determine the clinical and demographic characteristics of patients monitored at the LTVEM unit and the optimal duration of hospital stay required to diagnose and decide on treatment as medical, surgery, or none.

METHODS

We retrospectively analyzed all 96 patients monitored at the LTVEM unit of a tertiary healthcare center between August 2023 and February 2024. Clinical information including gender, age, age at diagnosis, indication for LTVEM unit referral, length of hospital stay, interval between the last seizure and LTVEM recording, latency to the first interictal epileptiform discharge (IED), latency to epileptic or non-epileptic seizure, duration and number of seizures during LTVEM, frequency of seizure in daily life, and anti-seizure medication (ASM) were recorded.

All EEGs were performed using a 32-channel video EEG (Micromed Sd ltm 128) according to the international 10-20 system. Standard bipolar montage and other montages were used.

Patients underwent LTVEM for differential diagnosis, localization of seizure focus, or defining therapy [medical, vagal nerve stimulation (VNS), or epilepsy surgery].

ASM were gradually decreased by one-third of the total daily dosage. If the patient had frequent and/or nonamenable seizures, the ASM was not changed, or dose reduction was performed more slowly.

Imaging findings were classified as localized encephalomalacia, focal cortical dysplasia, mesial temporal sclerosis, pachygyria, tumor, or non-specific findings (Table 1).

Patients' seizure types were classified as epileptic, psychogenic non-epileptic seizure (PNES), and mixed (both epileptic and non-epileptic) by three neurologists (one epileptologist, one clinical neurophysiologist, and one specialist) according to the International League Against Epilepsy 2017 classification.

The study was approved by the Local Ethics Committee of Ankara Etlik City Hospital (decision no: AEŞH-BADEK-2024-076, date: 06.03.2024).

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows, version 26.0 (IBM Corporation, Armonk, NY, USA). Descriptive analyses were presented using numbers, percentages, medians, and minimum-maximum range. Shapiro-Wilk test was used to determine whether

the variables were normally distributed. The Mann-Whitney U test was used to compare non-parametric data between two independent groups, and the Kruskal-Wallis test was used to compare three or more independent groups. The relationships between variables were evaluated using Spearman's correlation tests. A p value 0.05 was considered statistically significant. Figures and tables were created using Microsoft Word 2010 and SPSS.

RESULTS

The mean age of all patients was 35.83 ± 11.146 years (range, 20-64 years), 56 patients were women (58.3%), and the mean time since diagnosis was 15.74 ± 13.361 years. 83.3% of patients (n=80) had previously been diagnosed with epilepsy. 26.0% (n=25) of patients had been receiving monotherapy, and 51.0% (n=49) had been receiving polytherapy. Twenty-one patients were untreated (Tables 1, 2).

The indication for hospitalization for 50% (n=48) of patients was differential diagnosis (whether the patient has epilepsy or not), for 15.6% (n=15) to determine the epileptogenic zone, and for 34.4% (n=33) to decide the treatment modality (Table 1).

Fifty-eight patients were diagnosed with epilepsy; 13 patients had generalized-onset epilepsy and 41 with focal-onset epilepsy. We did not observe epileptic seizures or note interictal discharges during LTVEM in 3 out of the remaining 4 patients; however, based on the seizure videos recorded outside the hospital, we considered the diagnosis of epilepsy. It could not be determined whether the seizures of the remaining patient had a focal or generalized onset.

Thirty-four patients had PNES, but 9 of them had both epileptic and non-epileptic seizures. In 4 of the 96 patients, we identified pathologies such as syncope, which is attributed to cardiac etiology (n=1) and parasomnia (n=1), rather than epilepsy or PNES. No pathological findings were identified in the LTVEM recordings of the remaining patients.

Neuroimaging studies are summarized in Table 1. One patient did not undergo any cranial imaging.

