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Archives of
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CONTENTS

Original Articles

Archives of Epilepsy

EDITORIAL

Dear Colleagues,

Archives of Epilepsy continues to grow with your contributions. You can follow the articles published in the journal and share your comments, criticisms, and contributions with us in the form of letters to the editor.

We would like to inform you that you can see the abstracts of the 8th Epilepsy Symposium held on May 16-18, 2025, on our website.

Unfortunately, various therapeutic molecules developed in the treatment of epilepsy in recent years are not available in our country. Some of these drugs seem to work in resistant catastrophic epilepsies. I think we should voice more actively the demand for introducing these drugs. Members are invited to share their perspectives on what can be done in this regard with our association.

I wish you healthy and happy days.

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

Archives of Epilepsy

Original Article

Comparative Effectiveness of 100 mg/kg Levetiracetam Injection in Two Different Epilepsy Models: Temporal Lobe Epilepsy and Genetic Absence Epilepsy

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Abstract

Objective: Levetiracetam (LEV) is a broad-spectrum anti-seizure drug primarily prescribed for partial seizures. We aimed to compare the effects of LEV in two epilepsy models: the kindling model for temporal lobe epilepsy and the Genetic Absence Epilepsy Rats from Strasbourg (GAERS) model for absence epilepsy.

Methods: GAERS and Wistar rats underwent stereotaxic surgery for cortical recording electrodes implantation, while bipolar stimulation electrodes were implanted in the right basolateral amygdala of Wistar rats for kindling stimulations. For the kindling procedure, Wistar rats were stimulated at after discharge (AD) threshold twice daily. After three consecutive stage five seizures, the animals were considered kindled and randomly divided into two groups. Kindled animals received intraperitoneal injection of either saline or 100 mg/kg LEV 1 hour before stimulation. Seizure stage, amygdala AD, and total seizure duration were evaluated. GAERS rats were randomly divided into two groups, and spike-and-wave discharges (SWDs) were recorded for 2 hours after intraperitoneally injecting 100 mg/kg LEV or saline. Cumulative SWD duration, number of SWDs, and mean duration of an individual SWD were compared with the saline-treated control group.

Results: LEV significantly reduced the seizure severity and AD duration compared to controls. The mean seizure stage was 1.42±0.29 in the LEV group ($p<0.0001$) while all saline-treated kindled animals reached stage 5 seizure. LEV also lowered the total seizure duration (13.14±1.11 s) significantly compared to vehicle (86.76±12.59 s; $p<0.005$). In GAERS group, LEV suppressed the SWDs around 40 min after injection, and this anti-seizure effect lasted until the end of a 2-hour electroencephalography recording.

Conclusion: LEV, at a dose, 100 mg/kg, effectively reduced convulsive and non-convulsive seizures in two different epilepsy models. These results underscore the efficacy of LEV in mitigating seizure severity and duration across different epilepsy types, suggesting its potential as a promising therapeutic agent for managing both focal and absence seizures.

Keywords: Levetiracetam, temporal lobe epilepsy, absence epilepsy, kindling, Genetic Absence Epilepsy Rats from Strasbourg

INTRODUCTION

Levetiracetam (LEV), approved as a single agent in the early 2000s, is a widely used broad-spectrum second-generation anti-seizure drug (ASD) in the treatment of focal-onset seizures and focal to bilateral tonic-clonic seizures [previously known as partial seizures and partial seizures with secondary generalization, such as temporal lobe epilepsy (TLE)].[1] LEV is also prescribed for children with epilepsy characterized primarily by typical absence seizures. It is approved for adjunctive therapy for the treatment of myoclonic seizures in adults and juvenile myoclonic epilepsy in adolescents over the age of 12 years, and primary generalized tonic-clonic seizures in adults and children over five years old with idiopathic generalized epilepsy.[2-4] In a randomized, placebo-controlled trial of LEV in children and adolescents with newly diagnosed childhood or juvenile absence epilepsy, 23.7% of patients responded to LEV monotherapy.[5] In a short-term randomized, placebo-controlled study to determine whether LEV is efficacious in controlling typical absence seizures in patients with newly diagnosed childhood or juvenile absence epilepsy, LEV treatment caused an aggravation of childhood absence epilepsy patients and increased the daily number of absence seizures.[6] The progressive decrease of LEV dose was followed by a corresponding reduction in absence seizures in these patients.

