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EDITORIAL

Dear Readers,

Wishing you healthy and happy days.

One of the most significant developments in epilepsy research in recent years has been the progress made in the field of genetics. In our country as well, genetic panel testing is being requested for an increasing number of patients. Particularly in the pediatric population, this practice is rapidly becoming part of routine clinical care.

But how confident are we in interpreting the results we receive from genetic laboratories? Do we feel adequately equipped to understand and evaluate these reports? In the coming years, we may all need to become more proficient in reading and interpreting genetic test results. Being prepared for this shift will undoubtedly be beneficial.

In this issue, we also present an original research article reporting that a genetic etiology was identified in 2.5% of patients followed in an epilepsy outpatient clinic. Even this figure is noteworthy and highlights the growing importance of genetic evaluation in epilepsy.

The September issue marks the beginning of a new academic season. We wish everyone a productive, successful, and enjoyable winter.

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

Archives of Epilepsy

Review

Utilization of Complementary and Alternative Medicine among People with Epilepsy: A Narrative Review

Siti Nor Aqilah Mohd Noor, Umar Idris Ibrahim, Pei Lin Lua

Universiti Sultan Zainal Abidin (UniSZA) Faculty of Pharmacy, Kampus Besut, Terengganu, Malaysia

Siti Nor Aqilah Mohd Noor BSc,

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Corresponding Author: Pei Lin Lua, PhD, Universiti Sultan Zainal Abidin (UniSZA) Faculty of Pharmacy, Kampus Besut, Terengganu, Malaysia, **E-mail:** peilinlua@unisza.edu.my

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Abstract

Epilepsy is one of the most common chronic neurological disorders, affecting approximately 50 million people worldwide, with nearly one-third of patients experiencing drug-resistant seizures. Although antiepileptic drugs remain the cornerstone of epilepsy management, concerns regarding adverse effects, treatment costs, withdrawal symptoms, and persistent seizures have led many people with epilepsy (PWE) to seek complementary and alternative medicine (CAM). This review aims to summarize the prevalence, types, motivations, information sources, and perceived effects of CAM use among PWE. A literature search of PubMed, Scopus, and ScienceDirect was conducted for studies published between 2015 and 2024 using the keywords "epilepsy", "complementary and alternative medicine", "CAM", "traditional medicine", "prevalence", and "motivation". We included sixteen eligible studies in this narrative review. CAM utilization varied substantially across different countries and was influenced by cultural beliefs, accessibility, affordability, and dissatisfaction with conventional treatment. Herbal medicine, faith-based healing, dietary interventions, and mind-body practices were the most commonly reported CAM modalities. While many patients perceive CAM as beneficial for seizure control, stress reduction, and overall well-being, concerns regarding medication non-adherence, delayed conventional treatment, herb-drug interactions, and misinformation remain significant. Healthcare professionals should encourage open communication regarding CAM use and provide evidence-based guidance to ensure its safe integration into epilepsy management. Further research is warranted to establish the safety and effectiveness of commonly used CAM therapies and to support their appropriate role in comprehensive epilepsy care.

Keywords: Epilepsy, complementary and alternative medicine, therapy, integrative medicine, traditional

INTRODUCTION

Affecting around 50 million individuals globally, epilepsy is one of the most prevalent neurological disorders and is a chronic illness characterized by recurring, uncontrolled convulsions.[1] Its prevalence is significantly higher in low- and middle-income countries, which account for over 80% of cases and where access to specialized care is generally limited. Advances in antiepileptic drugs (AEDs) have not changed the fact that about 30% of people with epilepsy (PWE) remain drug-resistant, resulting in persistent seizures, cognitive deficits, psychiatric comorbidities, and a lower quality of life.[2]

Although AEDs are the usual therapy, many PWE seek complementary and alternative medicine (CAM) because of their adverse effects, steep prices, withdrawal symptoms, and possible aggravation of seizures.[3] In some areas, stigma, false information, and limited access to medical treatment postpone appropriate care and encourage CAM use. CAM comprises non-conventional healthcare approaches, including biologically based therapies (herbal medicine and supplements), mind-body interventions (meditation, yoga, and acupuncture), manipulative techniques (massage and chiropractic care), and traditional systems such as Ayurveda, traditional Chinese medicine (TCM), and spiritual healing.[4,5] Its use in epilepsy treatment differs among societies and medical systems, thereby affecting its frequency, types, and indications.[6,7]

Although scientific evidence of CAM's efficacy in seizure management is limited, PWE widely utilize it. Studies reveal extensive CAM use in Western countries, often alongside AEDs, while in many African and Asian regions CAM is routinely used as a primary treatment because of cultural beliefs, accessibility, and cost.[8-10] Common practices such as faith healing, herbal medicines, and energy therapies highlight the need for educational programs to encourage evidence-based therapies.[11] Additionally, hazards such as herb-drug interactions, toxicity, and delayed access to conventional treatment underscore the significance of studying the role of CAM in epilepsy management.

This review seeks to evaluate the incidence of CAM use among PWE, key motives for use, preferred types, sources of information, and perceived effects of CAM in epilepsy care.

METHODS

This narrative review was conducted in accordance with the Preferred Reporting Items for systematic reviews and meta-analyses (PRISMA) guidelines.[12] A comprehensive search of PubMed, Scopus, and ScienceDirect was performed to identify studies published between 2015 and 2024. The search strategy employed Boolean operators and the following key terms: "epilepsy", "complementary and alternative medicine (CAM)", "prevalence", "motivation", and "traditional medicine".

Studies were eligible if they were quantitative research articles published in English and examined CAM use in relation to epilepsy, including prevalence, motivations, types, information sources, and perceived outcomes. Exclusion criteria included review articles, qualitative studies, case reports, and studies not directly assessing CAM in epilepsy. The study selection process is illustrated in the PRISMA flow diagram in Figure 1.

Data extraction focused on sample size, study location, CAM usage prevalence, motivations, types of CAM, information sources, and perceived effects. Findings were synthesized narratively without quantitative meta-analysis. To categorize CAM types, this review adopted the framework of the National Centre for Complementary and Integrative Health, which groups practices into five domains: whole medical systems, mind-body approaches, biologically based practices, manipulative and body-based therapies, and energy therapies.[13]

RESULT

Prevalence and Motivation for CAM Use

The prevalence of CAM use among PWE varies across regions and cultures. In the Middle East, CAM use is ubiquitous, primarily influenced by religious and cultural views. Common approaches include spiritual healing, herbal medicines, and dietary adjustments, which are frequently considered holistic solutions. One study found that 71.0% believed in CAM, while actual usage rates remained uncertain.[14] In Türkiye, CAM prevalence ranged from 20.8% to 82.0% across six studies.[15-20] The reported motivations for CAM use included complementing medical treatment (86.4%), reducing seizure frequency (54.1%), and eliminating seizures (25.0%).[18] Up to 24.1% of participants used CAM on medical advice. However, concerns persist that restricted communication with physicians and faith-based dependence may lead to AED withdrawal.

MAIN POINTS

- Complementary and alternative medicine (CAM) is widely used among people with epilepsy, with utilization influenced by cultural beliefs, accessibility, and concern about conventional treatment.
- Herbal medicine, faith-based healing, dietary interventions, and mind-body practices are the most reported CAM modalities.
- Perceived benefits of CAM include improved well-being and seizure control, although scientific evidence remains limited.
- Inappropriate CAM use may contribute to medication non-adherence, delayed treatment, and herb-drug interactions.
- Open communication and evidence-based guidance are essential for the safe integration of CAM into epilepsy management.

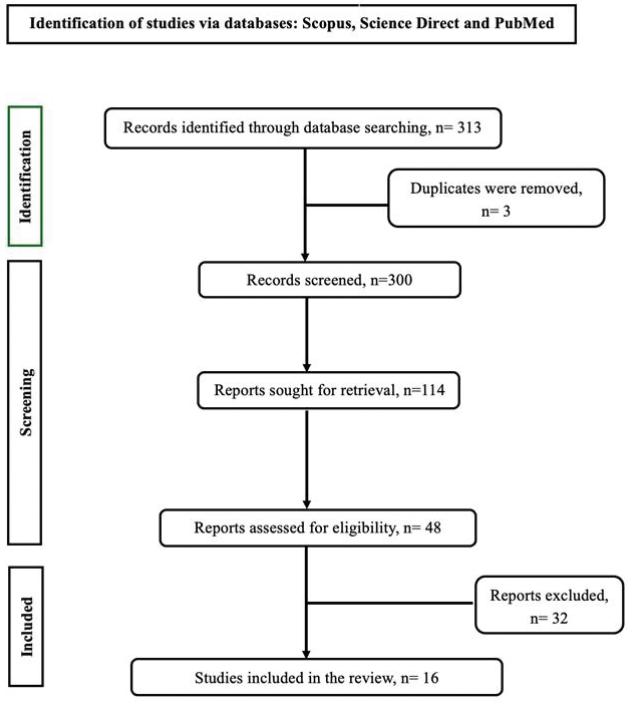

Figure 1. Flow summary of the article

In Europe, CAM is less common since the emphasis on evidence-based treatments predominates. Nonetheless, it is often used to alleviate stress and to improve well-being. In Germany, CAM use was 13.0%, and 81.0% of parents who used CAM utilized it owing to dissatisfaction with traditional therapies.[21] Among CAM users, motivations included improving health (31.5%), regulating seizures (25.2%), and managing AED adverse effects (22.1%).[22] Unlike users in certain countries, European users often combine CAM with AEDs and consult professionals before use.

In Asia, CAM is widely used, especially in low- and middle-income nations, because of cost, accessibility, and tradition. In Malaysia, prevalence ranged from 25.7% to 58.0%, with 72.5% claiming affordability and accessibility as significant reasons.[23-25] A separate study indicated that 27.5% of caretakers employed CAM; among these, 77.3% cited its natural basis and 55.3% cited seizure control as reasons.[26] In South Korea, prevalence reached 77.3%.[27] CAM in Asia is commonly used as both a primary and a supplementary therapy, while limited safety regulation raises safety concerns.

In North America, CAM is generally part of holistic care. One study indicated that 30% of caregivers used CAM for children with epilepsy, while 43.0% expressed future interest, frequently citing dissatisfaction with traditional therapy.[28] Another indicated that about 27.0% of patients had tried CAM.[29] CAM in North America is usually used alongside AEDs. Thus, CAM practices varied across locations according to culture, accessibility, and beliefs. A detailed summary of the prevalence rates and motivations for CAM use is presented in Table 1.

Types and Reasons for CAM Use

Whole Medical Systems include conventional techniques like homeopathy, which is used by 4.7% of Turkish users and 67.0%

Table 1. Prevalence and motivation for CAM use among PWE (2015-2024)

References	Population (n)	• Method • Study design • Data collection	• Prevalence (%) • n	Motivations to use CAM (%)	Country	Comments/key findings
Asadi-Pooya et al.[14]	PWE ≥18 years (n=101)	• Cross-sectional • Tool: - CIM perceptions and usage	• 70.0% • n=71	• N/A	Iran	Strong belief in CAM, but actual usage rate unknown.
Gündüz Oruç et al.[15]	PWE 18 to 70 years (n=101)	• Cross-sectional • Tools: - Use of CIM for epilepsy • Morisky medication adherence scale	• 20.8% • n=21 - 17.8% (used 1 CIM) • 3.0% (used 2 CIM)	• To improve general health (11.9%). • To control the seizure (8.9%).	Türkiye	Lower CAM use percentage compared to other Turkish studies.
Özer et al.[16]	PWE ≥18 years (n=150)	• Cross-sectional • Tools: - Fatalism Scale - Holistic Complementary and Alternative Medicine Questionnaire • Eight-item Morisky Medication Adherence Scale	• 82.0% • n=123	• N/A	Türkiye	Highest prevalence of CAM use reported (among all the articles in this review).
Tan and Kavurmaci[17]	PWE ≥18 years (n=96)	• Cross-sectional • Tools: - Questions related to epilepsy • Use of CAM	• 76.0% • n=73	• To complement medical treatment (86.4%). • To support epilepsy management (77.0%). • To reduce the frequency of seizures (54.1%). • To provide care and treatment (51.0%). • To eliminate seizures (25.0%).	Türkiye	CAM widely used alongside conventional treatment.
Duzgun et al.[18]	PWE ≥18 years (n=135)	• Cross-sectional • Tools: - Clinical characteristics - CAM use - Knowledge and opinions of CAM methods - Perception of Health Scale - Dispositional Hope Scale • Problem-Solving Inventory	• 29.0% • n=38	• Heard the success of CAM methods (39.4%). • Medical treatment failed (8.8.%). • Concerns of the side effects of medical treatments (10.0%). • CAM methods are safer (17.6%). • Physician advice (24.1%).	Türkiye	Physician recommendations played a role in CAM adoption.
Can et al.[19]	Parents of children with epilepsy <18 years (n=172)	• Descriptive and cross-sectional • Tools: - Use of CAM in the treatment for the children - Types of CAM - Effects of CAM • Source of information on CAM	• 28.5% • n=49	• More in line with the beliefs (42.9%). • Natural (34.7%). • Hope it might cure (28.6%). • Family members/acquaintances wanted (28.6%). • Reduce and control frequency of seizures (22.4%). • To improve general health (18.4%). • No improvement in symptoms (10.2%).	Türkiye	Belief systems strongly influence CAM usage.
İnce et al.[20]	Parents of children with epilepsy <18 years, (n=219)	• Cross-sectional • Tools: - Epilepsy management - Types of CAM - Methods and frequency of use CAM - Reasons use CAM - Effects of CAM • Source of information on CAM	• 30.1% • n=66	• To get rid of the disease (47.9%). • To reduce the symptoms of disease (49.3%). • Side effects of AEDs (24.7%).	Türkiye	Parents sought complete disease resolution through CAM.
Hartmann et al.[21]	Parents of PWE, <18 years (n=164)	• Prospective observational • Tools: - CAM use • Previous therapy	• 13.0% • n=21	• Desire to try every possible treatment option (95.0%). • CAM more natural (76.0%). • CAM has less side effects (81.0%). • Herbal and natural remedies are riskless (24.0%).	Germany	CAM seen as a last resort by parents seeking alternatives.

Table 1. Continued

References	Population (n)	• Method • Study design • Data collection	• Prevalence (%) • n	Motivations to use CAM (%)	Country	Comments/key findings
Bosak and Słowik[22]	PWE ≥18 years (n=473)	• Cross-sectional • Tools: - Types of CAM - Use of CAM - Source of information on CAM • Willingness of CAM in future	• 26.8% • n=127	• To improve general health (31.5%). • To control seizures (25.2%). • To counteract the side effects of AEDs (22.1%). • Natural and safe (21.2%).	Poland	Seizure control and general health were key concerns of CAM users.
Koh et al.[23]	PWE ≥18 years (n=140)	• Cross-sectional • Tool: • Access the usage of CAM amongst PWE	• 25.7% • n=36	• To try anything that help to alleviate the condition (86.1%). • Side effects AEDs (8.3%).	Malaysia	Symptom relief was the main reason for CAM use, while fewer users cited AED side effects as a concern.
Lau et al.[24]	PWE ≥18 years (n=61)	• Cross-sectional • Tools: - Practice of CAM • Beliefs about Medicine Questionnaire	• 42.6% • n=26	• Believed in CAM's efficacy (86.1%). • Satisfaction towards CAM (8.3%).	Malaysia	Higher satisfaction levels suggest strong belief in CAM effectiveness.
Farrukh et al.[25]	PWE ≥18 years (n=100)	• Cross-sectional • Tools: - Knowledge of CAM - Types and their perceived effectiveness of CAM - Attitude and practice of CAM • Malaysia Medication Adherence Scale	• 58.0% • n=58	• CAM is cheaper (62.1%). • CAM provides quick and additional belief (67.1%). • CAM was easily available (72.5%). • CAM provides a permanent cure (72.5%). • Use CAM due to fearing discomfort from allopathic medicines (76.4%). • CAM promotes self-healing (69.9%). • CAM providers give good information about CAM (67.6%).	Malaysia	High usage, mainly driven by affordability and accessibility.
Chen et al.[26]	PPE <21 years (n=178)	• Cross-sectional • Tools: - Epilepsy characteristics and conventional care utilization - Knowledge and usage of CAMs by caregivers	• 27.5% • n=49	• More natural treatment (73.7%). • Fewer side effects than AEDs (71.1%). • Reduce side effects of prescribed AEDs (47.4%). • Less expensive than AEDs (21.1%). • May improve child's seizure control and slow seizure progression (55.3%). • Seizure completely recovers (15.8%).	Singapore	Parents preferred CAM due to safety concerns and hopes of seizure control.
Jeong et al.[27]	Parents of PWE <19 (n=389)	• Cross-sectional • Tool: - Use of CAM in the past or present	• 77.3% • n=85	• N/A	Korea	High rate of CAM use among parents of children with epilepsy, but motivations remain unclear.
Beattie et al.[28]	Caregivers of children with epilepsy (n=225)	• N/A • Tools: - Information on religious beliefs and practices - Use of CAM	• 30.0% currently using CAM • 16.0% had used CAM • 43.0% to use in future • n=N/A	• Wishing to try other -prescribed treatments (27.0%). • Believed that prescribed medications were harmful (5.0%). • Medication inefficacy (14.0%). • Alternative therapies were more consistent with their beliefs (2.0%). • CAM methods worked for others (9.0%).	United States	Strong intention for future use, suggesting dissatisfaction with standard treatment.
Kenney et al.[29]	Parents of child with epilepsy (n=107)	• Cross-sectional • Tools: - Use CAM or not and the efficacy - Intend to continue the use of CAM	• 34.6% (used 1 CAM) • n=37 • 4.0% (used 3 or more CAM) • n=13	• N/A	United States	Limited data on motivations for CAM use.

CAM: Complementary and alternative medicine, PWE: People with epilepsy, CIM: Complementary and integrative medicine

of users in Germany.[18,21] Systems such as Ayurveda, TCM, Malay medicine, and Indian medicine are reported by 6.9%-25.0% of Malaysians.[23,25]

Mind-body approaches focus on spiritual and psychological well-being. Prayer and faith healing were extensively employed, with prevalence ranging from 38.4% in Malaysia to 88.0% in the U.S.[15,18,23,24,28] Use of yoga for stress alleviation ranged from 19.0% in Germany to 30.6% in Malaysia.[21,23] Meditation, hypnosis, and music therapy varied in popularity, with meditation being common among those seeking relaxation.[18,26]

Biologically based practices involve herbal medicines, diets, and supplements. Herbal medicine was reported by 25.6% of Turkish users and 67.0% of German users.[18,21] Dietary therapy ranged from 18.8% in Iran to 36.1% in Malaysia.[14,23] Supplement use, including vitamins and minerals, ranged from 30.0% to 45.0%.[20,25]

Manipulative and body-based therapies include physical therapies, such as massage therapy, ranging from 45.3% in Türkiye to 58.3% in Malaysia.[16,23] Chiropractic care was used by 10.0%-25.0% of participants, mainly in Germany and Malaysia.[21,25] Osteopathy, more widespread in the West, was reported by up to 57.0% of German users.[21] Other therapies included cupping (18.6%-27.3% in Türkiye) and reflexology.[16,23]

Energy therapies involve controlling energy fluxes. Prevalence of acupuncture use ranged from 6.3% in Iran to 47.2% in Malaysia.[14,23] Reiki was employed by 27.8% in Malaysia and other energy healing was employed by 31.5% in Poland.[22] These categories demonstrate diverse global usage and summary of CAM types and their prevalence is shown in Table 2.

Sources of CAM Information

Most PWE learned about CAM from family and friends, a process influenced by shared experiences and cultural norms.[15,28] Trust in social networks typically surpassed trust in expert guidance. Healthcare experts held conflicting views: some endorsed CAM as a supplement, while others highlighted safety concerns.[18,23] Online outlets and social media were major information sources, but were prone to misrepresentation.[22,24] Traditional healers and religious authorities strongly promoted faith-based approaches, such as prayer and Quranic healing.[28,29] Self-experimentation was also reported, particularly among those unsatisfied with traditional therapy.[19,25] Social, cultural, and healthcare access issues largely affected CAM decisions.

Perceived Effects of CAM Use

Positive Effects

Some interventions, such as acupuncture, relaxation techniques, and dietary adjustments, were associated with greater seizure control and stress reduction. Among TCM users, acupuncture appeared to reduce seizures.[27] Other consumers reported lower anxiety and greater well-being.[21,22]

The ketogenic and modified Atkins have demonstrated anticonvulsant potential. Many Malaysian CAM users reported

Table 2. Types of CAM used in epilepsy

Category	Types of CAM used (%)	Related studies	Comments/key findings
Whole medical systems	• TCM (13.7%) • Traditional Indian medicine (6.9%) • Traditional Malay medicine (12.0%) • Ayuverda (25.0%) • Homeopathy (4.7%-67.0%)	18,21-25	Traditional practices such as TCM, Ayurveda, and homeopathy show varied usage across regions.
Mind-body techniques	• Meditation (2.3%-12.8%) • Yoga (19.0%-30.6 %) • Prayer/faith-based healing (38.4%-88.0%) • Relaxation techniques (10.2%-43.8%) • Hypnotherapy (12.8%-26.7%) • Music therapy (6.1%-306%) • EEG biofeedback (22.0%)	15-19,21-24,26,28	Faith-based healing is the most common, while meditation and hypnotherapy have lower usage.
Biologically based practices	• Herbal medicines/traditional herbs (25.6%-67.0%) • Dietary supplements (32.3%-46.9%) • Diet therapy (10.2%-36.1%)	14-18,20-25	Herbal medicine and dietary supplements are the most commonly used biological treatments.
Manipulative and body-based therapies	• Massage therapy (6.1%-58.3%) • Reflexology (27.3%) • Cupping (18.6%) • Physiotherapy (13.7%) • Chiropractic (<7.0%-25.0%) • Spa/thermal therapy (34.0%) • Osteopathy (57.0%)	16,18,19,21-25,28	Massage therapy is widely used, while chiropractic and cupping therapy have lower prevalence.
Energy therapies	• Acupuncture (6.3%-47.2%) • Reiki (27.8%) • Energy healing (4.8%-31.5%)	14-16,18,22-26	Acupuncture is the most practiced, while Reiki and energy healing are less commonly used.

CAM: Complementary and alternative medicine, TCM: Traditional Chinese medicine, EEG: Electroencephalography

finding it beneficial and regarded it as curative.[25] Herbal medicines and spiritual practices were also considered to support emotional well-being.[18,23,28]

Negative Effects

Despite perceived benefits, concerns include delays in therapy or discontinuation of AEDs. Some studies have linked CAM use to poorer seizure control and increased emergency admissions owing to AED withdrawal.[14,16,25] False beliefs that CAM is a sole cure diminished adherence to medications.[18,28]

The lack of scientific validation and regulation also poses challenges. Herbal therapies can interact adversely with AEDs, reducing their effectiveness or increasing their side effects.[15,23] Studies have reported a decrease in seizure control associated with unsupervised herbal use.[22]

Caregivers of children often turned to CAM out of concern about the adverse effects of AEDs, despite insufficient clinical evidence.[28,29] Misinformation and limited awareness of the hazards of CAM may delay appropriate medical care when CAM is preferred over conventional treatment.[17] A summary of the perceived effects of CAM use is presented in Table 3.

DISCUSSION

This research highlights the widespread use of CAM among PWE, primarily in response to perceived limitations of conventional epilepsy therapies. Many patients sought CAM because of dissatisfaction with AEDs, concerns about side effects, and cultural or spiritual beliefs. While CAM is typically used alongside AEDs, some individuals accept it as a substitute, raising issues regarding treatment adherence, delays in medical intervention, and patient safety.[30,31] The expanding popularity of CAM underscores the need to critically analyse its impact on patient outcomes, physician-patient communication, and health policy.

A particularly striking conclusion was that healthcare providers recommended CAM. This undermines the prevailing notion that clinicians often discourage its use. Instead, it shows a lack of clearly defined clinical criteria, which may cause clinicians to acknowledge CAM without properly evaluating its benefits and risks.[18] Many patients perceived CAM as a more natural and safer alternative to AEDs, making it an attractive option for controlling epilepsy.[32,33] Although these views are typically rooted in valid concerns about AED side effects, misconceptions about the safety and effectiveness of CAM may lead to poorly informed treatment decisions, especially when CAM is taken without medical supervision.

Social and cultural forces also play a considerable role in CAM use. Many PWE rely on guidance from family members, religious leaders, or online sources rather than on medical experts.[34-36] In certain communities, epilepsy is regarded as a supernatural or spiritual ailment, leading individuals to seek traditional or faith-based therapies. While these treatments may offer emotional support, they typically lead to delays in seeking medical care, worsen seizure control, and raise the likelihood of poor outcomes. To bridge the gap between traditional practices and evidence-based care, culturally relevant instructional initiatives are needed.

Despite these issues, many patients use CAM in addition to, rather than as a substitute for, traditional therapy. This integrated strategy indicates confidence in the complementary benefits of CAM, especially given perceptions that CAM has fewer adverse effects than AEDs.[18,28,32] Some interventions, such as the ketogenic diet, have demonstrated therapeutic potential; however, many others remain uncontrolled and may pose considerable dangers, including drug interactions and variable dosing.[37]

A key issue is the delay in initiating conventional therapy among patients who prioritize CAM. Research has indicated that people who postpone AED use in favour of CAM often experience poorer seizure control, increased hospitalization, and avoidable

Table 3. Perceived effects of CAM use in epilepsy

	Perceived effect	Findings from studies	Related studies	Comment
Positive effects	Symptom and well-being	Stress reduction, seizure control in TCM users.	27	CAM could improve quality of life via symptom and well-being.
	Stress and anxiety reduction	CAM users reported less anxiety and stress, pursuing CAM for overall health enhancement.	21,22	CAM is perceived as beneficial for mental well-being.
	Dietary benefits	Ketogenic diet shows anti-convulsant properties.	25	Some CAM approaches could be beneficial.
	Emotional well-being	Herbal medicine and spiritual healing are commonly viewed as enhancing well-being, reinforcing CAM's appeal.	18,23,28	CAM is often chosen for psychological comfort and cultural reasons.
Negative effects	Dissatisfaction of AEDs and poor seizure control	Increased seizures due to AED discontinuation.	14,16,25	Worsened epilepsy was a negative consequent.
	False in cure belief	Some PWE believe CAM alone provides a permanent cure, contribution to medication non-adherence and higher seizure recurrence rates.	18,28	Misconceptions about CAM impact treatment adherence.
	Herb-drug interactions	Unregulated herbal medicine has resulted in side effects of AEDs.	15,23	CAM should be regulated for safety.
	Treatment delay	CAM use before AEDs treatment has led to prolonged seizure episodes.	17,28-29	Late access to medical care increase.

CAM: Complementary and alternative medicine, TCM: Traditional Chinese medicine, AED: Antiepileptic drug

consequences.[14,16] In extreme situations, some patients completely discontinue AEDs under the false belief that CAM offers a cure, thereby increasing the risk of seizure recurrence and life-threatening events.[18,28] The increased use of herbal medicines further complicates epilepsy care, as unregulated herbal medicines may interfere with AED metabolism, lower therapeutic efficacy, or cause toxicity.[15,23] These hazards underscore the importance of physician involvement in discussions about CAM to dispel misconceptions while preserving patient autonomy.

To address these issues, improved physician-patient communication is essential.[38,39] Patients must have access to reliable, evidence-based information regarding CAM, and clinicians must be trained to address CAM knowledgeably and respectfully. Public health campaigns should also aim to address CAM-related disinformation, especially on social media platforms, where untested treatments are widely promoted.[36] Integrating CAM information into medical training will enhance physicians' ability to assist patients in making safer, more effective treatment choices.[34]

Going forward, efforts should focus on strengthening CAM regulation, increasing public understanding, and enhancing healthcare providers' engagement in CAM-related debates. More rigorous clinical research is necessary to investigate the safety and efficacy of routinely used CAM therapies, particularly when coupled with AEDs. Health authorities must also adopt stringent quality- control standards for herbal and other alternative medicines to limit the hazards associated with self-medication and unregulated products.[15,21] Through a coordinated approach incorporating teaching, research, and regulatory supervision, healthcare systems can ensure that CAM is used appropriately and does not impair the quality of epilepsy care.