The mean duration of LTVEM was 4.81 ± 2.221 day (range, 1-11), and the duration was shorter in the generalized epilepsy group compared with the focal epilepsy group ($p < 0.05$). The focal epilepsy group showed a positive correlation between the latency of the first IED and the latency of the first seizure and also the duration of VEM. However, findings regarding the latency of the first IED showed no significant difference according to epileptic localization (generalized or focal) ($p > 0.05$) (Table 3).

A correlation analysis was conducted to determine the relationship between the duration of hospitalization (days), total number of PNES attacks, and total number of epileptic seizures during the LTVEM process (Table 4). There was no significant relationship between the duration of hospitalization and the total number of attacks or seizures ($p > 0.05$).

Our study showed that 35.4% (n=34) of all patients did not require epilepsy treatment, and 7 (20.5%) of these patients had previously been followed up with refractory epilepsy or drug-resistant epilepsy (DRE).

MAIN POINTS

- Referral delays (15.74 years in this study) for patients with epilepsy to tertiary centers significantly postpone surgical evaluations, underscoring the need for earlier referrals.
- A 5-day follow-up period in long-term video electroencephalography monitoring (LTVEM) units is sufficient, supporting the recommendation to align appointment scheduling with this timeframe to ensure clarity and efficiency.
- Six of our nine patients with coexisting psychogenic non-epileptic seizure (PNES) and epilepsy experienced a PNES episode followed by an epileptic seizure, highlighting the need for careful decision-making in cases with PNES.
- We did not diagnose epilepsy in approximately one-third of our patients, and approximately one-fifth of these were followed with a diagnosis of drug-resistant epilepsy (DRE), highlighting the importance of considering PNES in the differential diagnosis of DRE.

Table 1. Descriptive findings related to nominal data

		n	%
Gender	Female	56	58.3
	Male	40	41.7
Diagnosis of epilepsy	Yes	80	83.3
	No	16	16.7
Indication for hospitalization	Epileptic/non-epileptic differentiation	48	50.0
	Determining epileptic localization	15	15.6
	Determining treatment	33	34.4
Appropriate treatment	Medical	39	40.6
	Vagal nerve stimulation	11	11.5
	Surgery	10	10.4
	No epilepsy treatment	34	35.4
Radiological findings	Invasive EEG	2	2.1
	Normal MRI/non-specific findings	62	64.6
	Localized encephalomalacia	12	12.5
	Focal cortical dysplasia	4	4.2
	Mesial temporal sclerosis	13	13.5
	Pachygyria	1	1.0
	Tumor	2	2.1
Diagnosis of LTVEM	Cerebral hemiatrophy	1	1.0
	Epilepsy	49	51.0
	PNES	34	35.4
Treatment received before LTVEM	Epilepsy+PNES	9	9.4
	Monotherapy	25	26.0
	Polytherapy	49	51.0
Epileptogenic localization	No treatment	21	21.9
	Focal	41	42.7
	Generalized	13	13.5

EEG: Electroencephalography, LTVEM: Long-term video EEG monitoring, PNES: Pshycogenic non-epileptic seizure, MRI: magnetic resonance imaging

Table 2. Descriptive findings regarding continuous variables

	Min	Max	Mean	SD	Median
Age (years)	20	64	35.83	11.146	34
Duration of epilepsy	1	55	15.74	13.361	13
Length of hospital stay (days)	1	11	4.81	2.221	5
Time from first non-epileptic seizure during LTVEM (hours)	1	124	28.79	35.655	13
Time from first epileptic seizure during LTVEM (hours)	1	162	49.17	47.882	24
Time from first interictal epileptiform discharge during LTVEM (minutes)	1	6000	448.17	1120.654	79
Total number of seizures during LTVEM	0	19	2.95	3.712	2
Total number of non-epileptic seizures during LTVEM	0	14	0.71	1.886	0
Total number of epileptic seizures during LTVEM	0	19	2.24	3.600	0
The shortest seizure duration (seconds)	3	1200	69.91	164.881	37.5
The longest seizure duration (seconds)	6	1206	151.47	228.195	80
Avarage seizure duration (seconds)	6	1203	104.00	179.785	58.5
Time between last seizure and LTVEM admission (days)	1	3650	89.44	395.442	10