The primary mechanism of action is through the interaction with the synaptic vesicle protein 2A (SV2A), which is involved in vesicle trafficking and exocytosis and appears to exert a role in epilepsy pathophysiology.[7,8] Additional mechanisms are thought to include the gamma-aminobutyric acid (GABA)-mediated GABAergic system, modulation of targets related to cellular calcium (Ca^{2+}), a key modulator of neuronal excitability and synaptic transmission, direct or indirect interaction with noradrenaline, adenosine, serotonin receptors, and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors, among others. The integration of these mechanisms into a single mechanism of action explains the antiepileptogenic, anti-inflammatory, neuroprotective, and antioxidant properties of LEV.[8]

Animal models are used to study epilepsy/seizures, the mechanisms underlying these conditions, and to develop ASDs. As an animal model of secondary generalized convulsive seizures, the amygdala kindling model is an established experimental model of human TLE. This is because the amygdala possesses the lowest threshold for the induction of kindling, in which daily electrical stimulation results in a gradual progression and intensification of limbic motor seizures.[9,10] Potent protection has been observed with LEV in genetic and chronic epilepsy animal models, such as the amygdala-kindling model of TLE.[11-13]

Genetic absence epilepsy rats from Strasbourg (GAERS) have emerged as an animal model highly reminiscent of a specific form of genetic/idiopathic generalized epilepsy.[14] Both its electrophysiological [spike-and-wave discharges, (SWDs)] and behavioral features fit well with those observed in humans with typical childhood absence epilepsy. The sensitivity to anti-seizure medications match the clinic, making this model one of the most predictive and validated.[15]

This study aimed to provide insights into the therapeutic potential of LEV across different types of seizures (focal seizures vs generalized absence seizures) in both TLE and absence epilepsy rat models. For this purpose, we aimed to compare the effect of a 100 mg/kg dose of LEV on seizure activity and severity in experimental rat models representing these two distinct epileptic conditions: electrical kindling for secondary generalized convulsive TLE and the GAERS model for non-convulsive absence epilepsy.

METHODS

Animals

Adult (3-4 months old) 250-350 g male GAERS and Wistar rats were used in the experiments. Animals were obtained from Acıbadem Mehmet Ali Aydınlar University, Laboratory Animal Application and Research Center, and the experiments were performed there. Animals were kept on a 12-h light-dark cycle, in 21-24 °C room temperature, and were provided with standard food and water ad libitum. After stereotaxic surgery, each animal was placed in a separate cage. All procedures performed on rats were approved by the Ethical Committee for Experimental Animals of Acıbadem University (approval no: 2024/43, date: 24.07.2024), in accordance with the European Parliament and Council Directive 2010/63/EU for animal experiments and ARRIVE guidelines. A detailed representation of the experimental plan can be seen in Figure 1.

MAIN POINTS

- Levetiracetam (LEV) demonstrates efficacy in both temporal lobe epilepsy (TLE) and absence epilepsy model, effectively targeting different seizure types focal seizures in TLE and generalized absence seizures.
- While synaptic vesicle protein 2A binding plays a central role in LEV's mechanism of action in both models, additional mechanisms may differentially contribute to its anti-seizure effects in TLE and absence epilepsy.
- LEV has the potential to be effective across various epilepsy types; however, optimal dosing and tailored therapeutic strategies may be required for different conditions.