Study Limitations

This narrative review has several limitations. Limiting the search to three databases (Scopus, ScienceDirect, and PubMed) may have resulted in omission of pertinent studies from other sources. The emphasis on English-language publications may have excluded related studies in other languages, thereby impacting the thoroughness of the conclusions. The review predominantly focuses on the viewpoints of PWE, their parents, and caregivers and excludes comments from healthcare providers, CAM practitioners, and legislators. Understanding these holistic perspectives is crucial for enhancing physician-patient communication, strengthening policies, and incorporating CAM into clinical practice. As qualitative narrative review, our paper synthesises findings descriptively rather than providing quantitative analyses of statistical patterns, therapeutic efficacy, or cost-effectiveness. This review has identified significant gaps and potential avenues for future research, providing essential insights into the motivations, hazards, and obstacles associated with CAM use among patients with epilepsy.

CONCLUSION

The use of CAM among PWE is widespread across various regions, driven by dissatisfaction with AEDs, cultural traditions, and the pursuit of holistic and natural health approaches. Herbal therapies, faith-based healing, mind-body interventions, and dietary modifications were the most commonly utilized CAM modalities. While many patients reported benefits such as stress reduction and perceived seizure control, significant risks, including delayed access to medical care, medication non-adherence, and herb-drug interactions, were identified. These findings underscore the importance of healthcare providers actively engaging in open discussions with patients regarding CAM use to ensure informed decision-making and adherence to evidence-based treatments. Public health initiatives should address the spread of misinformation, promote culturally sensitive education, and advocate for better regulation of CAM products. Future research should focus on rigorous evaluation of the safety and efficacy of commonly used CAM therapies in epilepsy management. By addressing these critical challenges, healthcare systems can support the safer integration of CAM practices without compromising the treatment outcomes in patients with epilepsy.

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For transparency, the authors note that an artificial intelligence-assisted language model (ChatGPT, OpenAI) was utilized to support text editing and language correction. This assistance was limited to linguistic refinement; all scientific content, critical analysis, and final editorial decisions were made exclusively by the authors.

Footnotes

Authorship Contributions

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REFERENCES

1. World Health Organization. Epilepsy [Internet]. Geneva: World Health Organization; [cited 2024 Jun 24]. [Crossref]
2. Wahab A. Difficulties in treatment and management of epilepsy and challenges in new drug development. *Pharmaceuticals (Basel).* 2010;3(7):2090-2110. [Crossref]
3. Perucca E, Gram L, Avanzini G, Dulac O. Antiepileptic drugs as a cause of worsening seizures. *Epilepsia.* 1998;39(1):5-17. [Crossref]
4. Langevin HM. Moving the complementary and integrative health research field toward whole Person health. *J Altern Complement Med.* 2021;27(8):623-626. [Crossref]
5. Tabish SA. Complementary and alternative healthcare: is it evidence-based? *Int J Health Sci (Qassim).* 2008;2(1):V-IX. [Crossref]
6. Penson RT, Castro CM, Seiden MV, Chabner BA, Lynch TJ Jr. Complementary, alternative, integrative, or unconventional medicine? *Oncologist.* 2001;6(5):463-473. [Crossref]
7. World Health Organization. Legal status of traditional medicine and complementary/alternative medicine: a worldwide review [Internet]. Geneva: World Health Organization; 2001 [cited 2023 Feb 12]. [Crossref]
8. Neni SW, Latif AZ, Wong SY, Lua PL. Awareness, knowledge and attitudes towards epilepsy among rural populations in East Coast Peninsular Malaysia: a preliminary exploration. *Seizure.* 2010;19(5):280-290. [Crossref]
9. Krishnaiah B, Alwar SP, Ranganathan LN. Knowledge, attitude, and practice of people toward epilepsy in a South Indian village. *J Neurosci Rural Pract.* 2016;7(3):374-380. [Crossref]
10. Molla A, Mekuriaw B, Habtamu E, Mareg M. Knowledge and attitude towards epilepsy among rural residents in southern Ethiopia: a cross-sectional study. *BMC Public Health.* 2021;21(1):420. [Crossref]

11. National Cancer Institute. Complementary, alternative, or integrative health: what's in a name? [Internet]. Bethesda (MD): National Cancer Institute; [cited 2023 Dec 28]. [Crossref]
12. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med.* 2009;151(4):264-269, W64. [Crossref]
13. Koithan M. Introducing complementary and alternative therapies. *J Nurse Pract.* 2009;5(1):18-20. [Crossref]
14. Asadi-Pooya AA, Homayoun M, Sharifi S. Complementary and integrative medicine in epilepsy: what patients and physicians perceive. *Epilepsy Behav.* 2019;101(Pt A):106545. [Crossref]
15. Gündüz Oruç F, Atan G, Şeker D. The relationship between medication adherence and complementary medicine use in epilepsy patients. *Epilepsy Behav.* 2024;154:109761. [Crossref]
16. Özer Z, Bahçecioğlu Turan G, Karaman S. Effects of fatalism perception and attitudes towards complementary and alternative medicine on medication adherence in patients with epilepsy. *Eur J Integr Med.* 2023;61:102271. [Crossref]
17. Tan M, Kavurmaci M. Complementary and alternative medicine use in Turkish patients with epilepsy. *Altern Ther Health Med.* 2021;27(4):19-23. [Crossref]
18. Duzgun U, Yesiltas F, Karadas O, Beysan C, Sari O. Investigation of complementary and alternative medicine use in Turkish patients with epilepsy. *Int J Curr Med Biol Sci.* 2023;3(1):64-71. [Crossref]
19. Can V, Bulduk M, Ayşin N, Kurt Can E, Aydın N. Determination of complementary and alternative medicine use frequency and related factors in children with epilepsy: a descriptive cross-sectional study from eastern Turkey. *Epilepsy Behav.* 2024;160:110041. [Crossref]
20. İnce T, İnce G, Üzüm Ö, Aydın A. Parent-reported complementary and alternative medicine use among pediatric patients with epilepsy at two tertiary centers in Turkey - prevalence and predictors. *Epilepsy Behav.* 2023;143:109226. [Crossref]
21. Hartmann N, Neininger MP, Bernhard MK, et al. Use of complementary and alternative medicine (CAM) by parents in their children and adolescents with epilepsy - prevelance, predictors and parents' assessment. *Eur J Paediatr Neurol.* 2016;20(1):11-19. [Crossref]
22. Bosak M, Słowik A. Use of complementary and alternative medicine among adults with epilepsy in a university epilepsy clinic in Poland. *Epilepsy Behav.* 2019;98(Pt A):40-44. [Crossref]
23. Koh MY, Khor SB, Lim KS, et al. Use of complementary and alternative medicine among adult with epilepsy: experiences from a single epilepsy center in Malaysia. *Neurosci Res Notes.* 2022;5(1):109. [Crossref]
24. Lau BT, Makmor-Bakry M, Tan HJ, Ng SY, Md Redzuan A. Patient's practice of complementary and alternative medicine (CAM) for the management of epilepsy. *J Adv Pharm Educ Res.* 2020;10(4):1-7. [Crossref]
25. Farrukh MJ, Makmor-Bakry M, Hatah E, Jan TH. Impact of complementary and alternative medicines on antiepileptic medication adherence among epilepsy patients. *BMC Complement Med Ther.* 2021;21(1):50. [Crossref]
26. Chen C, Chong YJ, Hie SL, et al. Complementary and alternative medicines use among pediatric patients with epilepsy in a multiethnic community. *Epilepsy Behav.* 2016;60:68-74. [Crossref]
27. Jeong MJ, Lee HY, Lim JH, Yun YJ. Current utilization and influencing factors of complementary and alternative medicine among children with neuropsychiatric disease: a cross-sectional survey in Korea. *BMC Complement Altern Med.* 2016;16:91. [Crossref]
28. Beattie JF, Thompson MD, Parks PH, Jacobs RQ, Goyal M. Caregiver-reported religious beliefs and complementary and alternative medicine use among children admitted to an epilepsy monitoring unit. *Epilepsy Behav.* 2017;69:139-146. [Crossref]
29. Kenney D, Jenkins S, Youssef P, Kotagal S. Patient use of complementary and alternative medicines in an outpatient pediatric neurology clinic. *Pediatr Neurol.* 2016;58:48-52.e7. [Crossref]
30. Zhu Z, Dluzynski D, Hammad N, et al. Use of integrative, complementary, and alternative medicine in children with epilepsy: a global scoping review. *Children (Basel).* 2023;10(4):713. [Crossref]
31. Schachter SC. Complementary and alternative medical therapies. *Curr Opin Neurol.* 2008;21(2):184-189. [Crossref]
32. Sriranjini SJ, Sandhya K, Mamta VS. Ayurveda and botanical drugs for epilepsy: current evidence and future prospects. *Epilepsy Behav.* 2015;52(Pt B):290-296. [Crossref]
33. Lin CH, Hsieh CL. Chinese herbal medicine for treating epilepsy. *Front Neurosci.* 2021;15:682821. [Crossref]
34. Soto-Lara M, Silva-Loredo M, Monroy-Córdoba JR, Flores-Ordoñez P, Cervera-Delgadillo NG, Carrillo-Mora P. Alternative medicine therapies in neurological disorders: prevalence, reasons and associated factors. A systematic review. *Complement Ther Med.* 2023;73:102932. [Crossref]
35. Kissani N, Moro M, Arib S. Knowledge, attitude and traditional practices towards epilepsy among relatives of PWE (patients with epilepsy) in Marrakesh, Morocco. *Epilepsy Behav.* 2020;111:107257. [Crossref]
36. Shawahna R, Abdelhaq I. Important knowledge items with regard to the benefits of exercise for patients with epilepsy: findings of a qualitative study from Palestine. *Epilepsy Behav.* 2020;108:107099. [Crossref]
37. Pasca L, De Giorgis V, Macasaet JA, Trentani C, Tagliabue A, Veggiotti P. The changing face of dietary therapy for epilepsy. *Eur J Pediatr.* 2016;175(10):1267-1276. [Crossref]
38. Ricotti V, Delanty N. Use of complementary and alternative medicine in epilepsy. *Curr Neurol Neurosci Rep.* 2006;6(4):347-353. [Crossref]
39. Ng JY, Dhawan T, Dogadova E, et al. Operational definition of complementary, alternative, and integrative medicine derived from a systematic search. *BMC Complement Med Ther.* 2022;22(1):104. [Crossref]

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Original Article

In Vivo and *In Silico* Study of Lavender Extract in Pentylenetetrazol-induced Seizures Compared to Diazepam and Phenytoin in Male Mice

Simin Namvar Aghdahs, Saeed Alivand Paydari, Amir Pashaei

Azerbaijan Shahid Madani University Faculty of Basic Sciences, Department of Biology, Tabriz, Iran

Simin Namvar Aghdahs
Asst. Prof.,

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Corresponding Author: Asst. Prof., Simin Namvar Aghdahs, Azerbaijan Shahid Madani University Faculty of Basic Sciences, Department of Biology, Tabriz, Iran, **E-mail:** siminnamvar2@gmail.com

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Abstract

Objective: Lavender contains essential oils that can cross the blood-brain barrier and affect the activity of brain neurons. Therefore, its antiepileptic effects were investigated in this study.

Methods: Forty two male mice were randomly assigned to 7 groups of 6 mice each. Included: (1) control group receiving distilled water; (2) the kindled group receiving only pentylenetetrazol; (3) experimental groups that received extract at different doses of lavender; and (4) two experimental groups receiving diazepam and phenytoin. Epileptogenesis was assessed by monitoring chemical seizure scores. Memory was assessed using a novel object recognition (NOR) test. Histological changes were assessed by hematoxylin and eosin staining. The antioxidant effect of lavender extract was assessed by measuring malondialdehyde (MDA) levels. Binding affinities of phytochemical compounds were assessed by molecular docking.

Results: Data analysis indicated that treatment with *Lavadula* extracts had a pronounced effect on chemical kindling. The result of the NOR test demonstrated that lavender extract ameliorated memory impairment. Histological examination showed that lavender extract had neuroprotective effects in the CA3 region of the hippocampus. The data showed that pretreatment with lavender extract decreased brain MDA levels. *In silico* studies showed that lavender phytochemicals have a high affinity for $GABA_A$ receptors and voltage-gated sodium channels.

Conclusion: The findings suggest that lavender extract has considerable anticonvulsant, neuroprotective, and antioxidant effects on pentylenetetrazol-induced kindling in hippocampal tissue. These medicinal herbs may be beneficial for the treatment of seizures in humans; however, further investigation is warranted.

Keywords: Epilepsy, pentylenetetrazol, kindling, lavender, diazepam, phenytoin, hippocampus, *in silico* study

INTRODUCTION

Epilepsy is one of the most common disorders of the central nervous system (CNS); it is characterized by spontaneous seizures and affects about 1% of the world's population. Epilepsy cannot be cured, but seizures can be effectively controlled in about 70% of cases with medication alone. However, low availability, and side effects of antiepileptic drugs and drug-resistant epilepsy negatively affect the quality of life of patients in countries with weak health systems.[1,2] Diazepam and phenytoin, like other drugs used to treat this condition, have long been considered anticonvulsants. Since the 1960s, benzodiazepines have continued to play an important role in the control of epilepsy and are among the first-line drugs in convulsive states. The main clinical advantages of diazepam are its high efficacy, rapid onset of action, and low toxicity. Diazepam is a GABA receptor agonist (about 20-50% of all synapses use GABA as a neurotransmitter), which increases the inhibitory state of the brain and suppresses seizures.[3] GABA via $GABA_A$ receptors has an inhibitory effect on synaptic communication in the CNS. Phenytoin is commonly recognized as a broad-spectrum sodium-channel blocker and affects nearly all voltage-gated sodium channels. Its anticonvulsant effect is mainly achieved by disrupting the positive feedback mechanism responsible for the spread of rapid, repetitive neuronal action potentials, thereby reducing seizure activity and selectively blocks high-frequency neuronal activity through the voltage-dependent blockade of membrane sodium channels.[4,5] In addition, phenytoin has been shown to that phenytoin inhibits calcium influx into presynaptic terminals, suggesting a mechanism for its membrane stabilizing properties.[6]

Species of the genus *Lavadula* are widely recognized as important medicinal and aromatic plants and have considerable economic significance for the pharmaceutical sector. Lavender essential oil has been used as a therapeutic agent in traditional medicine for centuries because of its sedative and antidepressant properties. Lavender essential oil contains monoterpenes (linalool, terpinen-4-ol, α-terpineol, camphor, 1,8-cineol, and borneol).[7,8] Lavender oil has been suggested to be anticonvulsant, antianxiety, analgesic.[9,10]

Research has indicated that certain brain regions are more prone to triggering and developing seizure activity compared to other areas, the most important and best-known areas are the temporal lobe and hippocampus.[11] The hippocampus is the primary tissue in which epileptic attacks occur, and hippocampal sclerosis is the most common tissue damage observed in the temporal lobe.[12] One method of studying epilepsy is to create animal models using kindling. The kindling model is a well-known method for studying the mechanisms of epilepsy and investigating new anticonvulsant drugs. Pentylenetetrazol (PTZ)-induced kindling is one of the animal models used to study epilepsy.[13,14] Epilepsy is characterized by recurrent seizures that are frequently accompanied by cognitive impairments and psychosocial complications, although the underlying mechanisms have not yet been fully clarified. Stimulation with PTZ has been reported to markedly influence the hippocampus, a brain region that plays a central role in the formation of new declarative memories.[15] Evidence also suggests that oxidative stress contributes substantially to both the onset and progression of epileptic seizures. The results of several studies indicate that, under certain procedural conditions, temporary or permanent lesions of the hippocampus affect object memory processes as measured by the spontaneous object recognition task. Oxidative stress has been shown to play a significant role in the initiation and progression of epileptic seizures.[16] Malondialdehyde (MDA), a final product of the peroxidation of polyunsaturated fatty acids, is recognized as a major metabolite of arachidonic acid and a reliable marker of oxidative stress. Therefore, measuring MDA concentrations in biological systems is widely considered a useful approach for assessing lipid peroxidation under both *in vitro* and *in vivo* conditions associated with different pathological states.[17,18]

Plants represent an important reservoir of undiscovered compounds for early drug discovery. Many plant extracts and chemical compounds from around the world have demonstrated anticonvulsant properties in experimental animal models exhibiting the phenotypic characteristics of epilepsy. In addition, cognitive-enhancing, neuroprotective, and anti-inflammatory activities of many plant extracts and compounds may help in the treatment of epilepsy. Several studies have been conducted to investigate the effects of different types of lavender on neurodegenerative diseases. For example, it has been shown that in Alzheimer's disease, treatment with lavender extract improves spatial learning deficits.[19] It has also been shown in a PTZ-induced epilepsy model that in brain tissue homogenates, lavender treatment can modulate inflammatory factors such as MDA, nitric oxide, and superoxide dismutase.[20] Studies have also shown that the species lavender dentata can reduce pro-oxidant markers in hippocampal homogenates from a pilocarpine-induced kindling model. This study also showed that levels of inflammatory markers were reduced. Also, the extract of this plant can reduce the level of brain excitability by membrane repolarization.[21,22] However, due to limitations in research on the extract and essential oils of this plant, further studies are needed to draw conclusions about its effectiveness in treating epilepsy. In this study, we therefore used the PTZ kindling model of epilepsy in mice to assess the antiepileptic effects of lavender extract and to compare its activity with diazepam and phenytoin. In addition, cognitive, antioxidant, histological, behavioral, and computer modeling studies were simultaneously conducted, which allowed for more comprehensive information on the effectiveness of the extract in an animal model of epilepsy.

MAIN POINTS

- Lavender extract shows efficasy in pentylenetetrazol-induced seizures.
- Lavender antiepileptic effects were demonstrated in histological studies, antioxidants assessment and behavioral studying.
- *In silico* studies were also used to confirm the *in vivo* findings.

METHODS

Chemical Substances

PTZ (Sigma Chemical Co., United States) was used in this study. In this experiment, mice were intraperitoneally (i.p.) injected with PTZ dissolved in 0.9% normal saline. Phenytoin (Atipharmed Pharmaceuticals Co., Iran). was freshly dissolved in distilled water using dilute NaOH (final pH of the solution was approximately 11) and administered orally via gavage in a volume of 0.5 mL[23] and diazepam (Atipharmed Pharmaceuticals Co., Iran) dissolved in distilled water and administered orally via gavage in a volume of 0.5 mL.[24]

Preparation of the Aqueous Extract

In this experiment, an aqueous extract was prepared from lavender using the soaking method. 2 g of lavender powder was mixed with 50 mL of water, and the mixture was heated at 35 °C using a magnetic stirrer for 30 minutes. The mixture was then subjected to an ultrasonic bath for 30 min. One of the main advantages of ultrasonication is that it disrupts plant cell walls, facilitating the release of intracellular compounds and metabolites from lavender. After sonication, the extract was evaporated to separate the solvent from other components. For evaporation, sample was then dried in an oven (UF30; MEMMERT Co.) at 35 °C to prevent degradation of secondary metabolites.[25]

Experimental Animals

Swiss male albino mice (26-32 g) were obtained from Tabriz University and acclimatized in animal housing. They were kept under controlled conditions: temperature 23±2 °C, relative humidity 51±10%, and a 12:12 h light/dark cycle. Animals had free access to standard rodent chow and water.

Evaluation of Behavior-induced Induced Epileptic Animals

PTZ (45 mg/kg, i.p.) was injected 45 min after gavage, at a subconvulsive dose every 48 h, to induce seizures in the mice. This procedure was repeated 15 times at 48 h intervals. Animals were placed in a glass box to monitor their behavior after gavage with the extract and injection of the drug; their activity was recorded using a camera. Seizure behavior was observed for 30 min after each PTZ injection. The intensity of seizure responses was scored according to the chemical kindling scale: phase 0 (no response), phase 1 (myoclonic jerk), phase 2 (straub tail), phase 3 (clonic jerkwithout loss of righting reflex), phase 4 (clonic seizure with loss of righting reflex) phase 5 (tonic seizure) and phase 6 (death).[26,27]

Kindling is considered to occur when an animal reaches Stage 4 or Stage 5 for 3 consecutive days after PTZ administration. The experimental groups were as follows: Group 1: normal control (vehicle only); Group 2: kindling group (PTZ 45 mg/kg; i.p.);

Groups 3-5: treatment groups receiving different doses of lavender extracts. Group 3 received PTZ+LAV 200 (45 mg/kg PTZ+200 mg/kg lavender extract). Group 4 received PTZ+LAV 400 (45 mg/kg PTZ+400 mg/kg lavender extract). Group 5 received PTZ+LAV 800 (45 mg/kg PTZ+800 mg/kg lavender extract). Each doses of lavender extract was dissolved in distilled water and administered orally (0.5 mL) 30 min before PTZ injection.[22]

Phenytoin and Diazepam

Phenytoin and diazepam were used at doses of 40 mg/kg and 2 mg/kg, respectively.[27,28]

Histopathological Examination

The brains of the dissected mice were fixed in 10% formalin and embedded in paraffin. Formaldehyde infiltration into tissues depends on factors such as tissue type, fixation time, tissue-to-fixative volume ratio, and temperature. In this study, mice were first anesthetized, and their brains were removed within a golden period of 2 min. The tissues were then fixed at room temperature in formalin with a fixative-to-tissue ratio of 5:1 for 3 days. Laboratory experience has shown us that, because the softness and thickness of mouse brain tissue differ from those of rats, obtaining good-quality slices from mouse brains does not require transcardial perfusion fixation, unlike rat brains. Coronal 6µm thick sections were cut at the hippocampal level using a microtome and fixed on standard glass slides (75×25×1 mm).[29] Each section was deparaffinized in xylene, rehydrated through graded ethanol, and stained with hematoxylin and eosin (H&E). The slides were then stained and examined under a light microscope for histological examination.[30,31]

On the other hand, in the H&E-stained coronal sections of the CA3 across the different lavender extract and drug groups, pyramidal neurons were similar to those in the control group, and no obvious pathological changes were observed.

Novel Object Recognition Test

The novel object recognition test (NORT) is a behavioral test currently used to assess learning and memory in rodents. NORT is conducted over 4 days: one day for habituation, two days for training, and a final day for testing. The stages of NORT are shown in Figure 1. On the first day, each mouse was placed in a box with a length of 65 cm, a width of 45 cm, and a height of 45 cm for 5 min. During training, 24 h later, two identical objects (matched for color, shape, and texture) were placed in different corners of the box, each at a distance of 10 cm from the wall. On the third day, the same procedure was repeated. Animals were allowed to explore similar objects. On the test day, one of the familiar objects was replaced by a new object. The time spent exploring the familiar and novel objects was recorded. The difference in exploration time was considered an index of recognition memory. The test was performed every 48 h after PTZ administration and after extract and drug pretreatments.[32]

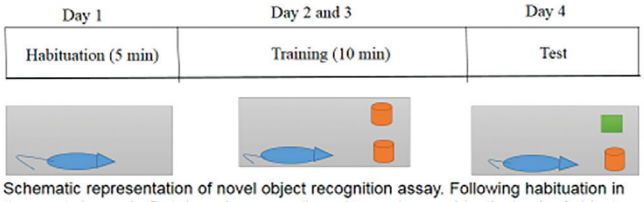


Figure 1. Schematic representation of NOR
NOR: Novel object recognition

Assessment of Antioxidant Index

Brain tissues from the experimental groups were rapidly removed after anesthesia of mice with ketamine and xylazine at doses of 100 mg/kg and 10 mg/kg, respectively,[33] frozen at -24 °C, and were homogenized in phosphate buffer (pH 7.4). Samples were then centrifuged at 10,000 rpm for 10 min, and the supernatant was collected. For derivatization of the MDA-thiobarbituric acid (TBA) complex, 50 µL of each supernatant was transferred to a 2 mL plastic tube, to which 50 microliters of 0.05% butylated hydroxytoluene solution, 100 microliters of 0.44 M phosphoric acid solution, and 100 microliters of 42 mM TBA solution were added, and the mixture was vortexed for 5 min. Samples were placed in a 100 °C water bath for one hour and then transferred to an ice bath for 5 min. After cooling the samples for MDA-TBA derivatization, 25 microliters of butanol were added to each sample. After 5 min, the samples were centrifuged at 10,000 rpm for 10 min to obtain a biphasic system. Finally, 200 µL of the supernatant solution containing MDA-TBA was collected, and fluorescence was measured at an excitation wavelength of 532 nm using a spectrophotometer.[34]

Molecular Docking

Molecular docking simulations were performed to identify target proteins and their ligands for epilepsy. The selected targets for this study were GABA and voltage-dependent sodium channel (VDSC). To perform molecular docking, we first prepared our files for the docking process; our ligands' chemical-induced dimerization identifiers are 6549, 11230, 3016, and 1775 for linalool, terpineol, diazepam, and phenytoin, respectively. For protein preparation, we retrieved our protein data bank (PDB) files from research collaboratory for structural bioinformatics PDB database. PDB ID of our proteins are: 8S9C, 6X3X respectively named after VDSC and $GABA_A$. After obtaining the required files, several modifications were performed: the ligand file formats were converted from structure data format to PDB format using Open Babel software. Subsequently, molecular docking was performed using PyRx software. Among the results achieved, the most suitable ones were chosen for further investigation. To achieve ligand-receptor interaction plot we used Discovery Studio software.[35,36]

Statistical Analysis

In this study, data are presented as mean ± standard deviations. Statistical analyses were performed using SPSS software. Comparisons between experimental groups were conducted using the Kruskal-Wallis test, followed by Dunn's post-hoc test to compare the maximum seizure stage among groups. To compare seizure onset latency and seizure duration, a one-way analysis of variance was performed, followed by Tukey's post-hoc test for multiple comparisons between groups. A p-value <0.05 was considered statistically significant.

Ethics Committee Approval

The study was approved by the Azarbaijan Shahid Madani University Research Ethics Committee (approval no: IR.AZARUNIV.REC.1404.013, date: 02.06.2025).

RESULTS

Effect of Different Doses of Lavender Extract on Seizure Onset Latency

Figure 2 compares seizure onset latency among the treatment groups (different doses of lavender extract), the drug-treated groups (diazepam and phenytoin), and the kindled group. Data are presented as mean ± standard deviation and a p-value <0.05 was considered statistically significant. Different doses of lavender extract, as well as diazepam and phenytoin, significantly increased latency to seizure onset compared with the kindled group (as shown in the graph). Statistical analysis demonstrated that the treatment and drug-treated groups differed significantly from the kindled group.

The Effect of Different Doses of Lavender Extract on the Duration of Seizure

Figure 3 compares seizure duration between the treatment groups, drug treated groups, and the kindled group. Data are presented as mean ± standard deviation and a p-value <0.05 was considered statistically significant. As shown in the graph, pretreatment with different doses of lavender extract reduced seizure duration compared with that in the kindled group. However, the reduction in seizure duration was not statistically significant compared with the kindled group. In contrast, pretreatment with diazepam and phenytoin significantly reduced seizure duration. Statistical analysis showed significant difference between the diazepam and phenytoin treated groups and the kindle group.