SD: Standard deviation, LTVEM: Long-term video electroencephalography monitoring, min: Minimum, max: Maximum

Table 3. Differences in time from epileptic localization to first interictal epileptiform discharge during LTVEM

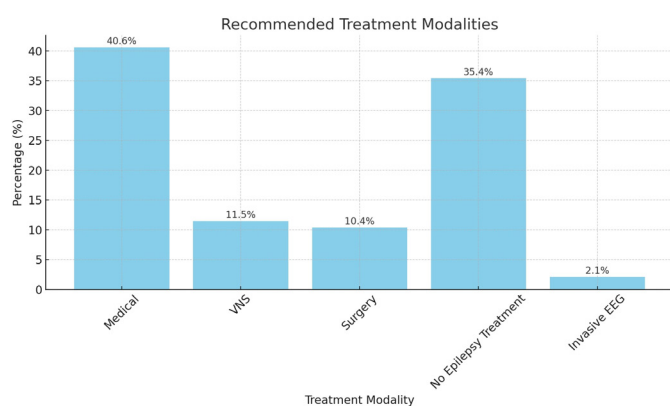
	Epileptic localization	n	Mean	SD	Mean rank	Z	p
Time to first interictal epileptiform discharge during LTVEM (minutes)	Focal	41	390.00	910.780	28.54	-1.876	0.061
	Generalized	11	151.91	380.084	18.91		

SD: Standard deviation, LTVEM: Long-term video electroencephalography monitoring

Table 4. Correlation analysis results between hospital stay length and total number of non-epileptic and epileptic seizures during LTVEM

		Total number of non-epileptic seizures during LTVEM	Total number of epileptic seizures during LTVEM
Length of hospital stay (days)	r	-0.030	0.117
	p	0.772	0.255

LTVEM: Long-term video electroencephalography monitoring

**Figure 1.** Treatment modalities based on LTVEM results

EEG: Electroencephalography, LTVEM: Long-term video EEG monitoring, VNS: Vagal nerve stimulation

VNS was deemed appropriate for 11.5% (n=11) of the patients, and LTVEM recorded with scalp electrodes was insufficient in 2 patients, so invasive EEG was considered. The treatment modalities proposed are detailed in Figure 1. Epilepsy surgery was indicated for 10.4% (n=10) of the patients, but according to the interdisciplinary joint session results, invasive EEG was proposed for five of the patients.

DISCUSSION

One of the key findings of this study is that referral of epilepsy patients to tertiary centers is delayed because we determined that the time elapsed from the time of diagnosis was 15.74 years (range, 1-55). Therefore, surgical evaluation of these patients is still being delayed. In studies conducted in developing countries where patients who underwent epilepsy surgery were scanned retrospectively, an average waiting time of 18.9,⁴ 23,⁵ and 20-21⁶ years was observed. In contrast, studies from industrialized countries have shown shorter times, ranging from 10.4⁵ to 16.9⁴ years. Because earlier surgery can prevent significant morbidity and premature death,⁷ it is crucial to encourage physicians from secondary healthcare centers, as well as patients with epilepsy, to refer to tertiary centers for surgical consideration.

Previous studies on the optimal duration of LTVEM showed conflicting results because of disparities across studies; however,

in our study, approximately 5 days (4.81±2.221) were found to be sufficient for patients followed in the LTVEM unit, and this finding is consistent with studies reporting heterogeneous groups of patients.⁸⁻¹⁰ In regions like our country, where centralized appointment systems are used, scheduling appointments for LTVEM patients at intervals of 5 days is recommended to prevent confusion. However, patients are not advised to adhere strictly to the 5-day rule because shorter or longer hospitalization periods may be necessary.