Stereotaxic Surgery

Wistar rats (n=14) were anesthetized with isoflurane (2.5-3%, oxygen's flow rate was 0.8 L/min) inhalation anesthesia and placed in a stereotaxic instrument (Stoelting Model 51600, Stoelting Co. Illinois, USA), and the scalp was shaved, and the skull exposed. For the kindling procedure, a bipolar twisted 2 channel electrode (MS303/1-B; Plastics One, Roanoke, VA, USA) targeting the right basolateral amygdala (BLA) was implanted according to the coordinates obtained from the rat brain in stereotaxic coordinates atlas [anteroposterior (AP)=-2.6 mm; mediolateral (ML)=-4.8 mm; dorsoventral=-8.5 mm from bregma].[16] Stainless steel screws, used for extradural ground and recording electrodes, were placed bilaterally over the fronto-parietal cortices (for frontal cortex AP=2.0 mm, ML=±1.7 mm; for parietal cortex AP=-6.3 mm, ML=±4.0 mm). Electrodes were connected by insulated wires to a micro connector for electroencephalography (EEG) recordings. Dental acrylic was used to protect each implant on the skull.

GAERS (n=16) were anesthetized with isoflurane (2.5-3%, oxygen's flow rate was 0.8 L/min) inhalation anesthesia and placed in a stereotaxic instrument (Stoelting Model 51600, Stoelting Co. Illinois, USA); the scalp was shaved, and the skull was exposed. For cortical EEG recordings from somatosensorial cortex, four cortical recording electrodes were placed bilaterally over the fronto-parietal cortices (for frontal cortex AP=2.0 mm, ML=±1.7 mm; for parietal cortex AP=-6.3 mm, ML=±4.0 mm) and two ground electrodes were implanted. Electrodes were connected by insulated wires to a micro connector for EEG recordings. Then all the implants were fixed to the skull with dental acrylic. After the surgeries, 100 mg/kg paracetamol was administered by intramuscular injection.

The animals were allowed to recover from surgery for ≥7 days before the first day of the experiment. Post-operative care was given for 3 days after surgery. Paracetamol (100 mg/kg, intramuscular) was injected. Their nutrition was checked by daily weight monitoring, and a saline injection (100 mL/kg, subcutaneous) was given if necessary.

Amygdala Kindling and Levetiracetam Treatment

After a 1-week recovery period, the animals were placed in plexiglas cages, and a baseline EEG was recorded for 20 minutes from the right and left cortex. To determine the after discharge (AD) threshold, a 2 s, 80-Hz monophasic square-wave stimulus of 1 ms per pulse was used, and the BLA of rats was stimulated with the stimulus intensity beginning at 50 μA. This intensity was subsequently increased in 50 μA steps until a first AD was obtained using the A310 Stimulator and A365 Stimulus Isolator (World Precision Instruments, Florida, USA). The animals were