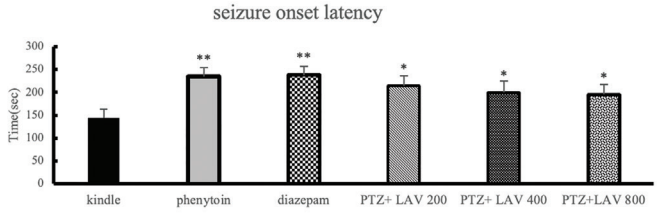


Figure 2. Pretreatment with diazepam, phenytoin and different dose of lavender extract compare to PTZ group significantly increased latency of seizure onset
*: p-value ≤0.05, **: p-value ≤0.01
PTZ: Pentylenetetrazol

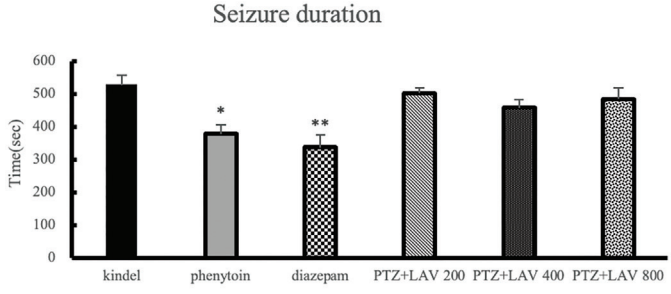


Figure 3. Pretreatment with diazepam and phenytoin significantly decreased seizure duration. Different dose of lavender extract in compare to PTZ group didn't decreased significantly. *: p-value ≤0.05, **: p-value ≤0.01
PTZ: Pentylenetetrazol

Effect of Different Doses of Lavender Extracts on the Progression of Seizure Stages

Figure 4 shows the progression of seizure stages over 15 days in groups treated with different doses of lavender extract and in drug-treated groups, compared with the kindled (PTZ) group. Data is presented as mean ± standard deviation and a p-value <0.05 was considered statistically significant. As shown in the graph, lavender extracts had an inhibitory effect on seizure progression compared with that in the kindled group. All doses of lavender extract kept seizure stages below Stage 5. Statistical analysis revealed a significant difference in seizure stage progression in the lavender extract-treated and drug-treated groups, compared with the kindled group.

Effect of Different Doses of Lavender Extract on the Discrimination Ratio

The novelty object recognition test, as shown in Figure 5, demonstrated that the discrimination index (DI) was significantly decreased in the kindled group compared with the control group. The discrimination ratio represents the proportion of time an animal spends exploring the novel object (T new) relative to the familiar object (Told), calculated with respect to the total exploration time (T total; Eq. 1). Findings from lesion-based and neurophysiological studies using the NORT paradigm indicate that the DI mainly reflects memory performance and sensitivity.

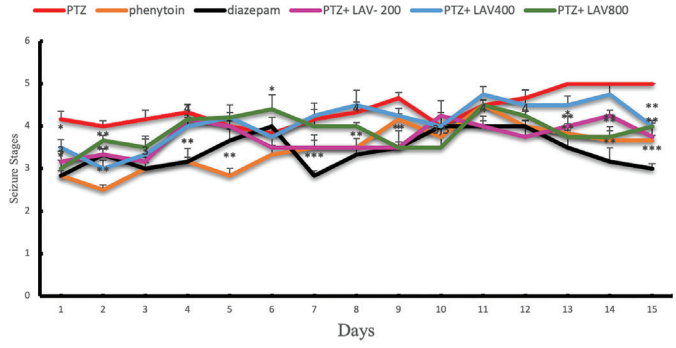


Figure 4. Pretreatment with diazepam and phenytoin and different doses of lavender extract significantly decreased seizure stages in compare to PTZ group. *: p-value ≤0.05, **: p-value ≤0.01 and ***: p-value ≤0.001
PTZ: Pentylenetetrazol

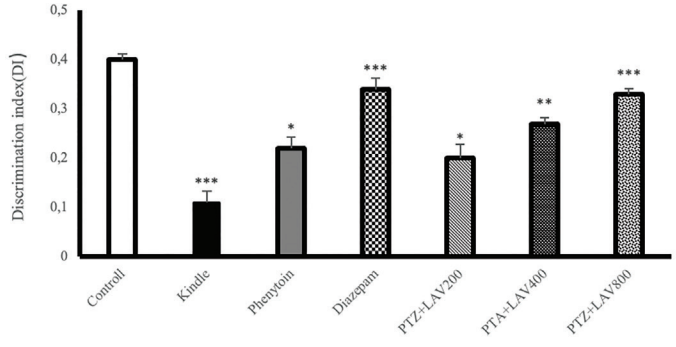


Figure 5. Pretreatment with different dose of lavender extract and diazepam and phenytoin improved of memory. In PTZ group memory decrease significantly in comparison to control group. Administration of diazepam, phenytoin and different doses of lavender extract improve memory significantly in comparison to kindle group. *: p-value ≤0.05, **: p-value ≤0.01 and ***: p-value ≤0.001
PTZ: Pentylenetetrazol

Pretreatment of animals with different doses of lavender extract predominantly increased the DI, an effect comparable to that of diazepam and phenytoin. Data is presented as mean ± standard deviation.

Equation 1: DI = T (new) – T (old) / T (total)

Fluorescence was measured using a spectrophotometer at an excitation wavelength of 532 nm. Data are presented as mean ± standard deviation.

Effect of Different Doses of Lavender Extract on the MDA Levels

As shown in Figure 6, MDA levels in hippocampal tissue, measured as an index of oxidative stress, were significantly increased in the kindled group compared with the control group. Absorbance measurements showed that the highest MDA levels were observed in the kindled group. Pretreatment with 200 mg/kg of lavender did not significantly change the MDA level. In contrast, pretreatment with dose 400 mg/kg decreased MDA levels, while 800 mg/kg produced a reduction comparable to the effects of diazepam and phenytoin. Fluorescence was measured using a spectrophotometer at an excitation wavelength of 532 nm. Data is presented as mean ± standard deviation.

Effect of Different Doses of Lavender Extract on the CA3 Region of the Hippocampus

Figure 7 shows the H&E staining of hippocampal tissue. Figure 7-A shows the general structure of hippocampal tissue in the control group. The coronal sections of the CA3 region of the hippocampus from the control group showed regular cellular architecture. The pyramidal cell layer(P)contained neurons that were uniform in size and distribution. Each neuron had a round, central nucleus with a prominent nucleolus (Figure 7-B). In contrast, H&E-stained sections of the CA3 region of the hippocampus in the kindled group did not show uniformity in neuronal size or distribution. The kindled group exhibited hyperchromatic nuclei and vacuolated cytoplasm (Figure 7-B). Pretreatment with diazepam and phenytoin (Figure 7-C), as well as with different doses of lavender extract (Figure 7-D), reduced neuronal degeneration in the hippocampus. Dark-stained neurons with severe degeneration are indicated by a thin arrow, whereas normal neurons are indicated by a thick arrow. Scale bar: 500 µm.

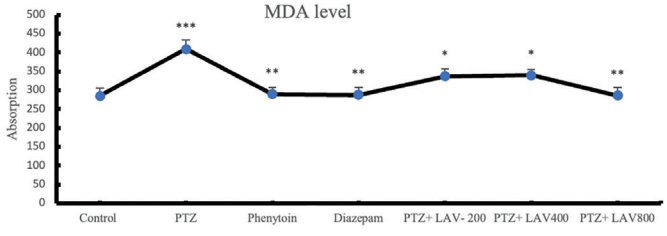


Figure 6. Administration of diazepam, phenytoin and different doses of lavender extract reduced MDA compared to the PTZ group. Administration of diazepam, phenytoin and different doses of lavender extract significantly, improved memory compared to the PTZ group. *: p-value ≤0.05, **: p-value ≤0.01 and ***: p-value ≤0.001
PTZ: Pentylenetetrazol, MDA: Malondialdehyde

Molecular Docking Studies of Linalool, Terpineol, Phenytoin and Diazepam with $GABA_A$ Receptor and VDSC Channels

In silico study of linalool showed this compound has high affinity for $GABA_A$ receptors and sodium channels. Recent studies have demonstrated that several monoterpenoids, including the acyclic compound linalool, potentiate $GABA_{ergic}$ currents through an allosteric mechanism *in vitro*, particularly after overexpression of inhibitory α1β2 $GABA_A$ receptors in different expression systems. In $GABA_A$ receptor: diazepam makes interactions with amino acids: tyrosine D: 160, glutamine D: 205, serine D: 204 and phenylalanine E: 77, tyrosine E: 58, histidine D: 102, phenylalanine D: 100. They also interact with these amino acids, exhibiting different interaction energies (ΔG). ΔG values for the compounds diazepam, phenytoin, linalool, and terpineol are -10.3 kJ, -7.7 kJ, -6.6 kJ, and -7.3 kJ, respectively.

In VDSC channels, diazepam interacts with the amino acids phenylalanine A: 1748, isoleucine A: 1744, tyrosine A: 1404, and alanine A: 1403. However, in this case, linalool binds to phenylalanine A: 1748, phenylalanine A: 1452, and other residues. But terpineol does not bind to the same amino acids as linalool and diazepam. The ΔG values for these compounds, diazepam, phenytoin, linalool, and terpineol, are -9.1 kJ, -8.6 kJ, -7.4 kJ, and -5.4 kJ, respectively.

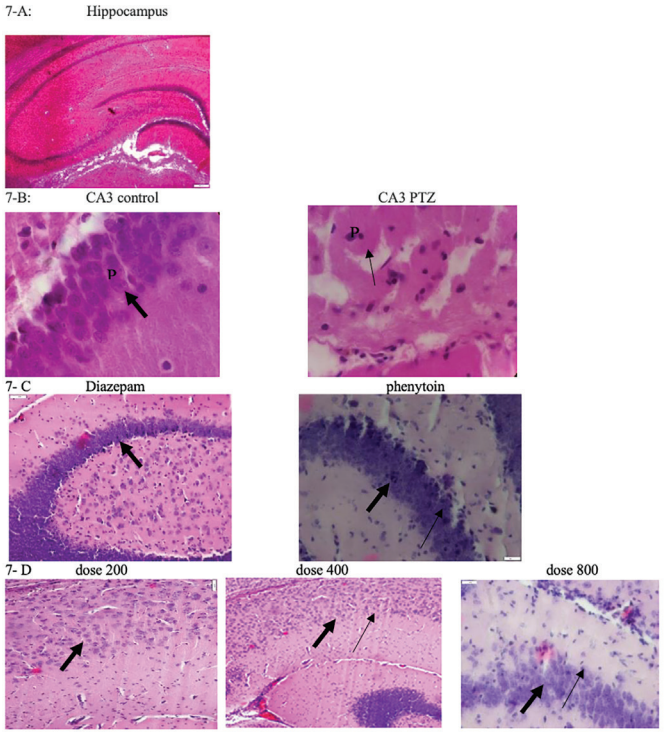


Figure 7. H&E staining of coronal sections of the hippocampal region in the PTZ kindling model. Figure of 7-A shows general shape of hippocampus in control group. 7-B: CA3 region of control and PTZ (×40). 7-C: CA3 region of diazepam and phenytoin group (×10) and 7-D: CA3 region of dose of 200 and 400 mg/kg of lavender extract (×10) and dose of 800 mg/kg 800 (40). Photomicrographs showing changes in staining of damaged neurons (dark-stained neurons with severe degeneration indicated by a thin arrow as compared to normal neurons indicated by a thick arrow. Scale bar: 500 µm
PTZ: Pentylenetetrazol, H&E: Hematoxylin and eosin

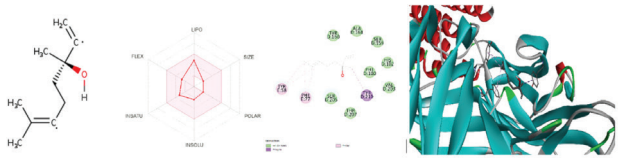
These compounds, linalool and terpineol, have shown acceptable binding affinity to $GABA_A$ receptors at the same binding site and with similar interacting amino acids as a diazepam and phenytoin. On the other hand, regarding VDSC, only linalool showed a binding pattern similar to that of phenytoin and diazepam, although with lower binding affinity. According to these results, with some modifications, linalool and terpineol may become suitable candidates as alternatives to diazepam and phenytoin. However, further investigation is required to fully evaluate their potential. The molecular docking results are shown in Figure 8. The binding affinities and ADME properties of compounds with target proteins are shown in Table 1.

DISCUSSION

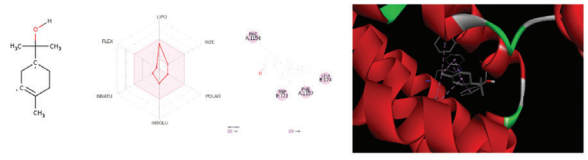
Different doses of lavender extract showed anti-seizure effects in PTZ-induced epilepsy. Administration of lavender extract 30 minutes prior to intraperitoneal injection of PTZ may allow its metabolites to reach the brain via the bloodstream, thereby reducing neuronal excitability. Consequently, the ability of PTZ to interact with the picrotoxin-binding site on GABA receptors is likely diminished; this reduction may contribute to the observed anticonvulsant effects.

Given that linalool and terpineol are the most abundant metabolites in lavender, the anticonvulsant effects are likely mediated by these compounds. Several studies have shown that linalool and terpineol can cross the blood-brain barrier and affect brain function. However, since lavender also contains other secondary metabolites, a more accurate conclusion requires comparing the effects of lavender extract with isolated of linalool and terpineol.[37,38]

Linalool is a secondary metabolite that can be isolated from a variety of aromatic plant species, such as lavender, *Ocimum,* and *Eucalyptus*. Among secondary metabolites, linalool is a major constituent (35-51%) of essential oils derived from various types of lavender. Several animal studies, have demonstrated that inhalation of linalool induces sedative-like behavior.[37] Recent studies have demonstrated that linalool, because of its low molecular weight and high lipophilicity, can cross the blood-brain barrier. This characteristic makes it a potential candidate for pharmaceutical applications aimed at influencing behavioral, cognitive, and sleep patterns. Linalool and its related compounds, by modulating different brain circuits, may have therapeutic potential in the management of several neurological and psychiatric conditions.[38] Evidence has demonstrated that linalool probably through anti-neuroinflammatory, antioxidant and neuroprotective effects, can be used for improvement of neurodegenerative diseases including Alzheimer's and Parkinson's.[38,39] In addition, some investigations suggest that linalool reduces glutamatergic hyper-stimulation and inhibits seizure and apoptotic processes.[39-41] Other studies have shown that linalool possesses anti-inflammatory properties and can decrease amounts of inflammatory cytokines, nitric oxide, and reactive oxygen species through inhibition of the NF-kB pathway.[42] Clinical studies have shown that inhaling lavender oil and petitgrain oil, both of which contain linalool, reduces anxiety-like behavior in humans. Another study in mice demonstrated that inhalation of linalool reduces anxiety-like behavior and improves sleep. Furthermore, the measurement of linalool in mouse brain tissue using a gas chromatography system equipped with a tandem quadrupole mass spectrometer revealed significant levels in different brain regions, indicating that it crosses the blood-brain

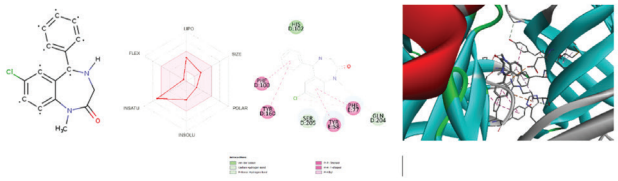


Linalool. (a) Structure (b) ADME radar graph (c) 2D interaction with $GABA_A$ graph (d) 3D interaction with $GABA_A$ graph



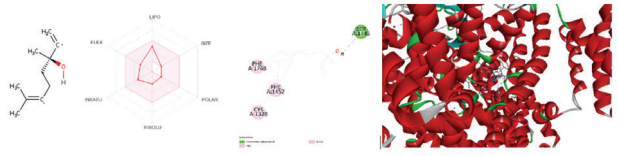
Terpineol. (a) structure (b) ADME radar graph (c) 2D interaction with $GABA_A$ graph (d) 3D ineraction with $GABA_A$ graph

Phenytoin. (a) Structure (b) ADME radar graph (c) 2D interaction with VDSC graph (d) 3D interaction with VDSC graph



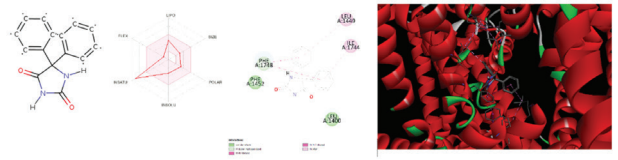
Diazepam. (a) Structure (b) ADME radar graph (c) 2D interaction with $GABA_A$ graph (d) 3D interaction with $GABA_A$ graph

Diazepam. (a) Structure (b) ADME radar graph (c) 2D interaction with VDSC graph (d) 3D interaction with VDSC graph



Linalool. (a) Structure (b) ADME radar graph (c) 2D interaction with VDSC graph (d) 3D interaction with VDSC graph

Terpineol. (a) Structure (b) ADME radar graph (c) 2D interaction with $GABA_A$ graph (d) 3D interaction with $GABA_A$ graph



Phenytoin. (a) structure (b) ADME radar graph (c) 2D interaction with VDSC graph (d) 3D interaction with VDSC graph

Figure 8. Molecular docking studies demonstrated intraction of linalool, terpineol, diazepam and phenytoin with $GABA_A$ receptors and VDSC channels VDSC: Voltage-dependent sodium channel

Table 1. Binding affinity and ADME properties of compounds with target proteins

	Binding affinity GABA (Kcal/mol)	Binding affinity VDSC (Kcal/mol)	Hydrogen bound GABA	Bioavailability score	Synthetic accessibility	GI absorption	BBB permeant
Linalool	-6.6	-7.4	0	0.55	2.67	High	Yes
Terpineol	-7.3	-5.4	1	0.55	3.17	High	Yes
Diazepam	-10.3	-9.1	0	0.55	2.68	High	Yes
Phenytoin	-7.7	-8.6	0	0.55	1.51	High	Yes

VDSC: Voltage-dependent sodium channel, GI: Gastrointestinal, BBB: Blood-brain barrier

barrier.[43] Results of some studies have shown that terpinen-4-ol, another phytochemical component found abundantly in lavender, efficiently reduces the severity of PTZ induced seizures and delays the onset of seizures.[44] Results of another study showed that terpinen-4-ol probably induces a depressant effect on the CNS through interaction with GABA receptors and suppresses convulsion activity of the brain significantly.[45] On the other hand, α-terpineol, an abundant compound in lavender, has neuroprotective effects in the hippocampus. It can inhibit neural damage and improve synaptic plasticity, which may in turn enhance hippocampal function and improve spatial memory following transient cerebral ischemia in rats.[46] In addition, investigations have demonstrated that α-terpineol, a phytochemical component of lavender, has antioxidant properties. Terpineol reduces nitric oxide synthase induces anti-inflammatory effects.[47] Recently, a study demonstrated the antioxidant, anti-inflammatory, and anti-fibrillatory properties of alpha-terpineol in an animal model of Alzheimer's, suggesting that this compound can cross the blood-brain barrier and affect brain tissue.[48] Another study showed that, in zebrafish with Parkinson's disease induced by the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), terpineol improved motor function and acetylcholinesterase activity in MPTP larvae. Terpineol also showed potent neuroprotective effects by reducing intracellular reactive oxygen species, lipid accumulation, and apoptosis markers.[49]

Lavender has antioxidant, anti-inflammatory, neuroprotective, and anticonvulsant properties, which are attributed to compounds such as linalool, terpinen-4-ol, and α-terpineol. The antioxidant effect of lavender is demonstrated by a reduction in MDA levels in hippocampal tissue. Evidence suggests that cellular death and tissue damage mediated by free radicals may contribute to neurological disorders.[50] MDA, an end-product of lipid peroxidation, was present at significantly higher levels in the kindling group than in the control group, and pretreatment with lavender extract significantly reduced MDA levels. As a result, lavender extract may act as a neuroprotective agent through a reduction in MDA levels, as seen in H and E-stained hippocampal slices and an improvement in memory in the NORT.

An *in silico* study of linalool showed that this compound has a high affinity for GABA receptors and sodium channels. Recent research has indicated that several monoterpenoid compounds, including the acyclic linalool, can increase $GABA_{ergic}$ currents through allosteric modulation *in vitro*, particularly when inhibitory α1β2 $GABA_A$ receptors are overexpressed in heterologous expression systems.[50-52]

In silico studies showed that linalool, terpineol, diazepam and phenytoin bind to $GABA_A$ receptors with high affinity. Interactions with affinity higher than -5 Kcal/mol are considered indicative of good binding. At these values, molecules bind tightly, forming a stable complex even at low concentrations.

Among these substances, diazepam has the highest and linalool the lowest affinity for $GABA_A$ receptors. Our results show that linalool, terpineol, diazepam, and phenytoin bind to VDSC with high affinity. Diazepam binds to this channel with the highest affinity, whereas terpineol binds with the lowest affinity.

Study Limitations

To confirm the effects of lavender extract, it would have been preferable to inject pure linalool and terpineol into an animal model; this approach could have validated *in silico* findings and would have yielded more accurate results.

CONCLUSION

These results suggest that phytochemicals in lavender extract, due to their low molecular weight and high lipophilicity, can cross the blood-brain barrier, enter the brain, and exert antioxidant, anti-inflammatory, and neuroprotective effects. *In silico* studies conducted as part of this research showed that lavender phytochemicals bind with high affinity to GABA receptors and to VSCD. Therefore, this plant may be considered a potential candidate for the development and synthesis of novel, effective drugs for patients with epilepsy and other neurological disorders.

Ethics

Ethics Committee Approval: The study was approved by the Azarbaijan Shahid Madani University Research Ethics Committee (approval no: IR.AZARUNIV.REC.1404.013, date: 02.06.2025).

Informed Consent: It was not deemed necessary, as it was an animal experiment.

Footnotes

Authorship Contributions

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

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

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Abdollahi Fard M, Shojaii A. Efficacy of Iranian traditional medicine in the treatment of epilepsy. *Biomed Res Int.* 2013;2013:692751. [Crossref]

2. Browne TR, Holmes GL. Handbook of epilepsy. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2008. [Crossref]
3. Riss J, Cloyd J, Gates J, Collins S. Benzodiazepines in epilepsy: pharmacology and pharmacokinetics. *Acta Neurol Scand.* 2008;118(2):69-86. [Crossref]
4. Yaari Y, Selzer ME, Pincus JH. Phenytoin: mechanisms of its anticonvulsant action. *Ann Neurol.* 1986;20(2):171-184. [Crossref]
5. Sohn RS, Ferrendelli JA. Anticonvulsant drug mechanisms. Phenytoin, phenobarbital, and ethosuximide and calcium flux in isolated presynaptic endings. *Arch Neurol.* 1976;33(9):626-629. [Crossref]
6. van Vliet EA, van Schaik R, Edelbroek PM, et al. Inhibition of the multidrug transporter P-glycoprotein improves seizure control in phenytoin-treated chronic epileptic rats. *Epilepsia.* 2006;47(4):672-680. [Crossref]
7. Radu D, Alexe P, Stănciuc N. Overview on the potential role of phytochemicals from lavender as functional ingredients. *Ann Univ Dunarea de Jos Galati Fascicle VI Food Technol.* 2020;44(2):173-188. [Crossref]
8. Białoń M, Krzyśko-Łupicka T, Nowakowska-Bogdan E, Wieczorek PP. Chemical composition of two different lavender essential oils and their effect on facial skin microbiota. *Molecules.* 2019;24(18):3270. [Crossref]
9. Aprotosoaie AC, Gille E, Trifan A, Luca VS, Miron A. Essential oils of Lavadula genus: a systematic review of their chemistry. *Phytochem Rev.* 2017;16(4):761-799. [Crossref]
10. Bahr TA, Rodriguez D, Beaumont C, Allred K. The effects of various essential oils on epilepsy and acute seizure: a systematic review. *Evid Based Complement Alternat Med.* 2019;2019:6216745. [Crossref]
11. Battaglia FP, Benchenane K, Sirota A, Pennartz CM, Wiener SI. The hippocampus: hub of brain network communication for memory. *Trends Cogn Sci.* 2011;15(7):310-318. [Crossref]
12. Marangoz C. Deneysel epilepsi modelleri. J Exp Clin Med. 2009;14(3):147-186. [Crossref]
13. McNamara JO. Kindling model of epilepsy. *Adv Neurol.* 1986;44:303-318. [Crossref]
14. Ahmadian SR, Ghasemi-Kasman M, Pouramir M, Sadeghi F. Arbutin attenuates cognitive impairment and inflammatory response in pentylenetetrazol-induced kindling model of epilepsy. *Neuropharmacology.* 2019;146:117-127. [Crossref]
15. Ahmadi M, Dufour JP, Seifritz E, Mirnajafi-Zadeh J, Saab BJ. The PTZ kindling mouse model of epilepsy exhibits exploratory drive deficits and aberrant activity amongst VTA dopamine neurons in both familiar and novel space. *Behav Brain Res.* 2017;330:1-7. [Crossref]
16. Shehta N, Kamel AE, Sobhy E, Ismail MH. Malondialdehyde and superoxide dismutase levels in patients with epilepsy: a case-control study. *Egypt J Neurol Psychiatry Neurosurg.* 2022;58(1):51. [Crossref]
17. Gaweł S, Wardas M, Niedworok E, Wardas P. Dialdehyd malonowy (MDA) jako wskaźnik procesów peroksydacji lipidów w organizmie [Malondialdehyde (MDA) as a lipid peroxidation marker]. *Wiad Lek.* 2004;57(9-10):453-455. Polish. [Crossref]
18. Khoubnasab Jafari M, Ansarin K, Jouyban A. Comments on "use of malondialdehyde as a biomarker for assesing oxidative stress in different disease pathologies: a review". *Iran J Public Health.* 2015;44(5):714-715. [Crossref]
19. Ahghari P, Afshar S, Dastan D, Ahmadieh Yazdi A. Protective effect of Lavadula officinalis on pentylenetetrazol-induced epilepsy in mice: expression of NOS genes and caspase-3. *Int J Ep.* 2024;10(01/02):11-19. [Crossref]
20. Kashani MS, Tavirani MR, Talaei SA, Salami M. Aqueous extract of lavender (Lavadula angustifolia) improves the spatial performance of a rat model of Alzheimer's disease. *Neurosci Bull.* 2011;27(2):99-106. [Crossref]
21. Antar A, Abdel-Rehiem ES, Al-Khalaf AA, et al. Therapeutic efficacy of Lavadula dentata's oil and ethanol extract in regulation of the neuroinflammation, histopathological alterations, oxidative stress, and restoring balance treg cells expressing FoxP3+ in a rat model of epilepsy. *Pharmaceuticals (Basel).* 2024;18(1):35. [Crossref]
22. Rahmati B, Khalili M, Roghani M, Ahghari P. Anti-epileptogenic and antioxidant effect of Lavadula officinalis aerial part extract against pentylenetetrazol-induced kindling in male mice. *J Ethnopharmacol.* 2013;148(1):152-157. [Crossref]
23. Löscher W, Reissmüller E, Ebert U. Kindling alters the anticonvulsant efficacy of phenytoin in Wistar rats. *Epilepsy Res.* 2000;39(3):211-220. [Crossref]
24. Khalid S, Rasool MF, Imran I, et al. A physiologically based pharmacokinetic model for predicting diazepam pharmacokinetics after intravenous, oral, intranasal, and rectal applications. *Pharmaceutics.* 2021;13(9):1480. [Crossref]
25. Tăbărașu AM, Anghelache DN, Găgeanu I, Biriș SȘ, Vlăduț NV. Considerations on the use of active compounds obtained from lavender. *Sustainability.* 2023;15(11):8879. [Crossref]
26. Akyüz E. A new view of the racine scoring system in the pentylenetetrazol epilepsy model. Harran Univ Tip Fak Derg. 2020;17(2):306-310. [Crossref]
27. Zivanovic D, Stanojlovic O, Susic V, Stojanovic J. The effects of phenytoin and phenobarbital on seizures induced by imipenem/cilastatin in rats. *Acta Neurol Belg.* 2004;104(1):20-26. [Crossref]
28. Naderi N, Aziz Ahari F, Shafaghi B, Najarkolaei AH, Motamedi F. Evaluation of interactions between cannabinoid compounds and diazepam in electroshock-induced seizure model in mice. *J Neural Transm (Vienna).* 2008;115(11):1501-1511. [Crossref]
29. Grizzle WE. Special symposium: fixation and tissue processing models. *Biotech Histochem.* 2009;84(5):185-193. [Crossref]
30. Tucker DK, Foley JF, Hayes-Bouknight SA, Fenton SE. Preparation of high-quality hematoxylin and eosin-stained sections from rodent mammary gland whole mounts for histopathologic review. *Toxicol Pathol.* 2016;44(7):1059-1064. [Crossref]
31. Fischer AH, Jacobson KA, Rose J, Zeller R. Hematoxylin and eosin staining of tissue and cell sections. *CSH Protoc.* 2008;2008:pdb.prot4986. [Crossref]
32. Lueptow LM. Novel object recognition test for the investigation of learning and memory in mice. *J Vis Exp.* 2017;(126):55718. [Crossref]
33. Levin-Arama M, Abraham L, Waner T, et al. Subcutaneous compared with intraperitoneal ketaminexylazine for anesthesia of mice. *J Am Assoc Lab Anim Sci.* 2016;55(6):794-800. [Crossref]
34. Agarwal R, Chase SD. Rapid, fluorimetric-liquid chromatographic determination of malondialdehyde in biological samples. *J Chromatogr B Analyt Technol Biomed Life Sci.* 2002;775(1):121-126. [Crossref]
35. Miller PS, Aricescu AR. Crystal structure of a human GABAA receptor. *Nature.* 2014;512(7514):270-275. [Crossref]
36. Shaheen U, Akka J, Hinore JS, et al. Computer aided identification of sodium channel blockers in the clinical treatment of epilepsy using molecular docking tools. *Bioinformation.* 2015;11(3):131-137. [Crossref]
37. Milanos S, Elsharif SA, Janzen D, Buettner A, Villmann C. Metabolic products of linalool and modulation of GABAA receptors. *Front Chem.* 2017;5:46. [Crossref]
38. da Silva PR, de Andrade JC, de Sousa NF, et al. Computational studies applied to linalool and citronellal derivatives against Alzheimer's and Parkinson's disorders: a review with experimental approach. *Curr Neuropharmacol.* 2023;21(4):842-866. [Crossref]
39. Kaur J, Famta P, Famta M, et al. Potential anti-epileptic phytoconstituents: an updated review. *J Ethnopharmacol.* 2021;268:113565. [Crossref]
40. Elisabetsky E, Brum LF, Souza DO. Anticonvulsant properties of linalool in glutamate-related seizure models. *Phytomedicine.* 1999;6(2):107-113. [Crossref]
41. Dos Santos ÉRQ, Maia JGS, Fontes-Júnior EA, do Socorro Ferraz Maia C. Linalool as a therapeutic and medicinal tool in depression treatment: a review. *Curr Neuropharmacol.* 2022;20(6):1073-1092. [Crossref]
42. Younis NS, Abdelnaby RM, Mohamed ME. Hepatoprotective effects of linalool against liver ischemia-reperfusion: the role of Nrf2/HO-1/NQO1 and TLR4/RAGE/NFκB pathways. *Eur Rev Med Pharmacol Sci.* 2023;27(20):10094-10111. [Crossref]
43. Oguro A, Fujiyama T, Sato H, Yoshida T, Miyara M, Kotake Y. Linalool inhalation in mice leads to brain accumulation and metabolite-driven neuronal activation. *Biochem Biophys Res Commun.* 2025;786:152716. [Crossref]