It is well known that the differential diagnosis of epilepsy and PNES continues to challenge physicians¹¹ and this differential diagnosis is crucial, as a misdiagnosis can lead to unnecessary medication for patients with PNES and may leave epilepsy patients untreated. It is evident that this can result in unintended consequences, such as unnecessary drug side effects, increased economic burden, leaving the epilepsy patient without treatment, and even death (e.g., SUDEP). In routine practice, we aim to make diagnostic decisions after observing an average of 3 seizures in our patients during LTVEM (average number of total seizures during LTVEM: 2.95±3.712). However, in this study, PNES episodes were observed less frequently than epileptic seizures (0.71±1.886 vs. 2.24±3.600). Although Foong and Seneviratne¹⁰ found that PNES episodes occur later, our study showed that PNES patients experience seizures earlier during the LTVEM process compared with epilepsy patients. (28.79±35.655 vs. 49.17±47.882 hours). The coexistence of PNES and epilepsy is not negligible according to our study (9.4%, n=9 patients had PNES and epilepsy) and literature.^{11,12} Another point is that 6 of 9 patients with mixed seizures had experienced PNES before epileptic seizure during LTVEM. Therefore, we suggest not rushing the discharge of LTVEM patients who experience a PNES episode.

As mentioned in the literature, identifying PNES constitutes a clinical challenge. For example, Sanabria-Castro et al.¹³ concluded that 12.8% of the DRE patients had PNES, moreover up to 50% of patients referred to an epilepsy center for VNS with a diagnosis of DRE were actually diagnosed with PNES in the study by Benbadis et al.¹⁴ In our study, similar to the literature, the number of patients who were previously diagnosed with DRE but were later found to have been misdiagnosed and did not require epilepsy treatment after LTVEM was not inconsiderable. According to the results of our study, no epilepsy was detected after LTVEM in 34 patients, however 7 of whom (20.5%) were followed up with a diagnosis of DRE previously.

The results of studies on the latency of the first IED in LTVEM patients are contradictory in the literature. Although some studies have found no difference between focal and generalized epilepsy,^{15,16} others have shown that IEDs emerge earlier in generalized epilepsies.¹⁷ In our study, the difference in the latency to the first IED between focal and generalized epilepsies was not significant (Table 3). The small sample size might be the reason for this. Although there was no significant difference in IED latencies, the average length of hospital stay for focal epilepsy patients was longer than that for those with generalized epilepsy. The possibility that focal epilepsy patients may be candidates for surgical treatment necessitated more careful and extended evaluations. Additionally, in some patients, the need for additional radiological imaging [such as functional magnetic resonance imaging (MRI), MRI corticography, or positron emission tomography] may have prolonged this duration.

Approximately 20% of the patients analyzed (10 requiring VNS, 12 requiring surgery and/or invasive investigations) required advanced treatment modalities, and when patients with PNES were excluded, this rate increased to nearly one-third. Moreover, our study, while slightly lower than non-selective studies in the literature,^{18,19} demonstrated that approximately one-third of the patients were diagnosed with PNES, further underscoring the significance of LTVEM.

Study Limitations

The limitations of this study include its retrospective design and small sample size. To enhance our understanding of LTVEM and optimize patient management, future research should focus on larger-scale, prospective studies.

CONCLUSION

In conclusion, our study highlights the significance of LTVEM by demonstrating a high rate of diagnostic changes before and after LTVEM. Additionally, this study may provide valuable insights into the duration of LTVEM hospitalization for different seizure types and assist in scheduling or appointment planning for LTVEM units.

Ethics

Ethics Committee Approval: The study was approved by the Local Ethics Committee of Ankara Etlik City Hospital (decision no: AEŞH-BADEK-2024-076, date: 06.03.2024).

Informed Consent: Retrospective study.

Presented in: This study was presented as an oral presentation at the 14th National Epilepsy Congress on May 18, 2024.