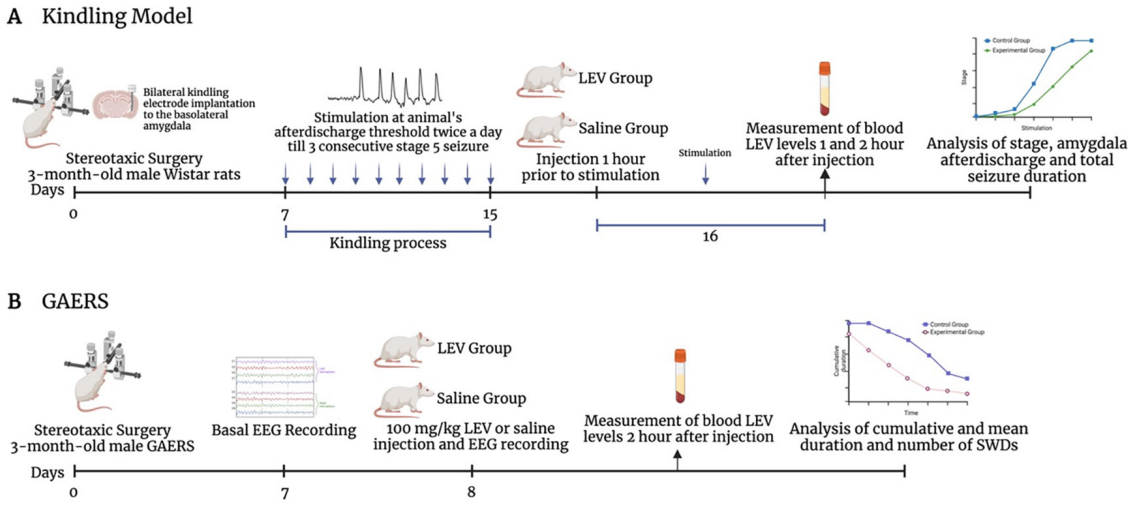

Figure 1. Experimental plan. **A.** levetiracetam's effect on kindling model and **B.** genetic absence epilepsy rats Strasbourg
LEV: Levetiracetam, GAERS: Genetic Absence Epilepsy Rats from Strasbourg, SWDs: Spike-and-wave discharges, EEG: Electroencephalography

then stimulated twice a day at the current AD threshold. Seizure stages observed after each stimulation were classified using Racine's scale: stage 1; facial movements; stage 2; rhythmic head movements, head nodding; stage 3; unilateral forelimb clonus; stage 4; bilateral forelimb clonus and rearing; and stage 5; falling and clonic convulsion. EEG was recorded before and after each stimulation. EEG was amplified, through a BioAmp ML 136 amplifier, with band pass filter settings at 1-40 Hz, recorded using Chart v.8.1 program (PowerLab8S ADInstruments, Oxfordshire, UK).

Once animals reached stage 5 seizures three consecutive times, they were considered "kindled". Subsequently, kindled animals were randomly divided into two groups. The following day, the LEV group received 100 mg/kg LEV via intraperitoneal (i.p.) injection and was stimulated one hour later. The control group received an equivalent volume of i.p. saline injection. Seizure stage, amygdala AD duration, motor seizure duration, and total seizure duration were then calculated for each group.

Genetic Absence Epilepsy Rats from Strasbourg and Levetiracetam Treatment

GAERS rats implanted with EEG electrodes were placed in a Plexiglas recording chamber and habituated for 20 minutes after the recovery period. Then, a 2-hour baseline EEG (from 9 a.m. to 11 a.m.) was recorded to confirm typical SWD occurrence after surgery. The next day after a 20-minute baseline EEG recording, GAERS rats were randomly divided into two groups and received either 100 mg/mL/kg LEV or an equivalent volume of i.p. saline injection. EEG was recorded for 120 min after i.p. injection. EEG was amplified through a BioAmp ML 136 amplifier, with band pass filter settings at 1-40 Hz, recorded using Chart v.8.1 program (PowerLab8S ADInstruments, Oxfordshire, UK).

Serum Concentrations of Levetiracetam

To monitor the serum levels of LEV in the blood, under light isoflurane anesthesia (% isoflurane), 1 mL of blood was collected from the jugular vein of amygdala-kindled Wistar rats at 1 and 2 hours after LEV injection, and from GAERS rats 2 hours after LEV injection. Serum was separated by centrifugation at 5000 rpm for 5 minutes, and sent to Acıbadem Labmed for measurement of LEV concentrations in blood. Blood LEV levels were measured with Shimadzu 8040 LC-MS/MS triple quadrupole mass spectrometer (Japan).

Statistical Analysis

For the TLE group, amygdala AD duration, total seizure duration and stages were calculated for each animal and analyzed with GraphPad Prism version 10.4.1 (Boston, Massachusetts, USA). For statistical analysis, two-way analysis of variance (ANOVA) and uncorrected Fisher's LSD test (GraphPad Software, San Diego, CA, USA) were used.

In the GAERS group, only SWD complexes with a train of SWD (7-11 Hz) and an amplitude at least twice that of the background EEG were found at periods longer than 1 second and were assessed during both the baseline recording and the post-administration recording. The cumulative SWD duration, number of SWDs, and the mean duration of an individual SWD were analyzed with two-way ANOVA and post-hoc Benferroni's multiple comparisons test. Data were expressed as mean±standard error of the mean.