44. de Sousa DP, Nóbrega FF, de Morais LC, de Almeida RN. Evaluation of the anticonvulsant activity of terpinen-4-ol. *Z Naturforsch C J Biosci.* 2009;64(1-2):1-5. **[Crossref]**
45. Vieira G, Cavalli J, Gonçalves ECD, et al. Antidepressant-like effect of terpineol in an inflammatory model of depression: involvement of the cannabinoid system and D2 dopamine receptor. *Biomolecules.* 2020;10(5):792. **[Crossref]**
46. Moghimi M, Parvardeh S, Zanjani TM, Ghafghazi S. Protective effect of α-terpineol against impairment of hippocampal synaptic plasticity and spatial memory following transient cerebral ischemia in rats. *Iran J Basic Med Sci.* 2016;19(9):960-969. **[Crossref]**
47. Gouveia DN, Costa JS, Oliveira MA, et al. α-terpineol reduces cancer pain via modulation of oxidative stress and inhibition of iNOS. *Biomed Pharmacother.* 2018;105:652-661. **[Crossref]**
48. Chinnappan D, Kuppamuthu A, Magudeeswaran S, Kandasamy S, Krishnan M, Elangovan N. A dual-target inhibitor of α-terpineol in Alzheimer's and Parkinson's diseases: a comprehensive active site analysis. *ChemistrySelect.* 2025;10(24):e05631. **[Crossref]**
49. Chinnappan D, Krishnan M, Kuppamuthu A, Elangovan N. Developmental and neuroprotective effects of α-terpineol in MPTP-induced parkinsonism in zebrafish larvae. *Neurochem Res.* 2025;50(3):158. **[Crossref]**
50. Hassan W, Noreen H, Rehman S, Kamal MA, da Rocha JBT. Association of oxidative stress with neurological disorders. *Curr Neuropharmacol.* 2022;20(6):1046-1072. **[Crossref]**
51. Xie HB, Sha Y, Wang J, Cheng MS. Some insights into the binding mechanism of the GABAA receptor: a combined docking and MM-GBSA study. *J Mol Model.* 2013;19(12):5489-5500. **[Crossref]**
52. Chowdhury R, Bhuia MS, Al Hasan MS, et al. Anticonvulsant effect of (±) citronellal possibly through the GABAergic and voltage-gated sodium channel receptor interaction pathways: In vivo and in silico studies. *Neurochem Int.* 2024;175:105704. **[Crossref]**

Genetic Etiologies of an Epilepsy Outpatient Clinic: Single-center Experience

Dilara Mermi Dibek[1,2], Alper Gezdirici[3], Bülent Uyanık[4], Leyli Şentürk[5], İbrahim Öztura[6], Barış Baklan[6], Sultan Cingöz[2,7]

[1]University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Clinic of Neurology and Clinical Neurophysiology, İstanbul, Türkiye

[2]Dokuz Eylül University Institute of Health Sciences, Department of Medical Biology and Genetics, İzmir, Türkiye

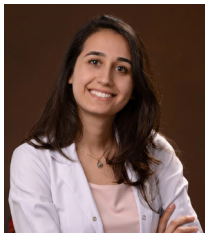
[3]University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Clinic of Medical Genetics, İstanbul, Türkiye

[4]Bezmialem Vakıf University Faculty of Medicine, Department of Medical Genetics, İstanbul, Türkiye

[5]University of Health Sciences Türkiye, Bağcılar Training and Research Hospital, Clinic of Medical Genetics, İstanbul, Türkiye

[6]Dokuz Eylül University Faculty of Medicine, Department of Neurology and Clinical Neurophysiology, İzmir, Türkiye

[7]Dokuz Eylül University Faculty of Medicine, Department of Medical Biology and Genetics, İzmir, Türkiye



Dilara Mermi Dibek MD,

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Corresponding Author: Dilara Mermi Dibek MD, University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Clinic of Neurology and Clinical Neurophysiology, İstanbul; Dokuz Eylül University Institute of Health Sciences, Department of Medical Biology and Genetics, İzmir, Türkiye, **E-mail:** dilara_mermi@hotmail.com

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Abstract

Objective: We aim to documented genetic etiology of epilepsy at a single-center epilepsy outpatient clinic in state hospital.

Methods: The patients' demographic data, clinical and electrophysiologic features, and gene analysis were re-evaluated from medical records of patients with epilepsies between August 2021 and January 2024. The detected variants were searched in gnomAD, ClinVar, DECIPHER, and PubMed databases. The common and distinct features of the phenotype of patients were compared with the literature.

Results: The medical records of 354 patients with epilepsy were reviewed. Forty (11.2%) patients were diagnosed with genetic generalized epilepsy. Among them, 37 patients (10.4%) were diagnosed with idiopathic generalized epilepsy, and 3 patients (0.8%) were diagnosed with epilepsy with eyelid myoclonia. We included patients with epilepsy and confirmed genetic etiology at diagnosis. Nine (2.5%) patients with epilepsy and confirmed genetic etiology were included; seven (1.9%) patients had rare monogenic variants in (*ZNF142, ZMYND11, DLG4, PEX11B, SCARB2* and *GRM-1*) genes and two (0.5%) had chromosomal abnormalities (1p36 deletion and 15q15.1 deletion).

Conclusion: This study reported genetic etiologies of epilepsy were determined in single-center state hospital. The reported families demonstrate that similar genotypic variations can lead to different phenotypic outcomes. Indeed, similar phenotypic features may result from two distinct genotypic alterations. Specifying the variants and their phenotypic features with diagnostic tools in every single-center are important starting to investigate across the country.

Keywords: *DLG4*, genetic etiology of epilepsy, genotype, gonadal mosaicism, *SCARB2*, phenotype, *CAPN10-ZMYND11, ZNF142*, 15q15.1

INTRODUCTION

Epilepsy affects almost 4% of the general population over a lifetime.[1] The primary goal of physicians should be to determine the underlying etiology of epilepsy. According to 2017 International League Against Epilepsy (ILAE) classification, one of etiological categories of epilepsy is genetic.[2] Idiopathic generalized epilepsy (IGE) makes up around 25% of all epilepsies.[3] In focal epilepsies, twin studies have shown higher concordance rates of mesial temporal lobe epilepsy in monozygotic twins compared to dizygotic twins.[4] Population studies have shown a 2.5-fold increased risk of focal epilepsy in first-degree relatives of patients with focal epilepsy compared to the general population.[5]

Since the first gene was identified in 1995,[6] thousands of genes have been found to be associated with monogenic epilepsy.[7] In contrast to traditional Sanger sequencing, next-generation sequencing (NGS) technologies enable an entire genome to be sequenced in a single experiment. This technology has transformed the approach to diagnostic testing, allowing multiple genes to be tested simultaneously rather

than one at a time. However, these technologies also increase the likelihood of uncertain results when rare sequence variants are detected in one or more genes.[8] The ILAE genetic literacy series-2 proposed three key questions during the evaluation of patients: 1) Is the gene in question an established genetic etiology for epilepsy? 2) Is the variant in this particular gene pathogenic by established variant interpretation criteria? 3) Is the variant considered causative in the clinical context?[8] This pathway is recommended to assist epileptologists and physicians in interpreting the reported variants.

Identifying the responsible genes which are lead to genetic epileptic etiology can help understanding which genes are common in area and following projects may lead to determine frequency of responsible variants. Detection of responsible variants give direction on diagnostic test protocols, panels and opening new doors for patients treatments. Nowadays, in state hospital there are some of genetic analyses are covered by health insurance. Although, clinical exomes analyses may be accessible with insurance in some areas, moreover disease-related gene panels are used for monogenic disease investigation. The creation of disease-related gene panels or clinical exome sequences based by literatures. This study aimed to document responsible genetic disease and rates of patients with epilepsy whom are genetic etiology at a single-center epilepsy outpatient clinic in a state hospital to get started reporting in across country. Secondly, common and distinct genotype-phenotype correlations were identified based on aforementioned questions.

METHODS

Patients and Procedures

Medical records of patients followed at the epilepsy outpatient clinic at University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital were reviewed from August 2021 to January 2024. Epilepsy etiology was classified according to the ILAE classification.[2,9,10] Treatment responses were categorized as seizure-free and drug-resistant epilepsy.[11]

Patients who were diagnosed with genetic etiology during follow-up were included in the study. Systemic and neurological features; age at seizure onset; seizure types; seizure triggers; electroencephalographic and neuro-imaging findings; treatment responses; and family history were recorded from medical records. Patients with a previous diagnosed were excluded. Patients in whom a genetic etiology could not be identified were excluded.

Scalp electroencephalography (EEG) was performed during routine wakefulness and/or sleep recordings in patients with epilepsy. Electrode placement followed the international 10-20 system, using both monopolar and bipolar montages (Fp1, Fp2, F3, F4, T3, T4, P3, P4, O1, O2, Fz, Cz, Pz). Cranial magnetic resonance imaging (MRI) or brain computed tomography (CT) was performed to evaluate brain anatomy, depending on the patient's level of cooperation and cognitive function.

The patients and/or their caregivers were informed that anonymized medical data might be used for academic purposes, and all provided their approval. Written informed consent was obtained from each patient and/or their caregiver. The study was approved by the University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital Scientific Research Ethics Committee (decision no: 2025-323, date: 03.09.2025).

Genetic Analyses

The patients were examined in detailed by corresponding author (Dilara Mermi Dibek), suspected gene was stated if it was determined and they were consulted to medical genetic. The patients with dysmorphism, mental retardation, or presence of history of maternal miscarriage were analyzed for chromosomal abnormalities first.

Array comparative genomic hybridization (CGH) was used to detect chromosomal abnormalities when karyotyping results were normal. The Agilent GeneSure Cyto 8x60K CGH Microarrays system was employed, and results were analyzed using the Agilent CitoGenomics software (v5.2.0.20).

Clinical exome sequencing (CES), whole-exome sequencing (WES), and clinic-specific gene panels were utilized to identify single nucleotide variants.

The "twist CES kit" was used to examine the exon and exon-intron splice regions of panel genes. These regions were amplified using polymerase chain reaction (PCR) and sequenced on a DNBSEQ-G400 (MGI Tech) genetic sequencer via NGS in a patient presenting with congenital cataracts, spontaneous nystagmus, polyneuropathy, and seizure. Sequencing coverage was at least 99.80% at 5x and at least 99.50% at 20x.

For WES, the "TWIST 36Mb capture" kit was used to sequence exon and exon-intron splice regions of panel genes, also amplified by PCR and analyzed on the MGI DNBSEQ-G400 via NGS. Sequencing coverage was at least 99.55% at 5x and at least 99.18% at 20x. One of patients with progressive myoclonia underwent CES targeting a 342-gene panel associated with myoclonic disorders. For a patient with suspected spinocerebellar ataxia, a clinic-specific gene comprising 43 genes was analyzed (Supplementary File 1). Identified variants were reviewed using PubMed, gnomAD, ClinVar, and DECIPHER databases (https://gnomad.broadinstitute.org, https://www.ncbi.nlm.nih.gov/clinvar/, https://www.deciphergenomics.org).

Statistical Analysis

IBM SPSS version 26.0 were used for statistical analysis. The distribution of epilepsy syndrome classifications were calculated with descriptive statistics, and were presented number and percentage (%).

MAIN POINTS

- Establishing a link between a gene variant and the genetic etiology of epilepsy requires an assessment of genotype-phenotype correlation.
- Patients can be affected by mutations in two genes, where as their relatives may carry a mutation in only one gene and present with a different phenotype.
- If variants of uncertain significance are identified, further investigations such as family segregation analyses and *in vivo* or *in vitro* functional studies should be conducted.
- Detection and reporting of patients with genetic epilepsy in each epilepsy clinic is important to adjust the diagnostic test protocols and treatment options across the country.

RESULTS

The medical records of 354 patients with epilepsy were reviewed. Forty (11.2%) patients were diagnosed with genetic generalized epilepsy (GGE). Among them, 37 patients (10.4%) were diagnosed with IGE and 3 patients (0.8%) were diagnosed with epilepsy with eyelid myoclonia. Forty-one patients with epilepsy (11.5%) had autism spectrum disorders or/and intellectual disability.

Eight patients with epilepsy (2.2%) who had been previously diagnosed at another epilepsy center before commencing follow-up at our center were excluded. Three patients (0.8%) were diagnosed with neuro-cutaneous syndromes (linear nevus syndrome, n=1; tuberous sclerosis, n=2). Four patients (1.1%) were diagnosed with neuro-metabolic syndromes (galactosemia, n=2; mucopolysaccharidosis, n=2). One (0.2%) patient was diagnosed with Bardet-Biedl syndrome.

Ultimately, we included nine patients with epilepsy (2.5%) in whom an identifiable genetic etiology was established. Of these, seven (1.9%) had rare monogenic variants [zinc finger protein 142 *(ZNF142)*, zinc finger MYND-type containing 11 *(ZMYND11)*, discs large MAGUK scaffold protein 4 *(DLG4)*, peroxisomal biogenesis factor 11 beta *(PEX11B)*, scavenger receptor class B member 2 *(SCARB2)*, and glutamate receptor metabotropic 1 *(GRM-1)*] and two (0.5%) had chromosomal abnormalities (1p36 deletion and 15q15.1 deletion).

Rare monogenic variants in *ZNF142*, *ZMYND11*, *DLG4*, and *SCARB2* were detected using WES. A monogenic variant in *PEX11B* was identified through CES, and a variant in *GRM1* was detected using a locus-specific gene panel for spinocerebellar ataxia.

A 24-year-old male patient presented to the epilepsy outpatient clinic. No significant perinatal history was reported. His parents are consanguineous, and his older brother (currently 35 years old) has a progressive speech disorder. However, the brother has no history of epilepsy, except for a single febrile seizure at the age of 2. The family pedigree is shown in Figure 1A. The patient experienced febrile seizures until the age of 8. After discontinuation of antiseizure medication (ASM), he developed motor convulsive status epilepticus with coma at the age of 20. Since then, he has been seizure-free under treatment with valproic acid (1000 mg/day). He is able to walk independently, but he exhibits cognitive decline and progressive speech disorder, although he had acquired speech by the age of 4. He also presents with renal agenesis, without evidence of renal failure. Notably, no hyperkinetic or hypokinetic movement disorders have been observed up to the age of 24. EEG during wakefulness showed background activity characterized by diffuse theta and delta frequencies (Figure 2A). Sleep graphoelements appeared synchronous and symmetric during stage II non-rapid eye movement (NREM) sleep. Cranial MRI was normal. The chromosomal microarray analysis revealed normal results: -arr[hg38] (1-22)x2, (X,Y)x1. WES identified a homozygous pathogenic variant in the *ZNF142* gene [(NM_001105537.4: c.3175 C>T), (NP_001099007.1:p.Arg1059Ter)], located at chr2:219508064 (patient no. 1 in Table 1).

A 23-year-old female patient (patient no. 2 in Table 1) was first evaluated in the EEG laboratory during an episode of non-convulsive status epilepticus (NCSE) with coma, following a bilateral tonic clonic motor seizure triggered by a respiratory infection (pneumonia), and accompanied by severe hyponatremia (Na:113 mEq/L). After treatment of the metabolic disturbance and infection, the NCSE resolved, and she recovered without sequelae. She had hypoxic birth and was hospitalized for one week in the neonatal intensive care unit. There is no biological relationship between her parents. Her younger brother has similar dysmorphism and has a history of seizures. The patient demonstrates cognitive decline and significant speech impairment, with a vocabulary limited to 5-10 words without evidence of progressive loss. Dysmorphic features include ocular hypotelorism, low posterior hairline, flat nasal bridge, and short stature. She began walking at age 4, although she had Achilles tendon contractures. She is ambulatory with support. She has been diagnosed with diabetes mellitus, hypothyroidism and hypergonadotropic hypogonadism. Seizures began at the age of 1 year. Infections and metabolic disturbances are primary seizure triggers. Seizures typically present as status epilepticus. In the absence of t metabolic imbalance or infection, she remains seizure-free under treatment with valproic acid (800 mg/day). Brain CT showed no gross pathology. EEG revealed slow background activity with bifrontal or left frontal spike and wave discharges, sometimes recorded as bilateral hypersynchronous. Less frequently, occipital spike-and-wave were recorded. (Figure 3A, B). Her younger brother, aged 15 (patient no.3 in Table 1), had no significant perinatal complications. He has

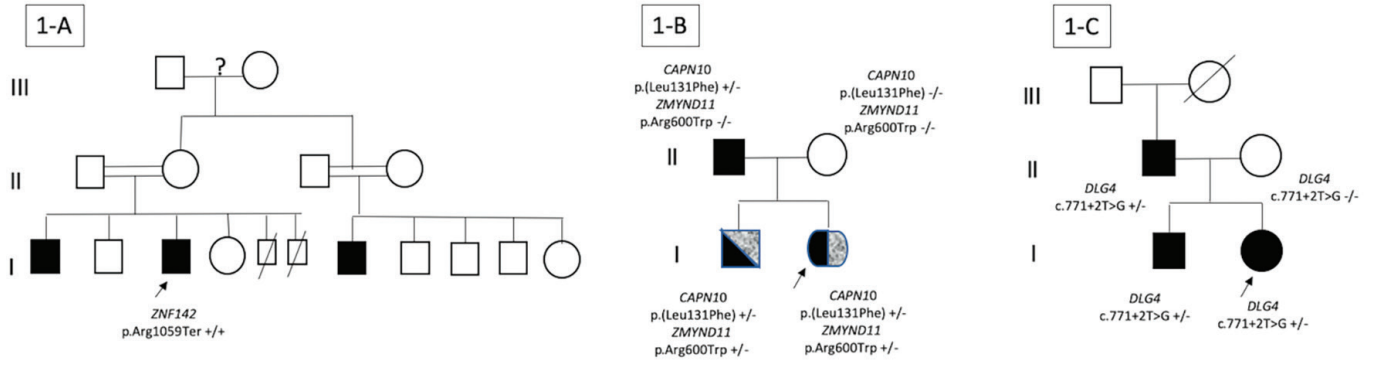

Figure 1. The pedigrees of the selected patients. Circles and squares indicate females and males, respectively. Solid symbols indicate affected individuals. +/+: Homozygous, +/−: +/−, heterozygous variant; −/−, homozygous reference. 1-A. The pedigree of patients with *ZNF142* homozygotes mutation (patient no.1 in Table 1). 1-B. The pedigree of patients with *CAPN10* with and without *ZYMND11* gene heterozygotes mutations (patient no.2 and no.3 in Table 1). 1-C. The pedigree of patients with *DLG4* heterozygotes mutation (patient no.4 in Table 1)

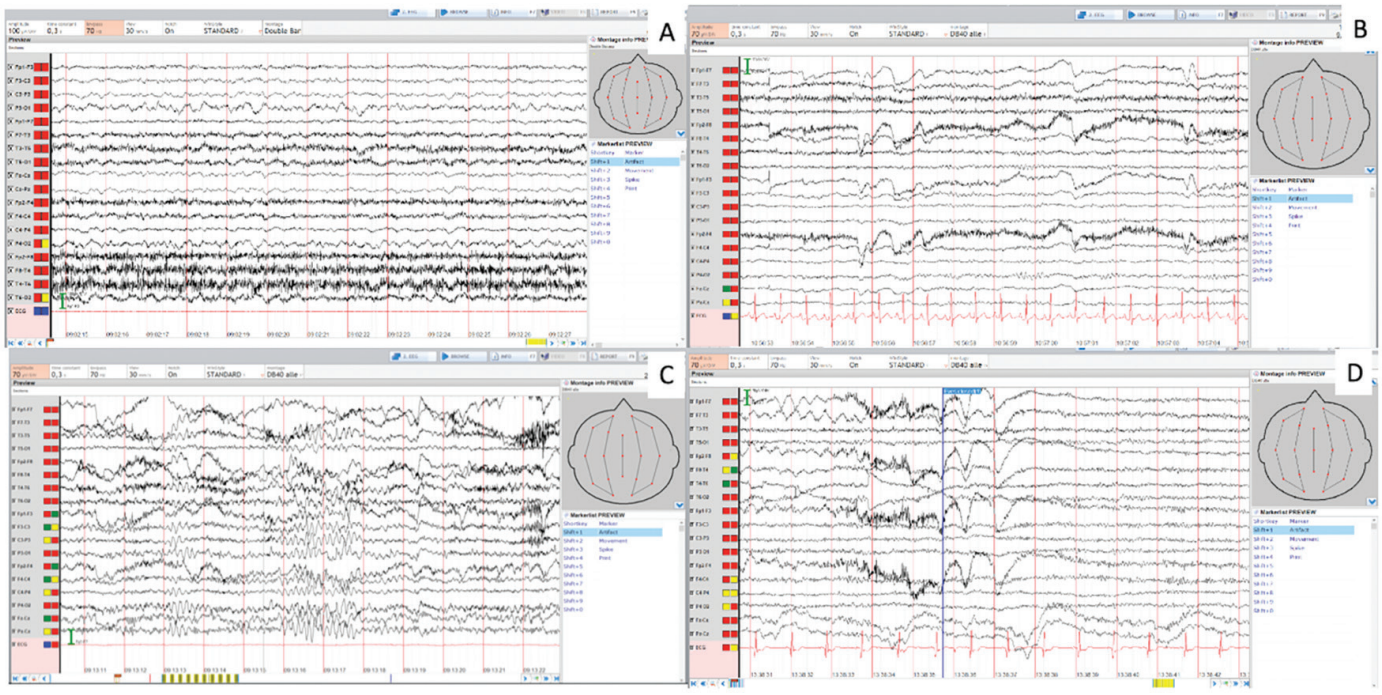

Figure 2. The EEG captures of the patients with changes on background activity. A. Slow background activity without epileptiform abnormality on EEG at the patients with *ZNF142* mutation (patient no.1 in Table 1). B. Slow background activity without epileptiform abnormality on EEG at the patients with *DLG4* mutation (patient no.4 in Table 1). C. Paroxysmal theta activity with higher amplitude on slow background activity on EEG at the patients with *PEX11B* mutation (patient no.5 in Table 1). D. Fast frequency and low amplitude in background activity on EEG at the patients with *GRM1* mutation (patient no.7 in Table 1)
EEG: Electroencephalography

a history of occasional seizures, typically triggered by metabolic disturbances or infections, but no history of status epilepticus. He exhibits similar dysmorphic features, including a depressed nasal bridge, ocular hypotelorism, low posterior headline, and short stature, but he does not have Achilles tendon contractures. He is ambulatory. He has cognitive decline. Although his speech is impaired, he can form sentences, with communication ability better than his sister's. He has also been diagnosed with diabetes mellitus and hypothyroidism. His EEG demonstrated slow background activity with bilateral fronto-centro-parietal sharp and spike-and-wave discharges, and bilateral hypersynchrony during NREM sleep without normal sleep graphoelements (Figure 3C, D). The mother has no notable phenotypic abnormalities. The father has diabetes mellitus but normal cognitive and motor development, and no history of seizures. His EEG during wakefulness was normal. During stage II NREM sleep, sleep graphoelements were synchronous and symmetric, though a transient left frontocentral asymmetric theta sharp contoured-slowing was observed (Figure 3E, F). Three family members- the father, daughter (patient no.2 in Table 1), son (patient no.3 in Table 1) have a calpain 10 *(CAPN10)* gene variation, while the mother did not. Chromosomal microarray analysis of patient no.2 normal: arr(1-22,X)x2. Additionally, WES revealed a heterozygous pathogenic variant in the *ZMYND11* gene [(NM_001370100.5 c.1798C>T), (NP_001357029.1:p.(Arg600Trp)] in both patient no.2 and patient no.3, but not in either parent. The family pedigree is shown in Figure 1B.

An 18-year-old female patient presented to the epilepsy outpatient clinic, there is no known consanguinity between her parents. Her mother, aged 40, had epilepsy during childhood but has remained seizure-free without ASM treatment since the age of 11. Her father, aged 43, has mild intellectual disability and mild dysphasia, he can speak comprehensively but has no history of seizures or musculoskeletal, cardiac, or gastrointestinal system disorders. Her 14-year-old brother has a intellectual disability and his speech more developed than his sister's but less developed than his father's. He also has long, thin, and elastic fingers, consistent with digital deformity. He does not present with seizures or other systemic abnormalities. The pedigree is shown in Figure 1C. The patient demonstrates cognitive decline and restricted-but non-progressive-speech ability. She required incubator care during the first week of life due to neonatal jaundice. Her first afebrile seizure, a bilateral tonic seizure, occurred in the neonatal period. After a seizure-free interval, she experienced a unknown onset bilateral tonic clonic motor seizure at age 7. She was initially treated with valproic acid, and seizures occured once or twice per month. No specific seizure triggers were identified. She has remained seizure-free for the past 3 years with on carbamazepine monotherapy. Neurological examination revealed limited left horizontal gaze, while other gaze directions were preserved. Motor development was normal, though she exhibited a mildly ataxic gait. Both Hoffman and Babinski reflexes were positive. She also had a history of patent ductus arteriosus and gastroesophageal reflux. EEG during wakefulness showed normal background activity (Figure 2B); however, poor morphology of sleep graphoelements was noted during stage II NREM sleep. Cranial MRI showed no gross abnormalities. Chromosomal microarray analysis was normal: arr[hg19] (1-22,X) x2 in the index case. WES identified a heterozygous pathogenic variant in the *DLG4* gene [(NM_001365.4: c.771+2T>G)] in the index patient, her father and her younger brother. The variant was not detected in her mother (patient no.4 in Table 1).