Footnotes

Authorship Contributions

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

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

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Epilepsy Surgery Due to Gliotic Scar Lesion in a Patient with Disconcordant Electroencephalogram Features

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Abstract

Surgical evaluation should be considered in all patients with refractory focal epilepsy. However, surgical treatment may be neglected in patients with refractory epilepsy associated with scar lesions. This case report presents a 20-year-old woman with refractory seizures who presented with a sequel gliotic lesion in the left frontal region due to intracranial hemorrhage during infancy. The patient's seizures were often hyperkinetic during sleep. She was evaluated as a surgical candidate because she had seizures 3-4 days a week under four antiseizure agents. The electroencephalogram revealed prominent interictal discharges in the contralateral hemisphere. Resective surgery was planned after discussion with the epilepsy surgery council. Frontal lobectomy was performed. The patient has been followed up for 5 months without seizures and motor deficits.

Keywords: Refractory, focal, epilepsy, resective, surgery

INTRODUCTION

Approximately 20-30% of patients with epilepsy are refractory and 5-10% may be candidates for surgery.¹ It has been shown that approximately 60% of patients with drug-resistant focal epilepsy become seizure-free 1 year after epilepsy surgery, and it is known that resective surgery is increasingly accepted as a curative treatment option.¹ Although the most successful outcomes of epilepsy surgery are hippocampal sclerosis, low-grade tumors, and vascular malformations, successful results are also obtained in epilepsy associated with glial scars. However, in clinical practice, surgical options may be neglected for refractory epilepsy associated with scar lesions.² Surgical evaluation should be considered in all patients with refractory focal epilepsy and presumed lesion.

Ictal and interictal discharges are usually expected ipsilateral to the lesion in patients with epilepsy. However, even rare, contralateral or bilateral ictal electroencephalogram (EEG) abnormalities can be observed in some patients with early-onset unilateral hemispheric lesions.³

In this report, we present the successful surgery of a patient with refractory epilepsy associated with scar tissue who presented with contralateral EEG findings.

CASE PRESENTATION

A 20-year-old female patient was admitted to the outpatient clinic with refractory seizures. She had intracranial hemorrhage due to late hemorrhagic disease in a newborn at the age of 45 days. Between 45 days and 2 years of age, the patient was followed up with phenobarbital because of seizures. After a seizure-free period between 2 and 9 years of age, seizures started again at the age of 9 years. The patient's seizures were often hyperkinetic seizures, such as fear, screaming, getting up, and trying to run in sleep with loss of awareness. The seizures occurred 3-4 nights a week and clustered 4-5 times a night. She had multiple traumatic injuries due to seizures. Motor mental development was normal. Cranial magnetic resonance imaging (MRI) revealed a large cystic encephalomalacia area in the left frontal