Table 1. Clinical and genetic features of the patients with monogenic variants and epilepsy

No, age (years), sex	Seizure onset	Seizure type	Other system symptomes	EEG	MRI/CT	Response of ASMs	Genetic analysis	Gene variants	Disease
No.1 24, M	2y febrile seizure 19y status epilepticus	Unknown onset bilateral tonic-clonic motor	CD, progressive speech disorders, renal agenesis	Slow background activity, Poor morphological changes in sleep grapho elements	Normal	Seizure free with VPA 1000 mg/day	NGS-WES	*ZNF142* Chr2 c.3175 C>T (p.Arg1059Ter) Homozygotes	Neurodevelopmental disorder with impaired speech and hyperkinetic movements
No.2 23, F	1y	Status or nonconvulsive status epilepticus triggered by infection or metabolic disturbances, unknown onset bilateral tonic-clonic motor	MMR, short stature, microcephaly typical face: ocular hypotelorism, low nape, flat nose, achilles contracture, hypogonodothropic hypogonadism hypothyroidism, DM	Slow background activity, diffuse slow and sharp waves	Normal	Seizure free with VPA 800 mg/day	CAPN10 gene analysis, NGS-WES	*CAPN10* c.391C>T, p.Leu131Phe Heterozygotes *ZMYND11* c1798C>T p.(Arg600Trp) Heterozygotes	Kalpain 10- Intellectual developmental disorder, autosomal dominant
No.3 15, M	4y	Unknown onset bilateral tonic-clonic motor	MMR, Short stature, microcephaly, typical face: ocular hypotelorism, low nape, flat nose, hypothyroidism, DM	Slow background activity, diffuse slow and sharp waves	NA	Low drug compliance, Refuse the usage of ASMs	CAPN10 gene analysis, NGS- WES	*CAPN10* c.391C>T, p.Leu131Phe Heterozygotes *ZMYND11* c1798C>T p.(Arg600Trp) Heterozygotes	Kalpain 10- Intellectual developmental disorder, autosomal dominant
No.4 18, F	1y	Unknown onset bilateral tonic-clonic motor	CD, partial ophtalmoparesis, ataxia, patent ductus arteriosus, gastro eusofageal reflux	Fast atenuated rhythm on background activity	Normal, coinsidental septum pellusidum	Seizure free with CBZ 800 mg/day	NGS- WES	*DLG4* c.771+2T>g Heterozygotes	Intellectual developmental disorder, autosomal dominant 62 wes
No.5 34, M	3y-11y febril and afebril seizures 32y afebril bilateral tonic-clonic seizures	Unknown onset bilateral tonic-clonic motor	MMR, Infantil cataract operation, spontanous nystagmus, sensorial neuropathy	Slow background activity with sharp contured high amplitüde paroxysmal sinusoidal transients	Cortical athrophy	Seizure free with LEV 1250 mg/day	NGS-CES	*PEX11B* chr1 c.595C>T Homozygotes	Peroksizom biogenesis disorders PBD14B
No.6 53, M	47y	Myoclonia triggered with photic stimulations, positive and negative myoclonia	Progressive tremor and myoclonia, parkynsonism	Slow bacground activity with generalized polyspikes, eye closed sensitivity with bioccipital spikes and waves photosensitivity: extremity myoclonia in IPS	Normal	DRE: progressive myoclonia despite of CLZ 4 mg/day, TPM 200 mg/day	342 genes related to myoclonia in WES	*SCARB2* chr4 c.1113+6T>A Homozygotes	Epilepsy progressive myoclonus 4 w/wo RF- EPM4C
No.7 20, M	3 months-infantil	Tonic, unknown onset bilateral tonic-clonic motor	MMR, dysphonic speech, spontanous rotatuar nystagmus, bilateral dysmetri, dystonic tremor, hipothyroidism	Fast atenuated rhythm on background activity	Cerebellar athrophy	DRE: 3-4 in a years with VPA 1000 mg/day, OXC 750 mg/day	NGS- 43 genes related to spinocerebellar ataxia panel	*GRM-1* (SCA-44) c.1610G>A p.(Arg537Gln) missense heterozygotes	Spinoserebellar ataksi-44

ASMs : Antiseizure medications, F: Female, M: Male, *CAPN10*: Calpain 10, CBZ: Carbamazepine, CES: Clinical exome sequencing, CLZ: Clonazepam, CD: Cognitive decline, *DLG4*: Discs large MAGUK scaffold protein 4, DM: Diabetes mellitus, DRE: Drug-resistant epilepsy, *GRM-1*: Glutamate receptor metabotropic 1, LEV: Levetiracetam, MMR: Mental-motor retardation, NA: Not applicable, NGS: New genome sequencing, OXC: Oxcarbazepine, *SCARB2*: Scavenger receptor class B member 2, *PEX11B*: Peroxismal biogenesis factor 11 beta, TPM: Topiramate, WES: Whole exome sequencing, VPA: Valproic acid, *ZMYND11*: Zinc finger MYND-type containing 11, *ZNF142*: Zync finger protein 142, EPM: Epilepsy, progressive myoclonus 4C, MRI/CT: Magnetic resonance imaging/computed tomography

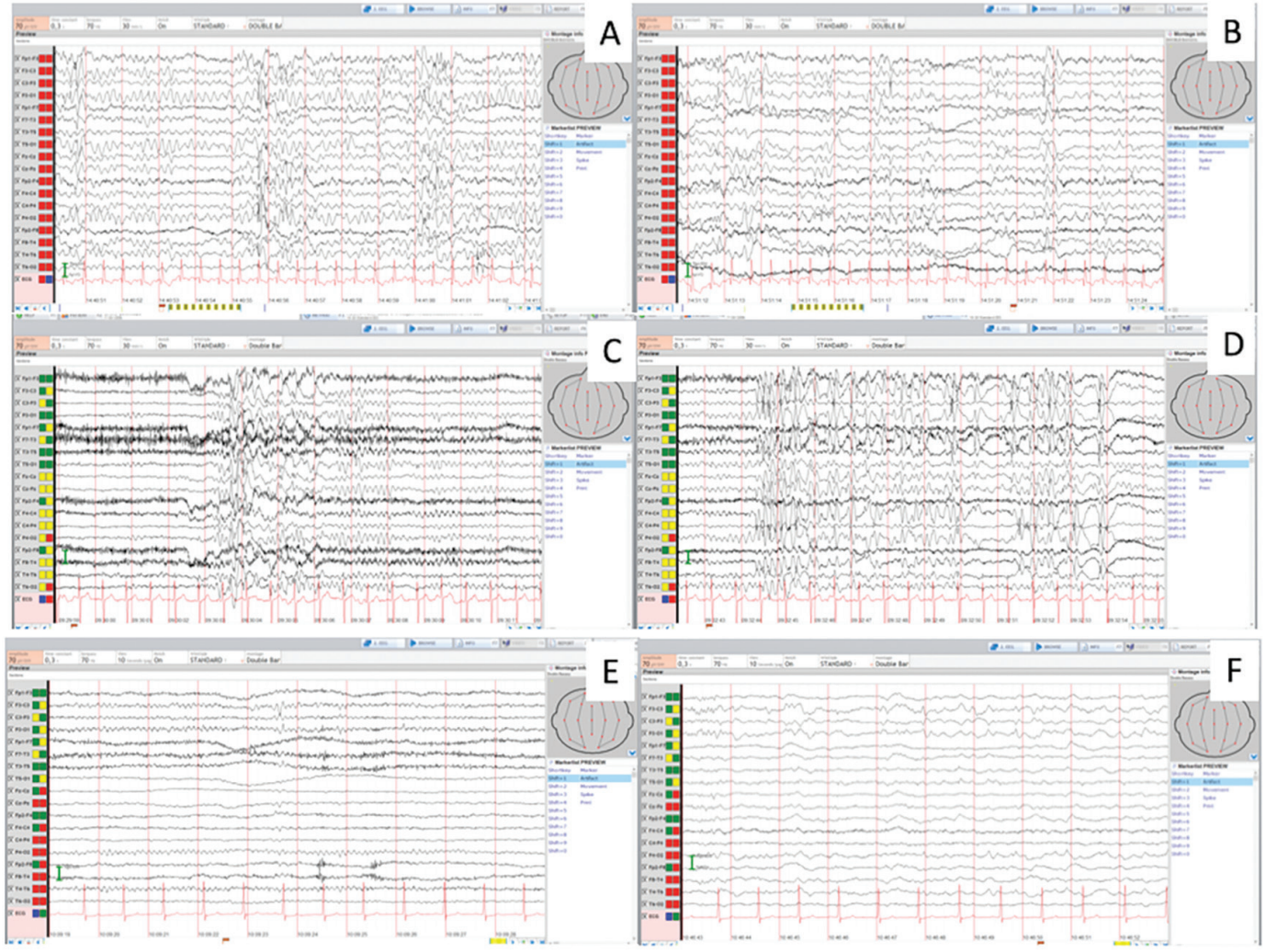

Figure 3. The EEG captures of the family members with mutation in *CAPN10* whit or without *ZMYND11*. A. Slow background activity and bilateral centroparietal sharp wave during wakefulness under 1000 mg/day VPA treatment; B. Left frontal spike and waves during NREM sleep stage at patient with mutation at *ZMYND11* and *CAPN10* (patient no.2 in Table 1); C. Left fronto-centroparietal predominant bilateral spike and sharp waves during wakefulness without treatment. D. Bilateral fronto-centroparietal predominant generalized sharp and waves during NREM sleep stage at patient with *ZMYND11* and *CAPN10* mutation (patient no.3 in Table 1). E. Normal background activity. F. Left centroparietal asymmetry and sharp waves during NREM II sleep stage at father of (patient no.2 and 3 in Table 1), who has *CAPN10* mutation without *ZMYND11* mutation
EEG: Electroencephalography, NREM: Non-rapid eye movement

A 34-year-old male patient presented to the epilepsy outpatient clinic with history of cognitive decline and motor retardation. He is ambulatory with the assistance of a wheelchair. His parents are consanguineous, he had no siblings, and there is no significant family history of neurological disorders. The patient experienced febrile seizures beginning at the age of 3 and was treated with valproic acid until age 11. Following a seizure-free period, ASM was gradually tapered and discontinued. At the age of 32, he experienced a unknown onset bilateral tonic clonic seizure without an identifiable trigger, after which levetiracetam was initiated. Since ten, he has had fewer than one seizure per year, typically occurring in the context of respiratory infections. He underwent bilateral cataract surgery at the age of 2 years and demonstrated spontaneous nystagmus and restricted horizontal gaze to the right. Although, he did not exhibit overt ataxia, sensorial polyneuropathy was identified via electroneuromyography. He also had a history occasional micturition syncope. EEG during wakefulness revealed background activity consisting of 5-6 Hz theta frequency. Additionally, paroxysmal sinusoidal activity with sharp contours and higher amplitude than background were observed at 7-7.5 Hz (Figure 2C). Cranial MRI showed mild to moderate cerebral cortical atrophy. CES identified a homozygous pathogenic variant in the *PEX11B* gene [(NM_003846.3: c.595C>T), NP_003837.1:(p.Arg199Ter)] located at chr1:145522734. Both parents were found to be heterozygous carriers of the same variant (patient no.5 in Table 1).

A 53-year-old male patient initially presented to EEG laboratory. His perinatal and family history were unremarkable. He was a retired insurance agent. His symptoms began six years prior to presentation, initially with fine hand jerks and low-amplitude tremors. Despite two years of treatment with primidone and propranolol, postural and kinetic tremors progressed, and sudden jerky hand movements emerged. Over time, he developed

progressively slow movements and speech. Eventually, he experienced falls without loss of consciousness, attributed to sudden myoclonic jerks. Neurologic examination revealed bradyphrenia, bradymimia, monotonous speech with hypophonia, bradykinesia predominantly affecting the left hand, and mild bilateral dysmetria without postural instability. Zonisamide and clonazepam were prescribed for myoclonus but yielded limited benefit. EEG performed during wakefulness showed background activity consisting of slow 5-6 Hz theta frequency. Bi-occipital predominance spike-and-wave discharges were observed with eyes closed (eye closed sensitivity). Additionally, photic stimulaton elicited photosensitivity and myoclonic activity in the upper extremities, coinciding with generalized polyspikes-and-wave discharges (Figure 4D-F). Cranial MRI showed no gross structural abnormalities. Clinically combination of symptoms and EEG findings was consistent with mild parkinsonism and progressive myoclonus. CES of 342 genes associated with myoclonus revealed a homozygous variant of uncertain significance in the *SCARB2* gene, NM_005506.4: c.1113+6T>A, located at chr4:77091014. This gene is implicated in progressive myoclonic epilepsy type 4 (PME4), with or without renal involvement. A full list of the analyzed genes is provided in Supplementary File 1 (patient no.6 in Table 1).

A 20-year-old male patient presented to the epilepsy outpatient clinic. There was no known biological relationship between his parents. He had an older brother and mother who were alive; his father was deceased. The family history was otherwise unremarkable. The patient experienced focal clonic and focal to bilateral tonic-clonic seizures. While receiving treatment with oxcarbazepine and valproic acid, seizure frequency was reduced to 3-4 times per year. In addition to cognitive decline, neurological examination revealed spontaneous rotatory nystagmus, bilateral asymmetry, an ataxic gait, and mild dystonic tremor. Cranial MRI demonstrated cerebellar atrophy (Figure $5A_{1,2,3}$). EEG revealed fast frequency, low amplitude background activity (Figure 1D).

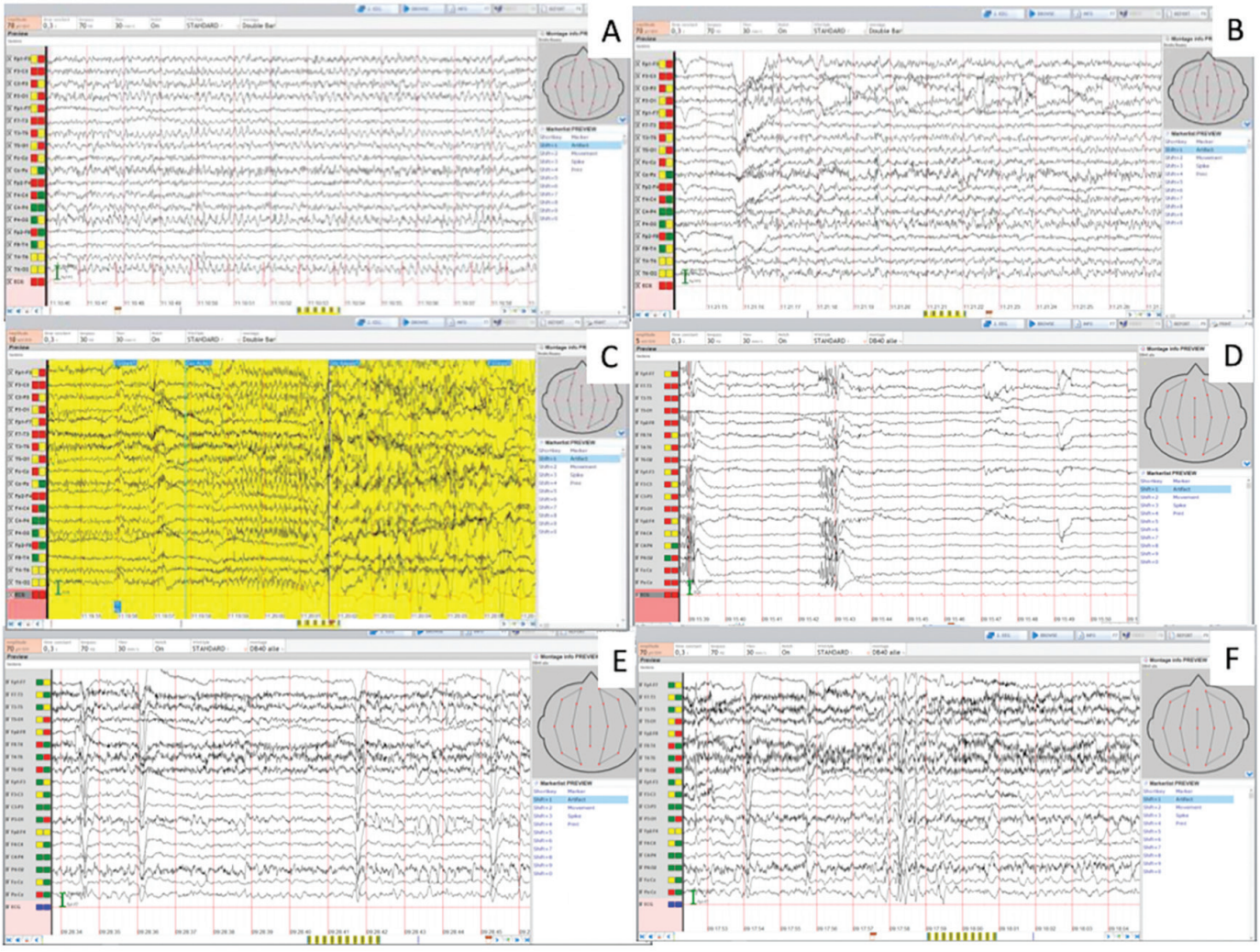

Figure 4. The EEG captures of the patients with special EEG features. A. Slow background activity during wakefulness, B. Eye closed sensitivity with bi-occipital spikes, and C. Generalized poly-spikes and waves with bilateral upper extremity myoclonia at 15 Hz frequency intermittent photic stimulation at patients with *SCARB2* gene mutation (patient no.6 in Table 1). C. Slow and attenuated background activity with generalized poly-spike train on EEG at patient with 1p36 deletion (patient no.1 in Table 2). D, E. Slow background activity with synchronous or asynchronous bi-occipital sharps waves, secondary bilateral hypersynchrony on EEG at patient with 15q15 deletion (patient no.2 in Table 2)
EEG: Electroencephalography

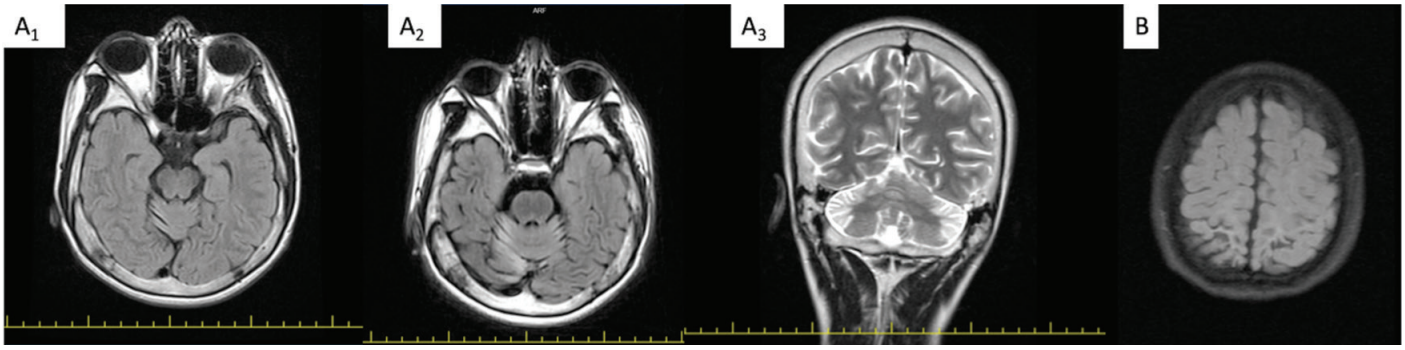

Figure 5. The brain MRI captures of the patients with structural changes. A_{1-3}. Cerebellar atrophy in cranial MRI in patients with mutation at *GRM1* (patient no.6 in Table 1). B. Bilaterally parietooccipital encephalomalacia in patients with deletion at 15q15.1 (patient no.2 in Table 2)
MRI: Magnetic resonance imaging

During NREM stage II sleep, synchronous and symmetric sleep graphoelements were recorded, without any epileptiform discharges. Genetic analysis using a disease-specific panel for spinocerebellar ataxia identified a heterozygous variant of uncertain significance in the *GRM1* gene [(NM_001278064.2: c.1610G>A), (NP_001264993.1:p.(Arg537Gln)]. This gene associated with autosomal dominant spinocerebellar ataxia 44 (patient no.7 in Table 1).

A 19-year-old female patient presented to epilepsy outpatient clinic. Her parents were consanguineous. She was a twin in utero; however, her co-twin died intrapartum. The patient had been experiencing atypical absence seizures 1 -2 times per month while on treatment with levetiracetam and topiramate. She has been present since the neonatal period. She exhibited cognitive decline and motor retardation. Dysmorphic features included short stature, a thick neck, ocular hypotelorism, and short fingers and feet. She was wheelchair-bound and unable to ambulate independently. Additionally, she had insulin intolerance and hypothyroidism. EEG revealed attenuated, slow background activity and frequent generalized poly-spikes discharges, also referred to as a generalized poly-spike train (GPT) were recorded (Figure 4C). Cranial MRI showed no gross abnormalities. Array-CGH identified a 1p36.33 deletion (patient no.1 in Table 2).

A 19-year-old male patient presented to epilepsy outpatient clinic. There was no known biological relationship between his parents. He had 2 male siblings, and there was no significant family history. He was born three weeks prematurely and required postnatal incubation. Seizures began at three months of age and were characterized by eye deviation occurring several times per day, often triggered by infections. He exhibited cognitive decline, spontaneous nystagmus, and ocular gaze deficits. EEG showed a background rhythm of 4-6 Hz theta activity. In addition, both synchronous and asynchronous occipital spikes and bilateral hypersynchronous sharp waves were recorded (Figure 4E, F). Cranial MRI revealed bilateral parieto-occipital encephalomalacia (Figure 5B). Karyotype analysis was normal. Array- CGH identified a heterozygous 15q15.1 deletion encompassing 52 genes over a 1.789 Mb region (Supplementary File 1). Parental array results were normal (patient no.2 in Table 2).

The patients' demographic characteristics, phenotypic features, responses to ASM, EEG and neuroimaging findings, as well as genetic analyses, are summarized in Tables 1 and 2.

DISCUSSION

In this study, we reported the 9 distinct genetic causes of epilepsy identified during follow-up at the epilepsy outpatient clinic of a state hospital. All patients exhibited cognitive impairment accompanied by neurological and/or other systemic findings. Four patients (44.4%) had a history of seizures triggered by metabolic imbalance or infections; in one patient, the seizure presented as status epilepticus. Four patients (44.4%) remained seizure-free without identifiable triggers, while another four (44.4%) had drug-resistant epilepsy. Notably, both patients with chromosomal abnormality had drug-resistant epilepsy. EEG revealed slow background activity in seven patients (77.7%). One patient with PME exhibited both eye closure sensitivity and photosensitivity. Cranial MRI showed cortical atrophy in two patients (22.2%) and cerebellar atrophy in one of patients (11.1%).

The *ZNF142* gene encodes the zinc finger protein 142, a member of the zinc finger protein superfamily-one of the largest groups of mammalian transcription factors.[12] Pathogenic variants in these proteins have been associated with various neurodevelopmental disorders.[13] To date, 42 patients have been reported in the literature with heterozygous *ZNF142* variants, typically presenting with neurodevelopmental disorder with impaired speech and hyperkinetic movements.[14,15] In the present study, we described a patient carrying a *ZNF142* variant who exhibited with a progressive speech impairment without hyperkinetic movements, dystonia, ataxia, or typical dysmorphic features. His seizures were well-controlled with ASMs, and he remained seizure-free for three years during follow-up. However, a relapse presenting as status epilepticus occurred upon ASM discontinuation. Given his positive family history and progressive speech difficulties, a genetic etiology was investigated.

The *ZMYND11* is a critical gene associated with the 10p15.3 microdeletion syndrome, which is characterized by developmental delay or intellectual disability, behavioral abnormalities, dysmorphic features, hypotonia, and seizures. To date, approximately 20 patients have been described in the literature with this condition.[16] In our study, two siblings were identified with mental and motor retardation, along with characteristic facial dysmorphism. Both, carried the same pathogenic variant in *ZMYND11*. However, the clinical severity differed: the sister exhibited severe symptoms, including status epilepticus triggered by infections or metabolic disturbances, whereas the brother had infrequent unknown onset

Table 2. Clinical and genetic features of the patients with chromosomal abnormality and epilepsy

No, age (years), sex	Seizure onset	Seizure type	Other system symptomes	EEG	MRI/CT	Response of ASMs	Genetic analysis	Chromosomal abnormality
No.1 19, F	New-born	Atypical absance, tonic atonic	MMR Short, ocular hypotelorism, nasal flattened, immobilise, bilateral Babinski sign	Atenuated slow background activity with generalized poly-spike trains	Normal	DRE: 1 in 2 months atypical absance with LEV 2000 mg/day, TPM 200 mg/day	Array-CGH	1p36 deletion
No.2 19, M	3 months-infant	Focal motor seizure with ocular deviation and rare focal onset bilateral tonic clonic motor	CD, autism spectrum disorders, steretypical movements, restricted eyes horizontal gaze	Slow background activity with asyncronous and syncronous bi-occipital spikes and frequent secondary bilateral hypersynchrony	Bilateral parietooccipital encephalomalasia	DRE: 1-2 seizures in a week with VPA 1000 mg/day, LEV 2000 mg/day, LCM 400 mg/day, LTG 300 mg/day, CLZ 2 mg/day	Array-CGH	15q15.1 heterozygotes deletion

ASMs: Antiseizure medications, F: Female, M: Male, CBZ: Carbamazepine, CD: Cognitive decline, LEV: Levetiracetam, CLZ: Clonazepam, LCM: Lacosamide, LTG: Lamotrigine, CGH: Comparative genomic hybridization, TPM: Topiramate, VPA: Valproic acid, MMR: Mental-motor retardation, MRI/CT: Magnetic resonance imaging/computed tomography, DRE: Drug-resistant epilepsy

bilateral tonic-clonic seizure. EEG findings also varied. The sister showed frequent frontal asynchronous sharp waves and bilateral hypersynchronous sharp waves, while the brother's EEG demonstrated longer-lasting bilateral hypersynchronous diffuse sharp-and-waves discharges. The sister was treated with valproic acid, whereas the brother declined ASM. These EEG differences may, in part, be attributable to the effect of valproic acid treatment. Additionally, both siblings and their father were diagnosed with diabetes mellitus and carried a variant in the *CAPN10* gene, which has been implicated in susceptibility to type 2 diabetes mellitus.[17] The father had no history of seizure and exhibited normal cognitive and motor development. His EEG was unremarkable except for transient theta slowing in the left centroparietal region during NREM sleep, which was considered clinically insignificant. The mother did not carry either the *ZMYND11* or *CAPN10* variants. Given that both siblings harbored the *ZMYND11* variant while neither parent carried it, gonadal mosaicism is the most plausible explanation. This family thus demonstrates combined phenotypic features resulting from pathogenic variant in two different genes- *ZMYND11* and *CAPN10*.

The *DLG4* (discs large MAGUK scaffold protein 4) encodes postsynaptic density protein 95, which is expressed in various tissues, including the brain. Pathogenic variants in *DLG4* have been associated *DLG4*-related synaptopathy, a neurodevelopmental disorder characterized by intellectual disability, autism spectrum disorders, muscular hypotonia, abnormal movements, epilepsy, ophthalmologic abnormalities, and marfanoid features. In the literature, approximately 54 patients with *DLG4*- related disorders have been described.[18,19] In the present study, a novel heterozygous splice-site variant [(NM_001365.4: c.771+2T>G)] in *DLG4* was identified in three family members. The index patient's younger brother, who carried the same variants, had intellectual disability, but spoke better than his sister, though not as fluently as their father. He had marfanoid joint deformities but no history of seizure or other systemic abnormalities. Their father, who carried same variants, had mild intellectual disabilities but otherwise systemically intact, enabling him to maintain employment. Interestingly, none of the three individuals with the *DLG4* variant exhibited dystonia. This family illustrates infrafamilial phenotypic variability associated with the same pathogenic variant. The inheritance pattern appeared to be autosomal dominant in the siblings, with a *de novo* origin in the father, suggesting this variant is novel in familial context.

The *PEX11B* encodes a peroxisomal membrane protein that is predicted to contain two transmembrane domains.[20] Homozygous variants in this gene have been associated with congenital cataracts, progressive deafness, polyneuropathy, gastrointestinal issues, and intellectual disability.[21] To date, seven patients with mutations have been reported in the literature.[22] Our patient carried a homozygous variant in the *PEX11B* gene. His parents, who were consanguineous, were both heterozygous carries. The patient presented with intellectual disability, speech impairment, spontaneous nystagmus, sensorial neuropathy, and epilepsy which remained seizure-free under monotherapy. EEG revealed slow background activity with high-amplitude sharply contoured paroxysms. Unlike previously reported cases our patient did not exhibit hearing loss.

The *SCARB2* encodes lysosomal integral membrane protein type-2 (*LIMP-2*).[23] Mutations that impair *LIMP2* function disrupt the biogenesis and maintenance of the lysosomal and endosomal compartments, leading to PME.[24] If the clinical history, examination findings, EEG, and MRI results suggest PME, genetic testing should be performed in accordance with recommendations from the ILAE regarding progressive myoclonic epilepsies.[25] Rubboli et al.[26] reported a patient with PME due to *SCARB2* mutation without renal failure. Similar to our case, their patient exhibited photic- and eye closure-induced myoclonus; however, their patient background EEG activity was normal.[26] While their patient was under 30 years old, ours was 53 years old. The slower EEG background in our patient may be attributable to age-related changes in brain activity, as background rhythms are known to slow over time. Previous studies have described 62 patients with *SCARB2*-related disorders, presenting with spectrum that includes action myoclonus renal failure syndrome, REM sleep behavior disorders, parkinsonism, PME with or without renal failure.[24,25,27] Our patients exhibited progressive myoclonus, tremor, and parkinsonism, but did not show REM sleep behavior disorders and renal failure. Further research is warranted to clarify the relationship between *SCARB2* variants of uncertain significance and these phenotypes.

The *GRM1* encodes metabotropic glutamate receptor 1, which plays a crucial role in slow excitatory postsynaptic transmission, synapse formation, synaptic plasticity, and motor control. The *GRM1* gene shows its highest expression in the cerebellum, beginning in early development and continuing throughout ontogenesis.[28,29] Mutations in this gene have been associated with autosomal dominant or recessive cerebellar atrophy, intellectual disabilities, cerebellar atrophy without cognitive impairment, late-onset mild symptoms, short sleep duration and efficiency, autism spectrum disorders, and schizophrenia in total of 12 reported individuals.[30-33] Our patient presented with intellectual disability, autism spectrum disorders, dysphasia with dysphonia, spontaneous nystagmus, dystonic tremor, and seizure. A missense heterozygous variant of uncertain significance was identified. The phenotypic features were consistent with those previously described in the literature. However, *in vivo* or *in vitro* functional studies, as well as parental segregation analyses, are necessary to confirm genotype-phenotype correlation.

1p36 deletion syndrome (del1p36) is characterized by developmental delay, behavioral abnormalities, hypotonia, seizures, brain abnormalities, visual impairment, orofacial cleft, congenital heart defects, cardiomyopathy, renal anomalies, short stature, and a distinctive gait.[34] Phenotypic differences between distal and proximal deletion have been described: distal deletions are more associated with microcephaly, whereas proximal deletions more frequently involve brain malformations, epilepsy and cardiomyopathy.[35] Epilepsy with patient eith del1p36 is often accompanied by cranial abnormalities.[35] Our patient had a distal del1p36 and presented mental and motor retardation, typical facial features, short stature, and drug-resistant epilepsy. EEG showed GPT, though her neuroimaging was normal. GPT has been described in patients with GGE associated with drug resistance epilepsy.[36] Our patient similarly exhibited drug resistance epilepsy.

A 15q15.1 deletion has been reported in association with limb girdle muscular dystrophies.[37] However, our patient did not show any myopathic features. He had a perinatal asphyxia and exhibited bilateral parieto-occipital encephalomalacia on MRI. Clinically, he presented with intellectual disabilities, aphasia, restricted eye gaze, stereotypical movements, and focal motor seizures characterized by forced conjugated lateral gaze. Although the deletion encompasses several genes related to epilepsy, the presence of encephalomalacia from perinatal asphyxia may also contribute to the phenotype. The absence of phenotypic abnormalities and chromosomal deletions in both parents suggests that the chromosomal anomaly detected in the patient is *de novo* and likely contributes to the observed phenotype. Nevertheless, the severity and complexity of his clinical features go beyond what would typically be expected from asphyxia alone, underscoring the importance of conducting genetic analysis in such cases.

Study Limitations

We reported the genetic etiology of patients with epilepsy followed in a single-center outpatient clinic. Patients who had been previously diagnosed at another center were excluded to avoid duplication in the literature. One of the main limitations of this study is retrospective design that all the reported genetic etiologies were based solely on clinical work-up which is lead to selection bias, and patients whose genetic investigations are still ongoing were not included. These factors contributed to small sample size which is major limitations of the study. Secondly, genetic testing was selected individually based on each patient's phenotypic findings, leading to variability in the genetic tests performed. For instance, among 41 patients with cognitive decline followed in the epilepsy outpatient clinic, a definitive genetic diagnosis was reached in only nine cases during 2.5 years follow-up period. This low diagnostic yield represents another key limitation of the study. Further research is needed to identify epilepsy-related variants, possibly through the use of comprehensive genetic epilepsy panels. Despite these limitations, our data included two notable findings: (1) two patients were affected by mutations in different genes due to inherited gonadal mosaicism; and (2) variable phenotypic features related to the same gene were observed within a single family. All reported patients and their parents were examined in detail and their findings were thoroughly documented. Finally, our study highlights the importance of conducting *in vivo* or *in vitro* functional studies to clarify the pathogenicity of variant uncertain significance.

CONCLUSION

In conclusion, when cognitive decline, autism spectrum disorders, dysmorphic features, or multisystem involvement are presented in patients with epilepsy, we should consider genetic etiology. Selecting appropriate genetic tests based on these clinical findings is essential for identifying the underlying genetic etiology. Reporting the patients with genetic epilepsy etiology from each epilepsy center to across the country will be improved the diagnostic tools and treatment options.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital Scientific Research Ethics Committee (decision no: 2025-323, date: 03.09.2025).

Informed Consent: Written informed consent form was obtained by each patient and/or their caregivers.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: D.M.D., A.G., B.U., L.Ş., Concept: D.M.D., İ.Ö., B.B, S.C., Design: D.M.D., İ.Ö., B.B, S.C., Data Collection or Processing: D.M.D., S.C., Analysis or Interpretation: D.M.D., A.G., B.U., L.Ş., İ.Ö., B.B, S.C., Literature Search: D.M.D., Writing: D.M.D., A.G., B.U., L.Ş., İ.Ö., B.B, S.C.

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Supplementary File 1. https://d2v96fxpocvxx.cloudfront.net/cf9d60d6-523c-458a-a2e6-78728d3ffbb0/content-images/ddec7c26-cbee-43b4-85ed-3dbda4deba2e.pdf

REFERENCES

1. Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935-1984. *Epilepsia.* 1993;34(3):453-468. [Crossref]
2. Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: position paper of the ILAE commission for classification and terminology. *Epilepsia.* 2017;58(4):512-521. [Crossref]
3. Loiseau J, Loiseau P, Guyot M, Duche B, Dartigues JF, Aublet B. Survey of seizure disorders in the French southwest. I. Incidence of epileptic syndromes. *Epilepsia.* 1990;31(4):391-396. [Crossref]
4. Berkovic SF, McIntosh A, Howell RA, Mitchell A, Sheffield LJ, Hopper JL. Familial temporal lobe epilepsy: a common disorder identified in twins. *Ann Neurol.* 1996;40(2):227-235. [Crossref]
5. Peljto AL, Barker-Cummings C, Vasoli VM, et al. Familial risk of epilepsy: a population-based study. *Brain.* 2014;137(Pt 3):795-805. [Crossref]
6. Steinlein OK, Mulley JC, Propping P, et al. A missense mutation in the neuronal nicotinic acetylcholine receptor alpha 4 subunit is associated with autosomal dominant nocturnal frontal lobe epilepsy. *Nat Genet.* 1995;11(2):201-203. [Crossref]
7. Ruggiero SM, Xian J, Helbig I. The current landscape of epilepsy genetics: where are we, and where are we going? *Curr Opin Neurol.* 2023;36(2):86-94. [Crossref]
8. Helbig I, Heinzen EL, Mefford HC; International League Against Epilepsy Genetics Commission. Genetic literacy series: primer part 2-paradigm shifts in epilepsy genetics. *Epilepsia.* 2018;59(6):1138-1147. [Crossref]
9. Wirrell E, Tinuper P, Perucca E, Moshé SL. Introduction to the epilepsy syndrome papers. *Epilepsia.* 2022 Jun;63(6):1330-1332. [Crossref]
10. Hirsch E, French J, Scheffer IE, et al. ILAE definition of the idiopathic generalized epilepsy syndromes: position statement by the ILAE task force on nosology and definitions. *Epilepsia.* 2022;63(6):1475-1499. [Crossref]
11. Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc task force of the ILAE commission on therapeutic strategies. *Epilepsia.* 2010;51(6):1069-1077. Erratum in: *Epilepsia.* 2010;51(9):1922. [Crossref]
12. Schwarz T, Striedner Y, Horner A, et al. PRDM9 forms a trimer by interactions within the zinc finger array. *Life Sci Alliance.* 2019;2(4):e201800291. [Crossref]
13. Al-Naama N, Mackeh R, Kino T. C_2H_2-type zinc finger proteins in brain development, neurodevelopmental, and other neuropsychiatric disorders: systematic literature-based analysis. *Front Neurol.* 2020;11:32. [Crossref]
14. Mir A, Song Y, Lee H, Montazer-Zohouri M, Reisi M, Tabatabaiefar MA. A deleterious frameshift insertion mutation in the ZNF142 gene leads to intellectual developmental disorder with impaired speech in three affected siblings: Clinical features and literature review. *Mol Genet Genomic Med.* 2023;11(12):e2261. [Crossref]
15. Khan K, Zech M, Morgan AT, et al. Recessive variants in ZNF142 cause a complex neurodevelopmental disorder with intellectual disability, speech impairment, seizures, and dystonia. *Genet Med.* 2019;21(11):2532-2542. [Crossref]
16. DeScipio C, Conlin L, Rosenfeld J, et al. Subtelomeric deletion of chromosome 10p15.3: clinical findings and molecular cytogenetic characterization. *Am J Med Genet A.* 2012;158A(9):2152-2161. [Crossref]
17. Li YY, Gong G, Geng HY, et al. CAPN10 SNP43 G>A gene polymorphism and type 2 diabetes mellitus in the Asian population: a meta-analysis of 9353 participants. *Endocr J.* 2015;62(2):183-194. [Crossref]
18. Rodríguez-Palmero A, Boerrigter MM, Gómez-Andrés D, et al. DLG4-related synaptopathy: a new rare brain disorder. *Genet Med.* 2021;23(5):888-899. [Crossref]
19. Tokunaga S, Shimomura H, Taniguchi N, et al. A novel DLG4 variant causes DLG4-related synaptopathy with intellectual regression. *Hum Genome Var.* 2024;11(1):1. [Crossref]
20. Schrader M, Reuber BE, Morrell JC, et al. Expression of PEX11beta mediates peroxisome proliferation in the absence of extracellular stimuli. *J Biol Chem.* 1998;273(45):29607-29614. [Crossref]
21. Ebberink MS, Koster J, Visser G, et al. A novel defect of peroxisome division due to a homozygous non-sense mutation in the PEX11β gene. *J Med Genet.* 2012;49(5):307-313. [Crossref]
22. Tian Y, Zhang L, Li Y, et al. Variant analysis of PEX11B gene from a family with peroxisome biogenesis disorder 14B by whole exome sequencing. *Mol Genet Genomic Med.* 2020;8(1):10.1002/mgg3.1042. [Crossref]
23. Vega MA, Seguí-Real B, García JA, et al. Cloning, sequencing, and expression of a cDNA encoding rat LIMP II, a novel 74-kDa lysosomal membrane protein related to the surface adhesion protein CD36. *J Biol Chem.* 1991;266(25):16818-16824. [Crossref]
24. Tian WT, Liu XL, Xu YQ, et al. Progressive myoclonus epilepsy without renal failure in a Chinese family with a novel mutation in SCARB2 gene and literature review. *Seizure.* 2018;57:80-86. [Crossref]
25. Cameron JM, Ellis CA, Berkovic SF; ILAE Genetics Commission; ILAE Genetic Literacy Task Force. ILAE genetics literacy series: progressive myoclonus epilepsies. *Epileptic Disord.* 2023;25(5):670-680. [Crossref]
26. Rubboli G, Franceschetti S, Berkovic SF, et al. Clinical and neurophysiologic features of progressive myoclonus epilepsy without renal failure caused by SCARB2 mutations. *Epilepsia.* 2011;52(12):2356-2363. [Crossref]
27. Krohn L, Heilbron K, Blauwendraat C, et al. Genome-wide association study of REM sleep behavior disorder identifies polygenic risk and brain expression effects. *Nat Commun.* 2022;13(1):7496. [Crossref]
28. Kapushesky M, Emam I, Holloway E, et al. Gene expression atlas at the European bioinformatics institute. *Nucleic Acids Res.* 2010;38(Database issue):D690-D698. [Crossref]
29. Lindsay SJ, Xu Y, Lisgo SN, et al. HDBR expression: a unique resource for global and individual gene expression studies during early human brain development. *Front Neuroanat.* 2016;10:86. [Crossref]
30. Protasova MS, Andreeva TV, Klyushnikov SA, Illarioshkin SN, Rogaev EI. Genetic variant in GRM1 underlies congenital cerebellar ataxia with no obvious intellectual disability. *Int J Mol Sci.* 2023;24(2):1551. [Crossref]
31. Watson LM, Bamber E, Schnekenberg RP, et al. Dominant mutations in GRM1 cause spinocerebellar ataxia type 44. *Am J Hum Genet.* 2017;101(4):638. Erratum for: *Am J Hum Genet.* 2017;101(3):451-458. [Crossref]
32. Shi G, Yin C, Fan Z, et al. Mutations in metabotropic glutamate receptor 1 contribute to natural short sleep trait. *Curr Biol.* 2021;31(1):13-24.e4. [Crossref]
33. Frank RA, McRae AF, Pocklington AJ, et al. Clustered coding variants in the glutamate receptor complexes of individuals with schizophrenia and bipolar disorder. *PLoS One.* 2011;6(4):e19011. [Crossref]
34. Battaglia A, Hoyme HE, Dallapiccola B, et al. Further delineation of deletion 1p36 syndrome in 60 patients: a recognizable phenotype and common cause of developmental delay and mental retardation. *Pediatrics.* 2008;121(2):404-410. Erratum in: *Pediatrics.* 2008;121(5):1081. Braley, Lisa L [corrected to Brailey, Lisa L]. [Crossref]
35. Jacquin C, Landais E, Poirsier C, et al. 1p36 deletion syndrome: review and mapping with further characterization of the phenotype, a new cohort of 86 patients. *Am J Med Genet A.* 2023;191(2):445-458. [Crossref]
36. Sun Y, Seneviratne U, Perucca P, et al. Generalized polyspike train: an EEG biomarker of drug-resistant idiopathic generalized epilepsy. *Neurology.* 2018;91(19):e1822-e1830. Erratum in: *Neurology.* 2018;91(24):1117. [Crossref]
37. Allamand V, Broux O, Richard I, et al. Preferential localization of the limb-girdle muscular dystrophy type 2A gene in the proximal part of a 1-cM 15q15.1-q15.3 interval. *Am J Hum Genet.* 1995;56(6):1417-1430. [Crossref]

Investigation of the Relationship between Intolerance of Uncertainty and Cyberchondria in Parents of Children with Epilepsy

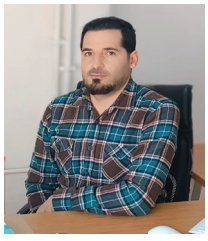
Yakup Sarpdağı[1], Metin Yıldız[2], Sinan Mean[3], Necmettin Çiftçi[4]

[1]Van Yüzüncü Yıl University Faculty of Health Sciences, Department of Nursing, Van, Türkiye

[2]Sakarya University Faculty of Health Sciences, Department of Midwifery, Sakarya, Türkiye

[3]University Health Sciences Türkiye, Van Training and Research Hospital, Doctoral Student, Van, Türkiye

[4]Muş Alparslan University Faculty of Health Sciences, Department of Nursing, Muş, Türkiye



Yakup Sarpdağı
PhD, Asst. Prof.,

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Corresponding Author: Yakup Sarpdağı, PhD, Asst. Prof., Van Yüzüncü Yıl University Faculty of Health Sciences, Department of Nursing, Van, Türkiye, **E-mail:** yakup_sys@hotmail.com

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Abstract

Objective: The aim of this study is to examine the relationship between the level of intolerance to uncertainty in parents of children with epilepsy and cyberchondria.

Methods: The study design was descriptive and cross-sectional. Data were collected between March and August of 2025. A total of 402 parents of children with epilepsy participated in the study. Data were collected using the sociodemographic data form, the Intolerance of Uncertainty Scale, and the Cyberchondria Severity Scale-Short Form.

Results: The findings show a moderate, positive, and significant relationship between intolerance of uncertainty and cyberchondria ($r=0.397$, $p<0.001$). Regression analysis indicates that intolerance of uncertainty significantly predicts cyberchondria severity ($\beta=0.380$, $p<0.001$), and the model explains 15.8% of the total variance.

Conclusion: As the intolerance of uncertainty among parents of children diagnosed with epilepsy increase, their levels of cyberchondria also increase, highlighting the importance of psychoeducation and digital health literacy programs for parents.

Keywords: Cyberchondria, epilepsy, intolerance of uncertainty, parents

INTRODUCTION

Epilepsy is a spectrum of neurological disorders that commonly affect individuals of all ages worldwide. Epilepsy, one of the most common chronic neurological disorders in childhood, accounts for approximately 1% of the global disease burden.[1,2] In Türkiye, the prevalence of epilepsy in children is reported to range between 0.6% and 0.8%.[3,4] Beyond the prevalence of the disease, its most challenging impact on families and healthcare systems stems from the profound uncertainty inherent in its nature. Many aspects of epilepsy, such as its underlying cause, the unpredictable timing and form of seizures, the variability in response to treatment, and long-term prognosis, are often uncertain.[5] Despite significant advances in epilepsy research, substantial uncertainties remain regarding various aspects of the disease, including its pathophysiology and optimal treatment strategies, which constitute a significant source of stress, particularly for parents directly involved in the patient's care.[6-8]

From a parental perspective, raising a child with epilepsy can be associated with a profound sense of uncertainty, anxiety, and stress due to unpredictable seizures, complex treatment regimens, and the need for constant supervision.[9,10] In this context, uncertainty about the disease process can be defined as an individual's inability to understand the situations they encounter or to predict events, resulting in a loss of control over their life.[11] However, more critical than this situational uncertainty is the individual's attitude toward it. Intolerance of uncertainty is a cognitive personality trait that involves interpreting uncertain situations as threatening and experiencing negative reactions.[12] Those with high intolerance of uncertainty find it more difficult to cope with uncertainty and exert intense effort to control or eliminate it. This can sometimes lead to the adoption of coping mechanisms with negative consequences.[13] Uljarević et al.[14] point out that as family members' intolerance of uncertainty increases, so do their anxiety levels, highlighting the importance of this relationship within the family.

Cyberchondria is a potential manifestation of negative coping mechanisms and an intolerance of uncertainty. This phenomenon occurs when a person's health concerns intensify as a result of repeated, excessive use of the internet to obtain medical information.[15,16] Initially, searching for health information online may serve to provide reassurance and reduce anxiety. However, in individuals with a high intolerance of uncertainty, unsuccessful or confusing results can paradoxically trigger a compulsive search cycle, thereby further increasing anxiety.[17,18] Parents often turn to the internet not only to address their own health concerns but also to evaluate their children's symptoms and determine whether they need medical help.[19,20] Studies show that parents worldwide use the internet extensively for their children's health.[21] Therefore, for chronic diseases such as epilepsy, which inherently involve a high degree of uncertainty, parents with a high intolerance of uncertainty are at increased risk of exhibiting cyberchondriac behaviours to alleviate their concerns about their child's condition. Indeed, intolerance of uncertainty is considered a key factor in the persistence of cyberchondria and reassurance-seeking behaviour.[15]

The severity of epilepsy, uncertainties in treatment, the rapid spread of digital technologies, and the growing demand for online health information have made parents' intolerance of uncertainty and cyberchondria important public health issues. However, a review of the literature reveals no studies directly addressing this relationship among parents of children with epilepsy. Against this backdrop, this study examines the relationship between intolerance of uncertainty and levels of cyberchondria among parents of children with epilepsy.

METHODS

Study Type

This cross-sectional descriptive study was conducted between March and August 2025.

Participants

The study participants were parents of children diagnosed with epilepsy who visited the pediatric neurology department of an educational and research hospital in eastern Türkiye. Convenience sampling was used to conduct the study. Using the sample formula ($n=t^2pq/d^2$) with t=1.96, p=q=0.5, and d=0.05, a sample size of 384 participants was determined to be sufficient. During data collection, the participants' responses were incorporated into the study, which was completed with 402 participants. We calculated the statistical power of our study using results from 402 participants. Based on the findings obtained from these individuals, a post-hoc power test was performed using the G*Power 3.1.9.7 statistical software program. This analysis determined that the study's power was 99% at a 95% confidence level and that the effect size was moderate.[22] The study included parents (one parent per child) who brought their child to the outpatient clinic, were literate, had internet access, were 18 years of age or older, had no mental health problems, had a child aged 1-18 years with epilepsy, and voluntarily agreed to participate in the study. Parents who were illiterate, who had mental health issues, who did not visit the outpatient clinic during the study period, or who did not wish to participate were excluded. The reporting of this research article is based on the STROBE guidelines.[23]

MAIN POINTS

- This study has revealed a significant and positive relationship between intolerance to uncertainty and cyberchondria among parents of children with epilepsy.
- The findings indicate that as the level of intolerance to uncertainty increases, parents' tendency to search for health information online and experience related anxiety also increases.
- It was determined that anxiety about the future has a particularly strong effect on cyberchondria.
- This highlights the importance of psychoeducation and digital health literacy programs for parents.

Data Collection

The research data were gathered using the sociodemographic data form, the Intolerance of Uncertainty Scale (IUS), and the Cyberchondria Severity Scale-Short Form (CSS-SF). The researchers collected the data through face-to-face interviews.

Sociodemographic Data Form

In line with relevant literature, the researchers prepared a questionnaire comprising ten questions on the the individual characteristics of parents and children and on the duration of illness.

Intolerance of Uncertainty Scale

IUS is a 12-item, 5-point Likert-type scale developed to measure individuals' tolerance levels for uncertainty. It was created by Nicholas Carleton et al.[24] and was adapted into Turkish by Sarıçam et al.[25] The scale consists of two subscales: prospective anxiety (the need for predictability of future events and anxious expectation) (Items 1-7) and inhibitory anxiety (the tendency to inhibit behavior and become paralyzed in the face of uncertainty) (Items 8-12). There are no reverse-coded items on the scale. Scores on the scale range from 12 to 60, with higher scores indicating greater intolerance. Cronbach's alpha was 0.88 for the entire scale.[25] In this study, it was 0.86.

Cyberchondria Severity Scale-short Form

The CSS-SF scale was developed by McElroy and Shevlin[26] and adapted into Turkish by Söyler et al.[27] The scale consists of 12 items and 4 dimensions (excessiveness, anxiety, reassurance-seeking, and compulsion). Responses are recorded on a 5-point Likert-type scale. There are no reverse items on the scale. Scale scores range from 12-60; as scores increase, the level of cyberchondria also increases. The Cronbach's alpha coefficient for the internal consistency of the scale has generally been reported as 0.86.[27] In this study, it was 0.83.

Statistical Analysis

Statistical analyses were performed using IBM SPSS 27. A post-hoc power analysis was conducted using G*Power 3.1.9.7 statistical software. Descriptive statistics were used to summarize the participants' demographic and clinical characteristics and scale scores. The normality of the distributions was assessed by examining Skewness and Kurtosis and by inspecting histograms.

Since these coefficients were within the range of -1.5 to +1.5, the data were considered normally distributed.[28] Comparisons between sociodemographic variables and scale scores were analyzed using independent samples t-tests and one-way analysis of variance. Pearson correlation analysis was first conducted to examine the bivariate relationships between intolerance of uncertainty and cyberchondria, as well as their associations with relevant sociodemographic and clinical variables. Following the identification of statistically significant relationships in these univariate analyses, simple linear regression was performed to further evaluate the predictive relationship between the main study variables. In the regression model, cyberchondria severity was the dependent variable, and intolerance of uncertainty was the sole independent variable to assess its unique contribution to cyberchondria. Prior to conducting the regression analysis, the model assumptions were examined and found to be met, including normality of residuals (assessed via histograms and normal probability plots), absence of multicollinearity (variance inflation factor <10), homoscedasticity, and independence of errors (Durbin-Watson statistic approximating 2).[29] All analyses were accepted at a p-value of <0.05.

Ethical Consideration

The research received approval from the Muş Alparslan University Scientific Research and Publication Ethics Committee (document date and number: 11.12.2023-120930) and institutional permission from the institution where the study will be conducted (number and date: E-36866945-508.01-270448016, 06/03/2025). Participants were provided with detailed information about the study and informed that it was voluntary. Written consent was obtained from the participants. The study adhered to the Declaration of Helsinki throughout its duration.

RESULTS

Among parents, 62.2% were female, 89.3% were married, 33.3% were university graduates, 48.8% had incomes lower than their expenses, and 38.1% often searched the internet for health-related information. The average age of parents was 36.98±8.47 (20-65) and the average daily internet usage time was 3.01±1.80 (1-9) hours (Table 1).

Of the children with epilepsy, 57% were male, with an average age of 8.93±4.87 (1-18) and an average diagnosis duration of 4.54±3.61 (1-18) (Table 2).

As shown in Table 3, the participants' overall mean score for IUS was 38.34±8.78, the mean score for the prospective anxiety subscale was 23.22±5.77, and the mean score for the inhibitory anxiety subscale was 15.12±4.42. The overall mean score for CSS-SF was found to be 35.24±8.40. When the subscales were analyzed, they were found to be excessiveness (9.46±3.03), anxiety (8.69±2.87), reassurance seeking (9.09±3.13), and compulsion (7.93±2.64) (Table 2). The Skewness and Kurtosis values for all scales and subscales were within acceptable limits (−1 to +1), indicating that the data were approximately normally distributed and suitable for parametric analyses (Table 3).