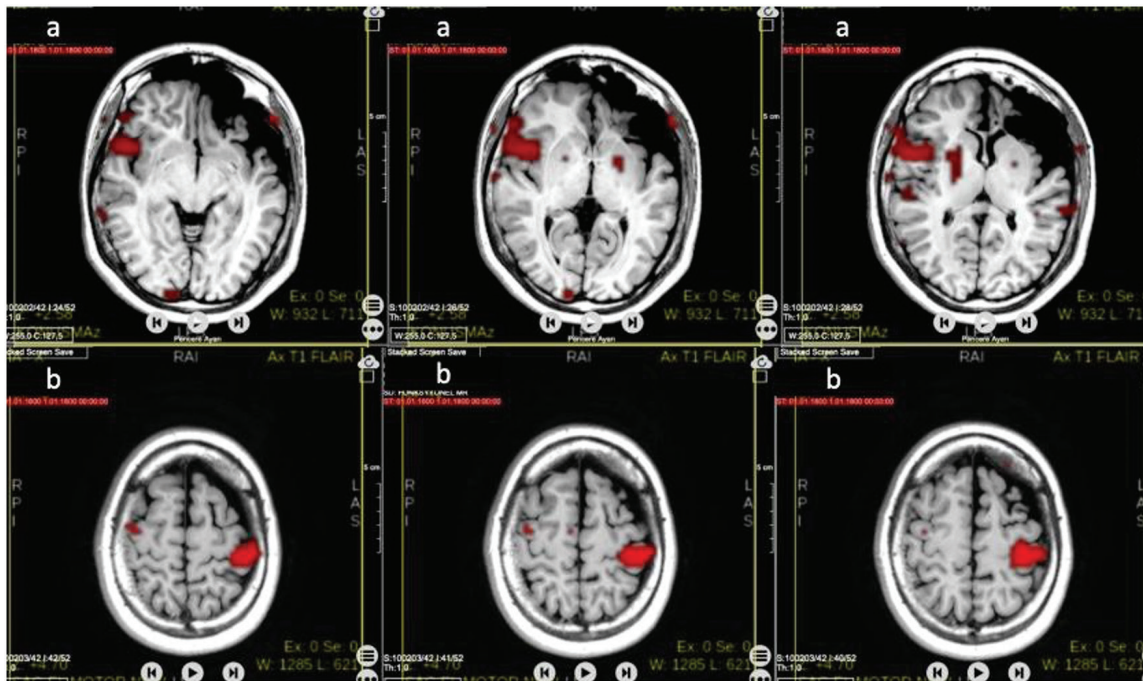


Figure 3. a) Language fMRI and, b) right hand motor function fMRI
MRI: Magnetic resonance imaging

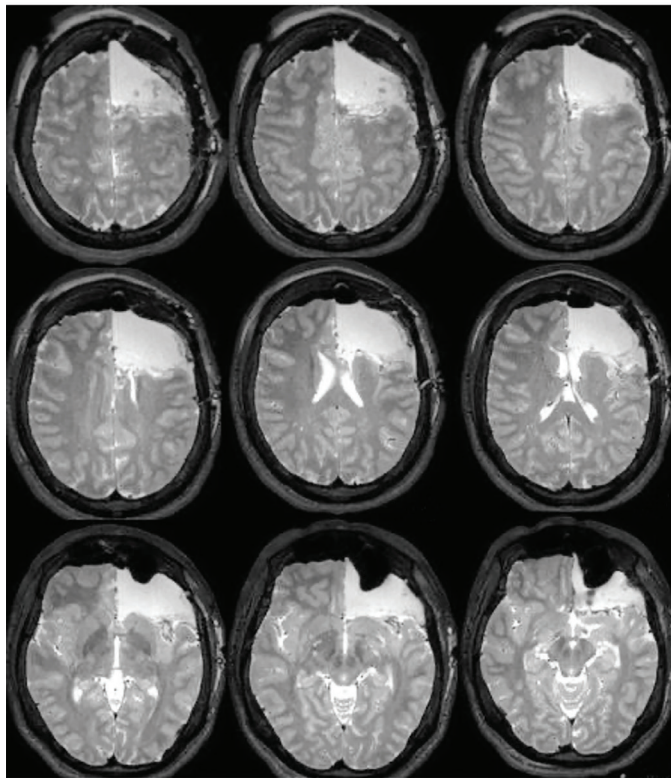


Figure 4. Postoperative MRI (axial T2) after frontal lobectomy
MRI: Magnetic resonance imaging

Surgical outcomes are believed to be worse in extratemporal lobe epilepsy than in temporal lobe epilepsy. However, the outcome may be good, especially in patients who underwent complete resection, as in our case.⁵

In the present case, interictal discharges occurred more frequently and with higher amplitude in the contralateral hemisphere. Contralateral or bilateral ictal EEG abnormalities although rare, can be observed in some patients with early-onset unilateral hemispheric lesions.^{1,3} One possible theory is that the damaged hemisphere initiates the seizure discharge but is unable to propagate it unilaterally; therefore, the discharge quickly spreads to the contralateral hemisphere. Another hypothesis is the deep location of the epileptogenic zone in the damaged hemisphere and scalp electrodes, leading to an asymmetric ictal pattern with reduced amplitude on the side of the lesion.³ Although interictal discharges are in the opposite hemisphere of the lesion, when the epileptic zone is compatible with lesion localization proven by other preoperative evaluation methods, the surgical option should not be ignored.