A statistically significant difference in parents' mean total IUS scores was found according to gender, educational status, and frequency of conducting disease-related research. Female parents

Table 1. Demographic characteristics of parents (n=402)

Variables		n (%)
Gender	Male	152 (37.8)
	Female	250 (62.2)
Marital status	Married	359 (89.3)
	Single	43 (10.7)
Education status	Just literate	34 (8.5)
	Primary school graduate	97 (24.1)
	High school graduate	137 (34.1)
	University graduate	134 (33.3)
Monthly income	Income less than expenditure	196 (48.8)
	Income equal to expenditure	163 (40.5)
	Income more than expenditure	43 (10.7)
Frequency of research on the disease	Never	20 (5.0)
	Rarely	51 (12.7)
	Sometimes	88 (21.9)
	Often	153 (38.1)
	Always	90 (22.4)
Age of the parent	**M ± SD (min-max)**	
	36.98±8.47 (20-65)	
Parent's average daily internet use (hours)	**M ± SD (min-max)**	
	3.01±1.80 (1-9)	

M: Mean, SD: Standard deviation, min: Minimum, max: Maximum

Table 2. Demographic characteristics of children with epilepsy (n=402)

Variables		n (%)
Gender of the child	Girl	173 (43.0)
	Boy	229 (57.0)
Age of the child	M ± SD (min-max)	
	8.93±4.87 (1-18)	
Duration of child's diagnosis (years)	**M ± SD (min-max)**	
	4.54±3.61 (1-18)	

M: Mean, SD: Standard deviation, min: Minimum, max: Maximum

had higher mean total IUS scores than male parents (t=4.262; p=0.001). Tukey honestly significant difference (HSD) post-hoc analysis was used to determine which groups differed in mean total IUS scores according to parents' educational level. Parents with a university education had higher mean IUS scores than the literate group (F=5.297; p=0.001; a<d). Tukey HSD analysis was used to determine which group accounted for the differences between parents' frequencies of disease-related research and their IUS total mean scores. The scores of parents who never researched were significantly lower than those of parents who researched sometimes, often, or always (F=9.746; p=0.001, a<c,d,e). In contrast, no statistically significant association was found between either marital status or monthly income status and the IUS total score (p>0.05) (Table 4).

A statistically significant difference was found between parents' mean total CSS-SF scores and their educational status (F=6.704; p=0.001). Tukey HSD post-hoc analysis was used to determine between which groups differences occurred. The CSS-SF scores of literate parents were significantly lower than those of elementary school graduates, high school graduates, and university graduates (a<b,c,d). A statistically significant difference was found between parents' frequency of conducting online research about illnesses and their mean total CSS-SF scores (F=11.895; p=0.001). A Tukey HSD post-hoc analysis was used to determine which groups differed. The CSS-SF mean scores of parents who often researched were significantly higher than those of parents who never, rarely, or sometimes researched (a,b,c<d). No statistically significant

Table 3. Distribution of parents' scores on IUS and CSS-SF: subscales and overall scores (n=402)

Scale and subscales	M ± SD (min-max)	Skewness	Kurtosis
IUS	38.34±8.78 (14-58.0)	0.015	-0.559
Prospective anxiety	23.22±5.77 (9-35.0)	-0.161	-0.582
Inhibitory anxiety	15.12±4.42 (5-25.0)	0.027	-0.710
CSS-SF	35.24±8.40 (12-56.0)	-0.141	-0.361
Excessiveness	9.46±3.03 (3-15.0)	-0.244	0.673
Anxiety	8.69±2.87 (3-15)	-0.098	-0.715
Seeking reassurance	9.09±3.13 (3-15.0)	0.116	-0.632
Compulsion	7.93±2.64 (3.0-14.0)	-0.123	-0.673

M: Mean, SD: Standard deviation, min: Minimum, max: Maximum, IUS: Intolerance of uncertainty, CSS-SF: Cyberchondria Severity Scale-Short Form

Table 4. Comparison of parents' demographic characteristics with scale total score averages (n=402)

Variables		IUS M ± SD	(Test, p)	CSS-SF M ± SD	(Test, p)
Gender	Male	36.00±8.33	t=4.262, **p=0.001***	34.35±7.82	t=1.661, p=0.097
	Female	39.77±8.76		35.78±8.70	
Marital status	Married	38.45±8.68	t=0.732, p=0.465	35.52±8.26	t=1.899, p=0.058
	Single	37.41±9.66		32.95±9.27	
Education status	Literate^{a}	34.05±8.77	F=5.297, **p=0.001**$^{*(a<d)}$	29.82±7.70	F=6.704, **p=0.001**$^{*(a<b,c,d)}$
	Primary school graduate^{b}	37.82±8.93		34.58±8.27	
	High school graduate^{c}	37.87±8.38		35.58±8.81	
	University graduate^{d}	40.29±8.67		36.75±7.68	
Monthly income	Income less than expenditure^{a}	38.08±8.89	F=0.191, p=0.826	36.00±8.34	F=1.776, p=0.171
	Income equal to expenditure^{b}	38.52±8.45		34.32±8.55	
	Income more than expenditure^{c}	38.86±9.67		35.30±7.92	
Frequency of research on the disease	Never^{a}	31.70±9.33	F=9.746, **p=0.001**$^{*(a<c,d,e)}$	26.90±8.03	F=11.895, **p=0.001**$^{*(a,c,b<d)}$
	Rarely^{b}	33.98±7.91		32.01±6.49	
	Sometimes^{c}	37.72±6.90		33.76±7.00	
	Often^{d}	39.35±9.08		37.43±7.86	
	Always^{e}	41.17±8.68		36.66±9.64	

^{a}t: Independent sample t-test, ^{b}F: One-way analysis of variance, M: Mean, SD: Standard deviation, HSD: Honestly significant difference test, *: p<0.05, post-hoc analysis: Tukey HSD, different superscript letters (^{a,b,c,d,e}) indicate statistically significant differences between groups according to the Tukey HSD post-hoc test

differences in CSS-SF total mean scores were found for gender, marital status, or monthly income (p>0.05) (Table 4).

A moderate, positive, and statistically significant correlation was observed between the average IUS total score and the average CSS-SF total score (r=0.397; p<0.001). When the subscales of the IUS were examined, the prospective anxiety subscale was found to be moderately positively correlated with the CSS-SF (r=0.417; p<0.001), while the inhibitory anxiety subscale showed a weaker but still significant correlation (r=0.245; p<0.001). Furthermore, a weak negative relationship was observed between parental age and the mean total IUS score (r=-0.113; p=0.024), whereas a weak positive relationship was observed between parents' average daily internet usage time and the mean total IUS score (r=0.182; p<0.001). A weak and negative correlation was determined between the child's age and diagnosis duration and the parent's IUS total score average (r=-0.121; p=0.015 and r=-0.136; p=0.006) (Table 5).

Moderate, positive, and statistically significant associations were observed between the IUS total score and the anxiety (r=0.351, p<0.001) and compulsion (r=0.343, p<0.001) subscales of the CSS-SF. In contrast, weak but significant positive relationships were observed between IUS and the subscales excessiveness (r=0.297, p<0.001) and reassurance-seeking (r=0.180, p<0.001). Furthermore, a weak negative correlation was found between the CSS-SF total scores and parents' age (r=-0.196, p<0.001), whereas parents' daily internet usage time demonstrated a weak positive correlation with CSS-SF total scores (r=0.238, p<0.001). Additionally, both the child's age and the duration of diagnosis were weakly but significantly negatively correlated with parents' CSS-SF total scores (r=-0.230, p<0.001, and r=-0.110, p=0.027, respectively) (Table 5).

Regression analysis (Table 4) indicates that IUS scores are significantly positively associated with CSS-SF scores. According to the analysis, each unit increase in IUS leads to a 0.380-unit increase in CSS-SF (Beta=0.380, p<0.001). The overall explanatory power of the model is limited because the R^2 value is 15.8%, indicating that IUS explains 15.8% of the variance in CSS-SF. Furthermore, the model's overall significance was confirmed by the F test (F=75.057, p<0.001); the high F-value indicates that the model is significant and that the IUS plays an important role in predicting CSS-SF (Table 6).

DISCUSSION

The findings of this study reveal that, among parents of children diagnosed with epilepsy, CSS-SF increases as IUS increases. When demographic factors were examined, female parents, parents with university degrees, and parents who researched the disease more frequently were found to have higher levels of intolerance to uncertainty. On the other hand, cyberchondria levels increased, particularly among parents with higher levels of education and those who frequently researched the illness. As both subscales of intolerance to uncertainty (prospective and

Table 5. Correlations between IUS and CSS-SF total and subscale scores and continuous variables

Variables	1	2	3	4	5	6	7	8	9	10	11	12
IUS	1											
Prospective anxiety	r=0.896 **p=0.001****	1										
Inhibitory anxiety	r=0.816 **p=0.001****	r=0.476 **p=0.001****	1									
CSS-SF	r=0.397 **p=0.001****	r=0.417 **p=0.001****	r=0.245 **p=0.001****	1								
Excessiveness	r=0.297 **p=0.001****	r=0.299 **p=0.001****	r=0.200 **p=0.001****	r=0.700 **p=0.001****	1							
Anxiety	r=0.351 **p=0.001****	r=0.354 **p=0.001****	r=0.235 **p=0.001****	r=0.793 **p=0.001****	r=0.416 **p=0.001****	1						
Reassurance seeking	r=0.180 **p=0.001****	r=0.244 **p=0.001****	r=0.039 **p=0**.431	r=0.616 **p=0.001****	r=0.230 **p=0.001****	r=0.263 **p=0.001****	1					
Compulsion	r=0.343 **p=0.001****	r=0.333 **p=0.001****	r=0.246 **p=0.001****	r=0.747 **p=0.001****	r=0.353 **p=0.001****	r=0.640 **p=0.001****	r=0.231 **p=0.001****	1				
Age of the parent	r=-0.113 **p=0.024**	r=-0.107 **p=0.031**	r=-0.084 p=0.094	r=-0.196 **p=0.001****	r=-0.274 **p=0.001****	r=-0.075 p=0.131	r=-0.087 p=0.083	r=-0.110 p=0.028	1			
Parent's average daily ınternet use (hours)	r=0.182 **p=0.001****	r=0.219 **p=0.001****	r=0.076 p=0.128	r=0.238 **p=0.001****	r=0.212 **p=0.001****	r=0.153 **p=0.002**	r=0.147 **p=0.003**	r=0.180 **p=0.001****	r=-0.139 **p=0.005**	1		
Age of the child	r=-0.121 **p=0.015**	r=-0.138 **p=0.006**	r=-0.061 p=0.224	r=-0.230 **p=0.001****	r=-0.244 **p=0.001****	r=-0.113 **p=0.023**	r=-0.177 **p=0.001****	r=-0.100 **p=0.045**	r=.605 **p=0.001****	r=0.045 p=0.367	1	
Duration of child's diagnosis (years)	r=-0.136 **p=0.006**	r=-0.125 **p=0.012**	r=-0.107 p=0**.032**	r=-0.110 **p=0.027**	r=-0.082 p=0.099	r=-0.049 p=0.331	r=-0.099 **p=0.048**	r=-0.070 p=0.160	r=.323 **p=0.001****	r=-0.118 **p=0.018**	r=0.457 **p=0.001****	1

r: Pearson's correlation, p<0.05, **: p<0.001, IUS: Intolerance of uncertainty, CSS-SF: Cyberchondria Severity Scale-Short Form

Table 6. Regression analysis results regarding the prediction level of IUS on CSS-SF (n=402)

	Beta	Standard defect	Standard beta	t	p	95% confidence interval	
Constant coefficient	20.669	1.726	-	11.974	0.001	17.275	24.062
IUS	0.380	0.044	0.397	8.664	0.001	0.294	0.466
R	0.397						
R^2/adjusted R^2	0.158/0.156						
R^2 change	0.158						
F	75.057						
VIF	1.000						
Durbin-Watson	1.304						

Simple linear regression, p<0.001, dependent variable: CSS-SF total score**,** independent variable: IUS total score, IUS: Intolerance of uncertainty, CSS-SF: Cyberchondria Severity Scale-Short Form, VIF: Variance inflation factor

inhibitory anxiety) increased, CSS-SF scores also increased. As all subscales of cyberchondria (anxiety, compulsion, excessiveness, and reassurance seeking) increased, IUS increased. As parents' ages, children's ages, and duration of diagnosis increased, levels of both intolerance of uncertainty and cyberchondria tended to decrease. As parents' average daily internet use increased, both IUS and CSS-SF rose. Intolerance of uncertainty significantly predicted parents' cyberchondria and explained part of the variance in parents' cyberchondria levels.

This study found that as parents' level of education increased, both intolerance of uncertainty and cyberchondria levels rose. This finding suggests that, despite individuals with higher educational levels having greater access to health-related information and a greater capacity to process that information, their perception of uncertainty may increase rather than decrease, particularly for chronic and unpredictable illnesses. The literature reports that individuals with higher educational levels have greater health literacy; however, this higher literacy is also associated with increased information-seeking behavior, greater exposure to conflicting online health information, and a tendency to evaluate risks in greater detail.[30,31] In cases such as childhood epilepsy, where the disease course is variable and perceived control is limited, increased information-seeking may make parents more aware of uncertainty rather than help them cope with it. This process may cause online health searches that are initiated to reduce uncertainty to turn into a cycle that reinforces cyberchondria over time.[32] Therefore, the emergence of a high educational level as a risk indicator for intolerance to uncertainty and cyberchondria in this study may be related to how information is structured and interpreted in a clinical context, rather than to its quantity.

This study has revealed that as parents increasingly search for information about their children's illnesses online, both their intolerance for uncertainty and the severity of their cyberchondria increase. The literature indicates that individuals seek information to regain a sense of control in situations of health-related uncertainty, but this process can increase rather than reduce uncertainty, particularly when it results in extensive exposure to unverified or conflicting online health information.[15,18] In this context, it has been suggested that frequent and repetitive internet searches lead to a mental expansion of possible disease-related scenarios in parents, thereby reinforcing intolerance to uncertainty, while increased perceived uncertainty may trigger anxiety, excessiveness, and reassurance-seeking behaviors specific to cyberchondria.[17,31] Particularly in chronic and unpredictable illnesses, it has been reported that parents' excessive reliance on online health information becomes a cyclical process that perpetuates anxiety, rather than serving as a strategy to regulate it.[33] Therefore, the study's findings suggest that internet-based health information search behaviors may play a reinforcing role, both directly and indirectly, in the relationship between intolerance of uncertainty and cyberchondria.

This study examined the structural relationship between intolerance of uncertainty and cyberchondria in parents of children diagnosed with epilepsy. Correlation analysis revealed a moderately positive and significant association between intolerance of uncertainty and cyberchondria severity. Regression analysis showed that intolerance of uncertainty was a significant predictor of cyberchondria severity, explaining 15.6% of its total variance. Intolerance of uncertainty is an important determinant of health anxiety resulting from online health information searches. It refers to individuals' beliefs in the necessity of certainty. It also refers to their capacity to cope with unpredictable changes. It is considered a risk factor for cyberchondria.[34-36] Intolerance of uncertainty has been suggested to be indirectly related to cyberchondria, particularly through its links to health anxiety.[17] Uncertainties about individuals' health status may cause them to search more frequently for medical information online, which increases the level of cyberchondria by inducing anxiety resulting from information overload.[17,37] Furthermore, research has revealed a notable link between cyberchondria and a tendency to feel uncertain. This association is characterized by a moderate to strong correlation.[18,38,39] When it comes to unpredictable illnesses such as epilepsy, parents' intolerance of uncertainty may lead to cyberchondria and a cycle of anxiety as they seek additional information online.

This study found that as the level of anxiety experienced by parents of children with epilepsy when faced with uncertainty increased, their tendency to turn to health-related internet research also increased. This finding is consistent with other studies. For example, it has been reported that factors such as intolerance of uncertainty and inhibitory anxiety prompt individuals to search the internet for medical information, which can result in negative emotional states by increasing catastrophizing thoughts.[17,18] Furthermore, Fergus[38] found that inhibitory intolerance of uncertainty and physical anxiety sensitivity were significantly associated with various dimensions of cyberchondria in a normative adult sample. In the literature, when examining the subdimensions of intolerance of uncertainty, the relationship between inhibitory anxiety and cyberchondria is stronger, whereas the relationship between prospective anxiety and

cyberchondria is weaker.[17,18,38-41] The significance and direction of the relationships between the factors in this study are consistent with those reported in the literature. However, the relationship between prospective anxiety and cyberchondria is stronger than that between inhibitory anxiety and cyberchondria. This suggests that anxiety about the future plays a more prominent role for parents of children with epilepsy than does their tendency to inhibit behavior in the face of uncertainty. These findings suggest that intolerance of uncertainty and anxiety lead to similar behavioral outcomes across groups, but anxiety about the future is particularly prominent among parents of children with epilepsy.

The study found that as parents' levels of extremism, worry, confidence-seeking, and compulsion increased, their ability to cope with uncertainty weakened and their tolerance for uncertainty decreased. These findings are consistent with other studies. Studies in adults, for instance, have shown that intolerance of uncertainty is associated with behaviors such as excessive health anxiety and information-seeking.[42-44] Parents of children with epilepsy experience similar anxieties when faced with uncertainty about their child's health status, which can lead to behaviors such as excessive information seeking, constant reassurance-seeking, or over-preparation. While these behaviors are not inherently dysfunctional, they can exacerbate intolerance of uncertainty when applied rigidly.[45,46] The findings of this study indicate that intolerance of uncertainty is associated with similar psychological and behavioral outcomes in both adults with health anxiety and parents of children with chronic illnesses, demonstrating that this trait consistently contributes to cyberchondriac behaviors across contexts. This relationship among parents of children with epilepsy may be explained by the persistent uncertainty and chronic stress related to their child's condition.

Study Limitations

This study has several limitations. First, due to its cross-sectional design, the study cannot establish causal relationships. Secondly, the data were collected from only one hospital in one region, and the sample size and diversity are limited. This may affect the generalizability of the findings. Thirdly, collecting data using self-report scales may lead to methodological limitations, such as social desirability bias. In addition, the low internal consistency coefficients for some sub-dimensions of the scales used in the study warrant caution when interpreting the results. In future studies, more comprehensive results could be obtained by using larger samples from different regions and employing longitudinal designs.

CONCLUSION

This study revealed a significant and moderate relationship between IUS and CSS-SF among parents of children with epilepsy. The findings show that both levels of intolerance of uncertainty and the severity of cyberchondria increase with parents' frequency of internet research related to the disease and with their educational level. The observation that future-focused anxiety, one of the subscales of intolerance of uncertainty, is more strongly associated with cyberchondria suggests that parents' perception of future uncertainty plays a decisive role in chronic diseases with unpredictable courses, such as epilepsy. Furthermore, the decrease in intolerance of uncertainty and in levels of cyberchondria as parental and child ages increase suggests that experience and adaptation to the disease process may mitigate these psychological responses. A simple linear regression analysis showed that intolerance of uncertainty was a significant predictor of cyberchondria severity, explaining 15.8% of the variance in cyberchondria. These findings emphasize the importance of strengthening skills for coping with uncertainty and health literacy when planning psychosocial support for parents of children with epilepsy.

Ethics

Ethics Committee Approval: The research received approval from the Muş Alparslan University Scientific Research and Publication Ethics Committee (document date and number: 11.12.2023-120930).

Informed Consent: Written consent was obtained from the participants.

Footnotes

Author Contributions: Concept: Y.S., M.Y., Design: Y.S., M.Y., Data Collection or Processing: Y.S., S.M., Analysis or Interpretation: M.Y., N.Ç., Literature Search: Y.S., M.Y., S.M., N.Ç., Writing: Y.S., M.Y., S.M., N.Ç.

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REFERENCES

1. Samia P, Hassell J, Hudson JA, et al. Epilepsy diagnosis and management of children in Kenya: review of current literature. *Res Rep Trop Med*. 2019;10:91-102. **[Crossref]**
2. Fiest KM, Sauro KM, Wiebe S, et al. Prevalence and incidence of epilepsy. *Neurology*. 2017;88(3):296-303. **[Crossref]**
3. Canpolat M, Kumandas S, Poyrazoglu HG, Gumus H, Elmali F, Per H. Prevalence and risk factors of epilepsy among school children in Kayseri City Center, an urban area in Central Anatolia, Turkey. *Seizure*. 2014;23(9):708-716. **[Crossref]**
4. Topbaş M, Ozgün S, Sönmez MF, et al. Epilepsy prevalence in the 0-17 age group in Trabzon, Turkey. *Iran J Pediatr*. 2012;22(3):344-350. **[Crossref]**
5. Singh A, Woelfle R, Chepesiuk R, et al. Canadian epilepsy priority-setting partnership: toward a new national research agenda. *Epilepsy Behav*. 2022;130:108673. **[Crossref]**
6. Wong S, Simmons A, Villicana JR, Barnett S. Estimating patient-level uncertainty in seizure detection using group-specific out-of-distribution detection technique. *Sensors*. 2023;23(20):8375. **[Crossref]**
7. Stirling RE, Cook MJ, Grayden DB, Karoly PJ. Seizure forecasting and cyclic control of seizures. *Epilepsia*. 2021;62 Suppl 1:S2-S14. **[Crossref]**
8. Jakobsen AV, Møller RS, Nikanorova M, Elklit A. The impact of severe pediatric epilepsy on experienced stress and psychopathology in parents. *Epilepsy Behav*. 2020;113:107538. **[Crossref]**
9. Rani A, Thomas PT. Stress and perceived stigma among parents of children with epilepsy. *Neurol Sci*. 2019;40(7):1363-1370. **[Crossref]**
10. Baca CB, Vickrey BG, Hays RD, Vassar SD, Berg AT. Differences in child versus parent reports of the child's health-related quality of life in children with epilepsy and healthy siblings. *Value Heal*. 2010;13(6):778-786. **[Crossref]**
11. Gümüş K, Sezgin S. The effect of intolerance of uncertainty in multiple sclerosis patients on suicidal ideation. *The Journal of International Social Research*. 2016;47(9):475-486. *Turkish* **[Crossref]**
12. Turhan M, Boyacıoğlu NE. Intolerance of uncertainty and death anxiety in patients diagnosed with Covid-19. *Sağlık ve Yaşam Bilimleri Dergisi*. 2022;4(3):272-278. Turkish **[Crossref]**

13. Alschuler KN, Beier ML. Intolerance of uncertainty. *Int J MS Care*. 2015;17(4):153-158. [Crossref]
14. Uljarević M, Carrington S, Leekam S. Brief report: effects of sensory sensitivity and intolerance of uncertainty on anxiety in mothers of children with autism spectrum disorder. *J Autism Dev Disord.* 2016;46(1):315-319. [Crossref]
15. Starcevic V, Berle D. Cyberchondria: towards a better understanding of excessive health-related internet use. *Expert Rev Neurother.* 2013;13(2):205-213. [Crossref]
16. Sarpdağı Y, Demir Gökmen B. Siberkondri. In: Demir Gökmen B, editor. Teknoloji Bağımlılığı ve Mücadele. 1st ed. Ankara: Akademisyen Kitabevi; 2022. p. 171-180. [Crossref]
17. Fergus TA. Cyberchondria and intolerance of uncertainty: examining when individuals experience health anxiety in response to internet searches for medical information. *Cyberpsychol Behav Soc Netw.* 2013;16(10):735-739. [Crossref]
18. Norr AM, Albanese BJ, Oglesby ME, Allan NP, Schmidt NB. Anxiety sensitivity and intolerance of uncertainty as potential risk factors for cyberchondria. *J Affect Disord.* 2015;174:64-69. [Crossref]
19. Yardi S, Caldwell PH, Barnes EH, Scott KM. Determining parents' patterns of behaviour when searching for online information on their child's health. *J Paediatr Child Health.* 2018;54(11):1246-1254. [Crossref]
20. Jaks R, Baumann I, Juvalta S, Dratva J. Parental digital health information seeking behavior in Switzerland: a cross-sectional study. *BMC Public Health.* 2019;19(1):225. [Crossref]
21. Kubb C, Foran HM. Online health information seeking by parents for their children: systematic review and agenda for further research. *J Med Internet Res.* 2020;22(8):e19985. [Crossref]
22. Cohen J. Statistical power analysis current directions. *Psychol Sci*. 1992;1(3):98-101. [Crossref]
23. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the reporting of observational studies in epidemiology (STROBE). *Epidemiology.* 2007;18(6):805-835. [Crossref]
24. Nicholas Carleton R, Sharpe D, Asmundson GJG. Anxiety sensitivity and intolerance of uncertainty: requisites of the fundamental fears? *Behav Res Ther.* 2007;45(10):2307-2316. [Crossref]
25. Sarıçam H, Erguvan FM, Akın A, Akça MŞ. The Turkish short version of the intolerance of uncertaınty (IUS-12) scale: the study of validity and reliability. *Route Educ Soc Sci J.* 2014;1(3):148-157. [Crossref]
26. McElroy E, Shevlin M. The development and initial validation of the cyberchondria severity scale (CSS). *J Anxiety Disord.* 2014;28(2):259-265. [Crossref]
27. Söyler S, Biçer İ, Çavmak D. Turkish validity and reliability study of the Cyberchondria Severity Scale Short Form. In: Uyar S, Kıra R, eds. Health with Behavioral Dimensions. 1st ed. Nobel Academic Publishing; 2021. p. 302. [Crossref]
28. Tabachnick BG, Fidell LS. Using multivariate statistics. 6th ed. Boston (MA): Pearson; 2013.
29. Flatt C, Jacobs RL. Principle assumptions of regression analysis: testing, techniques, and statistical reporting of imperfect data sets. *Adv Dev Hum Resour.* 2019;21(4):484-502. [Crossref]
30. Starcevic V, Berle D. Cyberchondria: an old phenomenon in a new guise. In: Aboujaoude E, Starcevic V, editors. Mental health in the digital age: grave dangers, great promise. Oxford: Oxford University Press; 2015. p. 106-117. [Crossref]
31. McMullan RD, Berle D, Arnáez S, Starcevic V. The relationships between health anxiety, online health information seeking, and cyberchondria: systematic review and meta-analysis. *J Affect Disord.* 2019;245:270-278. [Crossref]
32. Starcevic V, Berle D, Arnáez S. Recent insights into cyberchondria. *Curr Psychiatry Rep.* 2020;22(11):56. [Crossref]
33. Muse K, McManus F, Leung C, Meghreblian B, Williams JMG. Cyberchondriasis: fact or fiction? A preliminary examination of the relationship between health anxiety and searching for health information on the Internet. *J Anxiety Disord.* 2012;26(1):189-196. [Crossref]
34. Schenkel SK, Jungmann SM, Gropalis M, Witthöft M. Conceptualizations of cyberchondria and relations to the anxiety spectrum: systematic review and meta-analysis. *J Med Internet Res.* 2021;23(11):e27835. [Crossref]
35. Carleton RN. The intolerance of uncertainty construct in the context of anxiety disorders: theoretical and practical perspectives. *Expert Rev Neurother.* 2012;12(8):937-947. [Crossref]
36. Arsenakis S, Chatton A, Penzenstadler L, et al. Unveiling the relationships between cyberchondria and psychopathological symptoms. *J Psychiatr Res.* 2021;143:254-261. [Crossref]
37. Al Dameery K, Quteshat M, Al Harthy I, Khalaf A. Cyberchondria, uncertainty, and psychological distress among omanis during COVID-19: an online cross-sectional survey. Research Square. 2020. [Crossref]
38. Fergus TA. Anxiety sensitivity and intolerance of uncertainty as potential risk factors for cyberchondria: a replication and extension examining dimensions of each construct. *J Affect Disord.* 2015;184:305-309. [Crossref]
39. Fergus TA, Spada MM. Cyberchondria: examining relations with problematic Internet use and metacognitive beliefs. *Clin Psychol Psychother.* 2017;24(6):1322-1330. [Crossref]
40. Fergus TA, Spada MM. Moving toward a metacognitive conceptualization of cyberchondria: examining the contribution of metacognitive beliefs, beliefs about rituals, and stop signals. *J Anxiety Disord.* 2018;60:11-19. [Crossref]
41. Zangoulechi Z, Yousefi Z, Keshavarz N. Levels of cyberchondria, health anxiety and internet use in relation to psychological outcomes. *Adv Biosci Clin Med.* 2018;6(4):1-6. [Crossref]
42. Gunay Molu N, Ceylan B. Intolerance to uncertainty and cyberchondria during the COVID-19 pandemic. *Int J Caring Sci.* 2022;15(2):1556-1564. [Crossref]
43. Bajcar B, Babiak J. Neuroticism and cyberchondria: the mediating role of intolerance of uncertainty and defensive pessimism. *Pers Individ Dif.* 2020;162:110006. [Crossref]
44. Boysan M, Eşkisu M, Çam Z. Relationships between fear of COVID-19, cyberchondria, intolerance of uncertainty, and obsessional probabilistic inferences: a structural equation model. *Scand J Psychol.* 2022;63(5):439-448. [Crossref]
45. Bottesi G, Cerea S, Ghisi M, Carraro E, Martignon A. "I'm uncertain: what should I do?": an investigation of behavioral responses to everyday life uncertain situations. *Int J Cogn Ther.* 2019;12(1):55-72. [Crossref]
46. Sankar R, Robinson L, Honey E, Freeston M. 'We know intolerance of uncertainty is a transdiagnostic factor but we don't know what it looks like in everyday life': a systematic review of intolerance of uncertainty behaviours. *Clin Psychol Forum.* 2017;296:10-15. [Crossref]

Archives of Epilepsy

Original Article

Perceived Stigma and Social Misconceptions in People with Epilepsy

Kebire Eylül Arslan, İrem Fatma Uludağ

University of Health Sciences Türkiye, İzmir Tepecik Education and Research Hospital, Clinic of Neurology, İzmir, Türkiye

Kebire Eylül Arslan MD,

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Corresponding Author: Prof. Dr. irem Fatma Uludağ, University of Health Sciences Türkiye, İzmir Tepecik Education and Research Hospital, Clinic of Neurology, İzmir, Türkiye, **E-mail:** fatmairem@yahoo.com

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Abstract

Objective: Although advances in diagnosis and treatment have improved seizure control in epilepsy, the psychosocial burden of the condition remains substantial. Stigma, social misconceptions, and perceived barriers in education, employment, and interpersonal relationships continue to shape the lived experience of people with epilepsy. Understanding these challenges in contemporary clinical populations is essential for informing patient-centered care and public awareness strategies. To investigate the social, educational, occupational, and relational experiences of adults with epilepsy, with particular emphasis on perceived stigma and societal attitudes.

Methods: In this cross-sectional study conducted at a tertiary epilepsy clinic, 90 adult patients (mean age 36.8±12.0 years) completed a structured questionnaire consisting of Likert-type items and open-ended questions exploring experiences related to education, employment, social relationships, and stigma. Clinical data, including epilepsy type, seizure frequency, and treatment characteristics, were obtained from medical records. Responses were analyzed descriptively, and open-ended questions were thematically categorized.

Results: Participants reported a range of psychosocial challenges, including perceived negative reactions from others, concerns regarding relationships and family life, and difficulties in educational and occupational settings. A notable proportion of patients reported difficulties related to societal attitudes (38.8%). Open-ended responses indicated that difficulty in socializing (26.7%), fear of seizures (20%), and challenges in finding employment (15.6%) were among the most frequently reported concerns. Misconceptions in the community included beliefs that people with epilepsy may be dangerous to others (37.7%) or may be less productive at work (11.1%).

Conclusion: Despite advances in clinical management, epilepsy remains associated with substantial psychosocial burden and perceived stigma. These findings highlight the need for ongoing efforts to address public misconceptions, support patients in social and professional domains, and integrate psychosocial considerations into routine epilepsy care.

Keywords: Epilepsy, misconceptions, quality of life, social perceptions, stigma

INTRODUCTION

Epilepsy is one of the most common chronic neurological disorders worldwide, characterized not only by recurrent seizures but also by a broad spectrum of psychosocial consequences. Although advances in diagnostic techniques, pharmacological treatments, and surgical interventions have improved seizure control for many individuals, living with epilepsy continues to be associated with challenges that extend beyond the clinical manifestations of the disease.[1]

Stigma has long been recognized as a central aspect of the experience of epilepsy. It encompasses both enacted stigma, referring to experiences of discrimination, and felt stigma, which reflects internalized perceptions of shame, social distance, or fear of negative judgment. Theoretical models suggest that stigma arises through complex interactions among cultural beliefs, social power dynamics, and misconceptions regarding the nature of the condition.[2] Even in settings where medical understanding of epilepsy has advanced considerably, stigma persists as a significant contributor to reduced quality of life and social participation.[3,4]

Research has demonstrated that stigma and negative societal attitudes toward epilepsy can affect multiple domains of life, including education, employment, interpersonal relationships, and family formation. Misconceptions—such as beliefs that epilepsy is contagious, associated with mental illness, or indicative of reduced competence—continue to influence how individuals with epilepsy are perceived and treated within their communities.[3] Moreover, psychosocial factors such as depression, social support, and socioeconomic conditions have been shown to interact with perceived stigma, further shaping individual experiences.[5]

While previous studies have examined stigma and psychosocial outcomes in diverse populations, there remains a need for contemporary clinical data reflecting the real-world experiences of patients receiving routine care. Understanding how individuals with epilepsy perceive their condition within their social environments may help identify ongoing barriers and inform interventions aimed at reducing stigma and improving overall well-being.[2]

The present study aimed to explore the educational, occupational, relational, and social experiences of adults with epilepsy in a tertiary care setting, with particular attention to perceived stigma and common societal misconceptions. By combining structured questionnaire data with patients' own perspectives, we sought to provide a comprehensive view of the psychosocial dimensions of living with epilepsy in the modern era.

METHODS

This study was conducted in January 2026 at the Neurology Clinic of the University of Health Sciences Türkiye, İzmir Tepecik Education and Research Hospital. The study protocol was approved by the University of Health Sciences Türkiye, İzmir Tepecik Education and Research Hospital Non-Interventional Research Ethics Committee (approval no: 2026/01-14, date: 02.02.2026) and was conducted in accordance with the principles of the Declaration of Helsinki.[6] Informed consent was obtained from all subjects.

A total of 90 adult patients with epilepsy who were followed up at the epilepsy outpatient clinic and who voluntarily agreed to participate were included in the study; 57 were female and 33 were male. The mean age of the participants was 36.8±12.0 years (range: 19-63 years).

During their routine outpatient visits, participants were asked to complete a questionnaire administered by the investigators. The questionnaire was developed by the investigators specifically for this study and consisted of 15 Likert-type items and additional open-ended questions. Patients who had psychiatric or neurological conditions that could interfere with their ability to respond to the questionnaire, such as aphasia or cognitive impairment, were excluded.

The first 90 consecutive patients who met the inclusion criteria—being between 18 and 65 years of age, having regular follow-up and available medical records, having no condition that would prevent them from answering the questionnaire, and providing voluntary consent—were enrolled in the study. No additional selection criteria were applied with respect to epilepsy type, seizure type, or treatment regimen.

MAIN POINTS

- Epilepsy continues to impose a substantial psychosocial burden beyond seizure control.
- Perceived stigma affects education, employment, relationships, and social integration.
- Patients report persistent societal misconceptions and fears of negative reactions.
- Psychosocial concerns remain prominent even in patients under regular clinical follow-up.
- Targeted stigma-reduction strategies are needed alongside medical treatment.

Internal consistency was assessed exclusively for the 15 Likert-type items using Cronbach's alpha. Responses to open-ended questions in which participants expressed their views (e.g., "In your opinion, what is the greatest challenge of living with epilepsy?") were categorized into thematic groups and analyzed descriptively using frequencies and percentages.

Statistical Analysis

In addition to the information obtained from the questionnaire on the day of assessment, data regarding epilepsy type, seizure frequency, and use of antiseizure medications were verified by review of patients' medical records. Frequency analyses and descriptive statistics were performed using SPSS software version 27 (IBM Corp., Armonk, NY, USA).

RESULTS

The demographic and clinical characteristics of the patients are presented in Table 1. Eighty patients (88.9%) reported attending regular medical follow-up visits even in the absence of symptoms, whereas 10 patients (11.1%) stated that they consulted a physician only in emergency situations. Nine patients (10.0%) reported difficulties in accessing healthcare services. Among the 21 patients (23.3%) who had applied for disability-related benefits, 8 had their applications approved.

Regarding educational status, 3 patients (3.3%) had never attended school, 35 (38.9%) had completed primary education, 36 (40.0%) had completed high school, and 16 (17.8%) had completed university education.

Sixteen patients (17.8%) reported difficulties in their education due to epilepsy, while 43 patients (47.8%) stated that epilepsy did not affect their education. Thirty-one patients (34.4%) did not respond to this question (Figure 1).

Table 1. Demographic and clinical features

Patients (n)	**90**
Age	36.8±12.0 (19-63) years ± SD
Female/male	57/33
Disease duration	16.9±11 (1-48) years ± SD
Focal/generalized/combined/unknown epilepsy	21/63/4/2
The most common pre-ictal symptoms	Restlessness (7 patients) Fear (7 patients each)
The most common seizure trigger	Fatigue (12 patients) Stress (16 patients)
Seizure frequency (mean seizure/year)	
0	8
1-12	70
≥12	12
Number of anti-seizure medications currently used	
0	8
1	47
2	22
≥3	13

SD: Standard deviation

In terms of employment status, 33 patients (36.7%) were employed full-time, 7 (7.8%) were employed part-time, 36 (40.0%) were unemployed, 10 (11.1%) were retired, and 4 (4.4%) were students. The difficulties experienced throughout the patients' educational and occupational trajectories are shown in Figure 2.

Among the patients, 42 (46.7%) were single and 48 (53.3%) were married. Patients' views on romantic relationships, marriage, and having children are presented in Figure 3.

Thirty-five patients (38.8%) reported experiencing various difficulties related to societal attitudes toward epilepsy (Figure 4).

The most frequently reported responses to the questions "What is the greatest challenge of living with epilepsy?" and "What is the most common misconception about epilepsy in society?" are presented in Table 2.

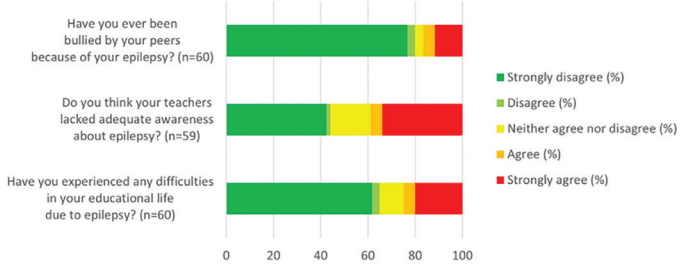

Figure 1. Educational impact

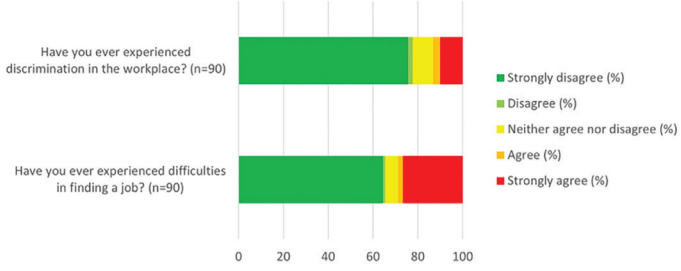

Figure 2. Workplace impact

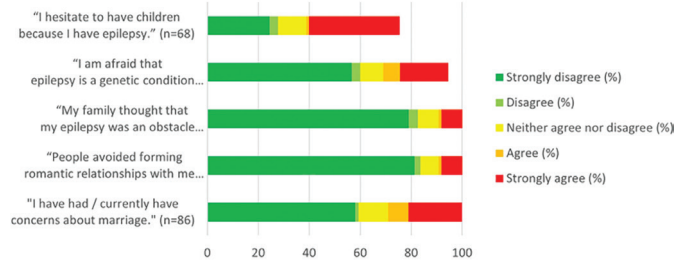

Figure 3. Relationship concerns

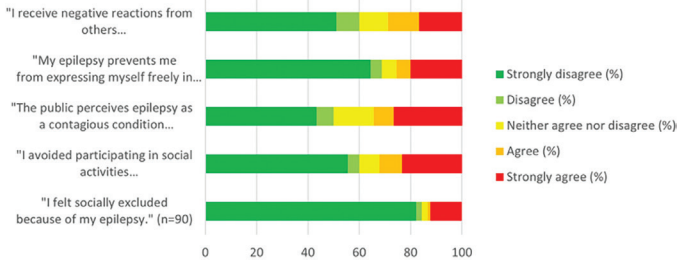

Figure 4. Perceived stigma

DISCUSSION

Our study aimed to re-examine the social, familial, and professional challenges experienced by people with epilepsy in the context of contemporary advances in awareness and treatment. Despite improvements in seizure control, reductions in medication side effects, and increased public education efforts, our findings indicate that people with epilepsy continue to face substantial psychosocial difficulties.

During their education, 20% of our patients reported that their education was more difficult in some respects due to epilepsy, and 40% stated that their teachers' awareness of epilepsy was insufficient (Figure 1). Previous studies have shown that awareness of epilepsy among teachers, and especially among high school students, is quite high, and that attitudes toward people with epilepsy are generally positive.[7,8] Although general attitudes and tendencies are positive, beliefs such as the idea that children with epilepsy should be kept separate from other children have also been reported among teachers at non-negligible rates.[9,10] Educational difficulties may have long-term implications, potentially influencing future employment opportunities and social participation.

Employment-related findings in our cohort are consistent with the literature documenting challenges in workplace integration for people with epilepsy.[11,12] A total of 26.7% of patients had difficulty finding a job, and 10% reported experiencing discrimination in the workplace due to epilepsy (Figure 2). A study conducted in Poland reported that three-quarters of respondents did not consider working with an individual with epilepsy problematic. According to this study, only 55% of employed people with epilepsy had informed their coworkers about their condition, and the majority attempted to conceal their condition for fear of job loss or mistreatment.[13] A study conducted in Australia reported workplace discrimination at a rate of 47%.[14]

Our observation that many patients avoid romantic relationships or express concerns about having children is in line with previous research showing that misconceptions about epilepsy may affect attitudes toward marriage and parenthood (Figure 3). A study conducted among healthcare professionals in Riyadh showed that even 13.4% of healthcare workers believed that patients with epilepsy should not have children.[15] In another study conducted among healthcare workers in Nigeria, the proportion of respondents who did not object to marrying a person with epilepsy was found to be only 12%.[16] These results underscore the persistence of deeply rooted beliefs that may shape interpersonal experiences.

Social withdrawal was also common in our sample, with a notable proportion of patients avoiding social activities due to epilepsy (Figure 4). Such avoidance may reflect fear of seizures occurring in public, anticipated stigma, or prior negative experiences.[17]

Patients frequently reported that epilepsy made socializing, finding employment, and forming a family more difficult, emphasizing the broad impact of the condition on daily life (Table 2).

Importantly, our findings indicate that a considerable proportion (1/3) of patients believes that society perceives them as potentially

Table 2. Most common challenges of living with epilepsy and societal misconceptions

		n (%)
The greatest challenge of living with epilepsy	Fear of having seizures	18 (20%)
	Difficulty in socializing	24 (26.7%)
	Difficulty in finding employment	14 (15.6%)
	Concerns regarding marriage and having children	12 (13.3%)
	Inability to obtain a driver's license	6 (6.6%)
The most common misconception about epilepsy in the community	People with epilepsy may be dangerous to others	34 (37.7%)
	Epilepsy manifests only as generalized tonic–clonic seizures	23 (25.5%)
	Epilepsy is a mental illness or is related to religious beliefs	11 (12.2%)
	Individuals with epilepsy are less productive at work than those without epilepsy	10 (11.1%)

dangerous (Table 2). This perception highlights the ongoing need to address public attitudes toward epilepsy and improve understanding of epilepsy, as such beliefs may contribute to self-limiting behaviors and reduced social participation.[18]

Taken together, our results reinforce the notion that epilepsy should be understood not only as a neurological disorder but also as a condition with significant social implications.

Recent qualitative syntheses have further deepened understanding of stigma in epilepsy by demonstrating that stigma can affect quality of life to a degree comparable to the physical burden of seizures. A meta-synthesis of qualitative studies identified recurring themes, including societal misconceptions, internalized shame, concealment behaviors, and the need for supportive relationships, and highlighted that stigma was experienced across cultural contexts despite differences in healthcare systems and levels of public awareness.[2] These observations resonate with our findings, in which participants reported concerns related to social participation, relationships, and perceived public attitudes, suggesting that stigma remains a multidimensional construct that affects everyday functioning.

The literature also emphasizes that individuals with epilepsy frequently adopt coping strategies such as selective disclosure or avoidance of social situations to mitigate anticipated negative reactions. Such adaptive behaviors may inadvertently reinforce social isolation and reduce opportunities for engagement, contributing to a cycle in which stigma and withdrawal perpetuate each other.[5] The patterns observed in our cohort, including reports of social exclusion and concerns regarding interpersonal relationships, are consistent with this conceptual framework.

Furthermore, previous studies have highlighted the importance of sociocultural context in shaping stigma experiences. Cultural narratives, religious interpretations, and community beliefs can influence whether epilepsy is perceived primarily as a medical condition or as a source of social difference. The persistence of misconceptions—including fears related to contagion or diminished competence—underscores the need for culturally sensitive educational initiatives.[1] Our findings, particularly those related to perceived public attitudes, support the notion that improving community awareness remains a critical component of comprehensive epilepsy care. Continued efforts aimed at improving public awareness, supporting patients in educational and occupational settings, and addressing misconceptions among both the general population and professionals may help reduce the burden experienced by people with epilepsy.

Another aspect underscored in prior research is that stigma can affect major life decisions, including employment, marriage, and family planning. Concerns about disclosure in the workplace or fears of being perceived as unreliable have been reported as barriers to career advancement, while anxieties related to relationships may influence decisions about partnership and parenthood.[19] The relational concerns identified in our study align with these observations and reinforce the broader impact of epilepsy beyond clinical symptoms.

These findings support the view that epilepsy continues to carry a psychosocial burden beyond its clinical manifestations. Stigma appears to remain a central factor in understanding these challenges. Importantly, stigma has been conceptualized as operating at multiple levels—anticipated, enacted, and internalized—each contributing differently to patient experience. Many of the difficulties reported by our patients—including perceived social distance, concerns about being viewed as dangerous, and avoidance behaviors—may reflect both internalized fears and lived experiences within their social environments. Recognizing these dimensions may help clinicians better identify individuals at risk of psychosocial distress and guide interventions that address both individual coping and societal attitudes.[2,20]

This study has several strengths. It provides contemporary data from a real-world tertiary epilepsy clinic, capturing patient experiences within routine clinical care. The use of both structured questionnaire items and open-ended responses allowed for a more nuanced understanding of psychosocial challenges. Additionally, examining multiple domains—including education, employment, relationships, and perceived stigma—enabled a comprehensive assessment of the lived experience of epilepsy.

Study Limitations

Several limitations should be acknowledged. The cross-sectional design limits the ability to draw causal inferences regarding the relationship between clinical variables and psychosocial outcomes. Data were collected from a single tertiary center, which may limit the generalizability of the findings to broader populations or to different healthcare settings. Self-reported measures are subject to recall bias and may be influenced by individual perceptions. Furthermore, psychiatric comorbidities, such as depression and

anxiety, were not systematically assessed, although these factors are known to interact with stigma and quality of life.

CONCLUSION

In conclusion, the findings of this study indicate that despite significant advances in the medical management of epilepsy, the condition continues to be associated with substantial psychosocial challenges. Patients still report difficulties related to education, employment, interpersonal relationships, and social participation, many of which appear to be closely linked to persistent societal misconceptions and perceived stigma. These observations highlight that improving seizure control alone may not be sufficient to address the broader impact of epilepsy on daily life. Efforts aimed at increasing public awareness, promoting accurate knowledge about epilepsy, and supporting patients in educational, occupational, and social environments remain essential components of comprehensive epilepsy care. Addressing stigma through targeted educational initiatives and patient-centered interventions may contribute to improvements in social integration and overall well-being among people living with epilepsy.

Ethics

Ethics Committee Approval: The study protocol was approved by the University of Health Sciences Türkiye, İzmir Tepecik Education and Research Hospital Non-Interventional Research Ethics Committee (approval no: 2026/01-14, date: 02.02.2026) and was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Informed consent was obtained from all subjects.

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For transparency, the authors note that an artificial intelligence-assisted language model (ChatGPT, OpenAI) was utilized to support language correction. This assistance was limited to linguistic refinement; all scientific content, critical analysis, and final editorial decisions were made exclusively by the authors.

Footnotes

Author Contributions

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

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

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REFERENCES

1. Fiest KM, Birbeck GL, Jacoby A, Jette N. Stigma in epilepsy. *Curr Neurol Neurosci Rep.* 2014;14(5):444. [Crossref]
2. Fernandes PT, Snape DA, Beran RG, Jacoby A. Epilepsy stigma: what do we know and where next? *Epilepsy Behav.* 2011;22(1):55-62. [Crossref]
3. Leaffer EB, Hesdorffer DC, Begley C. Psychosocial and sociodemographic associates of felt stigma in epilepsy. *Epilepsy Behav.* 2014;37:104-109. [Crossref]
4. Baker GA, Brooks J, Buck D, Jacoby A. The stigma of epilepsy: a European perspective. *Epilepsia.* 2000;41(1):98-104. [Crossref]
5. Kaufman KR. Epilepsy and secondary perceived stigma in a social setting: a night at the theater. *Epilepsy Behav.* 2016;61:138-140. [Crossref]
6. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA.* 2013;310(20):2191-2194. [Crossref]
7. Alkhamra H, Tannous A, Hadidi M, Alkhateeb J. Knowledge and attitudes toward epilepsy among school teachers and counselors in Jordan. *Epilepsy Behav.* 2012;24(4):430-434. [Crossref]
8. Bielen I, Zobić I, Sruk A, Ivaković A, Dogan D. Changes of attitudes toward epilepsy in college-preparatory high school students population: an indicator of global campaign successfulness? *Seizure.* 2012;21(10):775-779. [Crossref]
9. Zanni KP, Matsukura TS, Maia Filho Hde S. Beliefs and attitudes about childhood epilepsy among school teachers in two cities of southeast Brazil. *Epilepsy Res Treat.* 2012;2012:819859. [Crossref]
10. Paschal AM, Hawley SR, St Romain T, et al. Epilepsy patients' perceptions about stigma, education, and awareness: preliminary responses based on a community participatory approach. *Epilepsy Behav.* 2007;11(3):329-337. [Crossref]
11. Nishida T, Terada K, Ikeda H, Inoue Y. Seizures, accidental injuries at work, and reasons for resignation in people with epilepsy. *Epilepsy Behav.* 2020;111:107237. [Crossref]
12. Taylor RS, Sander JW, Taylor RJ, Baker GA. Predictors of health-related quality of life and costs in adults with epilepsy: a systematic review. *Epilepsia.* 2011;52(12):2168-2180. [Crossref]
13. Majkowska-Zwolińska B, Jędrzejczak J, Owczarek K. Employment in people with epilepsy from the perspectives of patients, neurologists, and the general population. *Epilepsy Behav.* 2012;25(4):489-494. [Crossref]
14. Bellon M, Walker C, Peterson C, Cookson P. The "E" word: epilepsy and perceptions of unfair treatment from the 2010 Australian Epilepsy Longitudinal Survey. *Epilepsy Behav.* 2013;27(1):251-256. [Crossref]
15. Alaqeel A, Alebdi F, Sabbagh AJ. Epilepsy: what do health-care professionals in Riyadh know? *Epilepsy Behav.* 2013;29(1):234-237. [Crossref]
16. Ekenze OS, Ndukuba AC. Perception of epilepsy among public workers: perspectives from a developing country. *Epilepsy Behav.* 2013;26(1):87-90. [Crossref]
17. Thorbecke R, Pfäfflin M, Bien CG, et al. Have attitudes toward epilepsy improved in Germany over the last 50 years? *Epilepsy Behav.* 2023;138:108982. [Crossref]
18. Yeni K, Tulek Z, Bebek N. Factors associated with perceived stigma among patients with epilepsy in Turkey. *Epilepsy Behav.* 2016;60:142-148. [Crossref]
19. Smeets VM, van Lierop BA, Vanhoutvin JP, Aldenkamp AP, Nijhuis FJ. Epilepsy and employment: literature review. *Epilepsy Behav.* 2007;10(3):354-362. [Crossref]
20. Lim YJ, Chan SY, Ko Y. Stigma and health-related quality of life in Asian adults with epilepsy. *Epilepsy Res.* 2009;87(2-3):107-119. [Crossref]

Exercise Avoidance as a Learned Behavioral Pattern in Epilepsy

Okan Sökmen

University of Health Sciences Türkiye, Atatürk Sanatoryum Training and Research Hospital, Clinic of Neurology, Ankara, Türkiye

Okan Sökmen MD,

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Corresponding Author: Okan Sökmen MD, University of Health Sciences Türkiye, Atatürk Sanatoryum Training and Research Hospital, Clinic of Neurology, Ankara, Türkiye, **E-mail:** drokansokmen@gmail.com

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Dear Editor,

The recent study of physical activity in epilepsy reported that fear of seizures was the primary reason for avoiding exercise, whereas seizure frequency itself was not related to physical activity levels.[1] This suggests that exercise restriction in epilepsy may depend less on actual seizure burden and more on how patients perceive risk.

Many patients with epilepsy judge danger according to the unpredictability of seizures rather than seizure frequency alone. Even patients with relatively rare seizures may continue to see exercise as unsafe because the possibility of suddenly losing control remains frightening. Over time, avoidance behavior may continue even when seizure burden is low. This may partly explain why some patients remain physically inactive despite stable epilepsy.

One possible explanation is that avoiding exercise may gradually become a learned behavior. Patients who repeatedly avoid physical activity and do not experience seizures may start to believe that inactivity itself is protective. In this way, remaining sedentary may unintentionally strengthen the idea that restriction is necessary. Temporary caution may turn into long-term self-imposed restrictions, even among patients without severe epilepsy. Importantly, this process may continue even after the original medical concern becomes less relevant. As avoidance becomes routine, patients may stop evaluating whether the restriction is still clinically necessary.

The findings of the study also suggest that this process may be reinforced by both social and clinical factors. Most patients had never discussed physical activity with their physicians, and many reported being discouraged from exercising by people around them.[1] In daily practice, physician silence may not always be neutral. When exercise is never discussed during follow-up visits, some patients may interpret this as a sign that physical activity is unsafe. Warnings from family members may further strengthen avoidance behavior. In this setting, fear may gradually shift from being a response to seizures toward becoming part of everyday activities.

This may explain why physically restrictive lifestyles remain common despite increasing evidence that exercise is safe and beneficial in epilepsy.[2,3] The problem may therefore involve more than low motivation. In some patients, inactivity may gradually become part of living with epilepsy itself, reinforced by others' fear and caution.[4] This may create a mismatch between actual epilepsy severity and daily functional limitations. Patients with relatively controlled epilepsy may therefore continue to live with restrictions associated with severe disease.

The study raises an important question: are some behavioral restrictions in epilepsy maintained more by learned fear than by ongoing medical necessity? If so, physical restriction in some patients may persist less because of ongoing medical necessity and more because fear itself has gradually been reinforced. Epilepsy care may therefore need to address not only seizures but also the learned restrictions that persist after the actual risk has changed.

Footnotes

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References

1. Yücel Z, Günay MA. Assessment of physical activity behaviors and perspectives in epilepsy patients. *Arch Epilepsy.* 2026;32(1):25-30. [Crossref]
2. Capovilla G, Kaufman KR, Perucca E, Moshé SL, Arida RM. Epilepsy, seizures, physical exercise, and sports: a report from the ILAE task force on sports and epilepsy. *Epilepsia.* 2016;57(1):6-12. [Crossref]
3. Johnson EC, Helen Cross J, Reilly C. Physical activity in people with epilepsy: a systematic review. *Epilepsia.* 2020;61(6):1062-1081. [Crossref]
4. Mayor R, Gunn S, Reuber M, Simpson J. Experiences of stigma in people with epilepsy: a meta-synthesis of qualitative evidence. *Seizure.* 2022;94:142-160. [Crossref]