CONCLUSION

In this case report, we aimed to emphasize the importance of surgery for epilepsy associated with scar tissue. In addition, contralateral localization of interictal discharges should not be considered as a contraindication for surgery unless proven with other tests. Although the lesion was located in the left hemisphere, the patient had no motor deficit in the early period or during the current follow-up period after lobectomy. Resective surgery for the treatment of destructive space-occupying glial scar tissue resulted in a successful outcome with a seizure-free and motor deficit-free clinical outcome.

Ethics

Informed Consent: A written informed consent form was obtained from each patient.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Ö.E.Ç., B.G.A.T., C.İ., M.U., Concept: E.K., B.G.A.T., Design: E.K., B.G.A.T., Data Collection or Processing: Ö.E.Ç., B.G.A.T., E.T., Ç.Ö., Analysis or Interpretation: Ö.E.Ç., C.İ., M.U., Literature Search: Ö.E.Ç., B.G.A.T., Writing: E.K.

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

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Seizure Control in Patients with Dual Pathologies

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Keywords: Dual pathology, epilepsy, resective surgery

Dear Editor,

Temporal lobe epilepsy (TLE), the most common form of focal epilepsy, is resistant to treatment in 30% of cases. Dual pathologies (DP) with neocortical lesions such as hippocampal sclerosis and accompanying focal cortical dysplasia, vascular malformation, or tumor are important causes of failure in TLE surgery.^{1,2}

A total of 125 patients who underwent surgery for TLE in our clinic between January 2005 and February 2023 were retrospectively reviewed. Thirty-one patients who were diagnosed with DP due to neocortical tumor formation together with hippocampal sclerosis were included in the study. The control group consisted of 34 patients randomly selected from the same age group who were reported as mesial temporal sclerosis (MTS) by pathology. Patient characteristics, preoperative seizure characteristics, postoperative outcomes and complications were recorded. The mean ages of the DP and control groups were 30.3±14.8 (17 female, 14 male) and 30±11.2 years (10 female, 24 male), respectively. All patients presented with complaints of seizures. The age at first seizure was significantly older in the DP group (9.2±7.8 vs. 26.5±15.9, p<0.001), and JTC-type seizures were more common (n=17, 54.8%; p=0.0119). Total resection was performed in 24 DP patients (77.4%). The most common pathological diagnoses in this group were oligodendroglioma (n=12, 38.7%) and DNET (n=7, 22.6%). Engel 1A seizure control: was achieved in 19 DP patients (61.3%) and in 23 controls (67.6%). There was no difference between the groups in terms of postoperative seizure freedom (p=0.6143). During the mean follow-up period of 44.8±35.1 months, 10 DP patients were reoperated due to recurrence. Postoperative hydrocephalus developed in 1 case (2.9%) in the control group. Two patients (6.5%) in the DP group were reoperated urgently due to postoperative intracerebral hematoma. Three patients (9.7%) in this group received treatment due to wound infection. There was no difference between the groups in terms of postoperative complications (p=0.0951).

In conclusion, DP should be considered in young adult-onset TLE in cases with MTS, and neocortical tumor. Therefore, in patients with DP, high seizure control can be achieved with low complications after resection of both lesions.

Footnotes

Authorship Contributions

Surgical and Medical Practices: P.E., A.B.D., A.B., Data Collection or Processing: P.E., Analysis or Interpretation: P.E., A.B.D., A.B., Writing: P.E.

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