RESULTS

Amygdala Kindling

The mean number of stimulations needed for a rat to reach a stage 5 seizure was 12.6±1.1 stimulations; whereas the mean number of stimulations needed to reach the first stage 5 seizure was 10.4±1.2 stimulations. The mean amygdala AD duration on the last day of kindling for stage 5 was 76.4±8.3.

The Effect of Levetiracetam on Kindling Model

We tested the effects of LEV on the amygdala kindling model of TLE after animals experienced 3 consecutive stage 5 seizures and were considered to be kindled. The kindled animals were then

randomly divided into two groups. The next day, animals were treated with either saline (control group) or LEV (LEV group) one hour before receiving the next stimulation. All animals in the control group remained at stage 5; however, following the stimulation, seizure stage was significantly decreased to a non-convulsive stage (stage 1.42±0.29; p<0.0001) in LEV group (Figure 2A).

Amygdala AD duration (6.4±1.29 s; p<0.0001) and the total seizure duration (13.14±1.11 s; p<0.0001) in the LEV group were significantly decreased compared to the control group (amygdala AD duration: 62.37±8.92 s; total seizure duration: 86.76±12.59 s) and the last day of the kindling (amygdala AD duration: 75.84±8.48 s; p<0.05; total seizure duration: 89.01±7.02 s; p<0.0001) (Figure 2A and B). Supporting this, serum LEV concentrations were within the therapeutic range 140±10.6 µg/mL and 76.5±10.9 µg/mL in blood samples taken 1 hour and 2 hours post-injection, respectively (Figure 3).

The Effect of Levetiracetam on Spike-and-wave Discharges

In GAERS, LEV significantly reduced the cumulative duration of SWDs within the 40 min post injection period (115.8±40.8, p<0.001) compared to the saline-treated vehicle group (406.3±33.7). The number of SWDs was also significantly reduced after the LEV injection (12.8±3.5, p<0.05) compared to saline (30.8±2.4) (Figure 4A and B). There was a statistically significant difference in the mean duration of an individual SWD only during the 20-40 min post-injection period. This seizure suppression effect on the SWDs correlated with the serum LEV concentrations measured at 2-h (98.15±8.0 ug/mL) post injection within the therapeutic range.

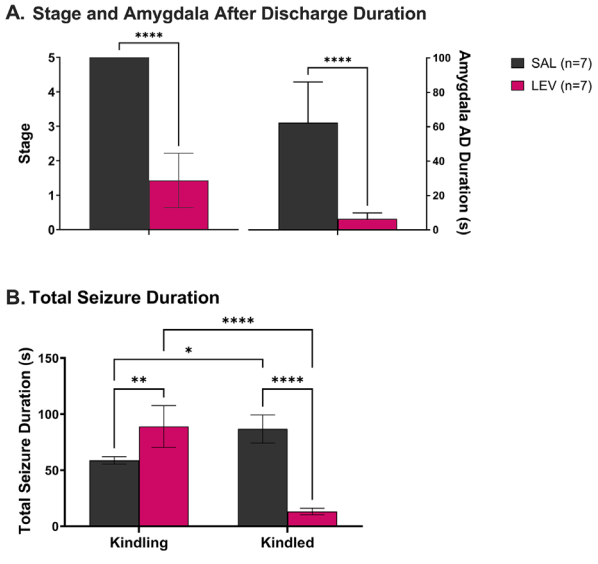

Figure 2. The effect of intraperitoneal 100 mg/kg LEV or saline injection in kindling model of convulsive seizures with secondary generalization on seizure stage and amygdala AD duration **(A)**, and total seizure duration **(B)**. Data expressed as mean±SEM
*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001, LEV: Levetiracetam, AD: After discharge, SEM: Standard error of the mean, SAL: Saline

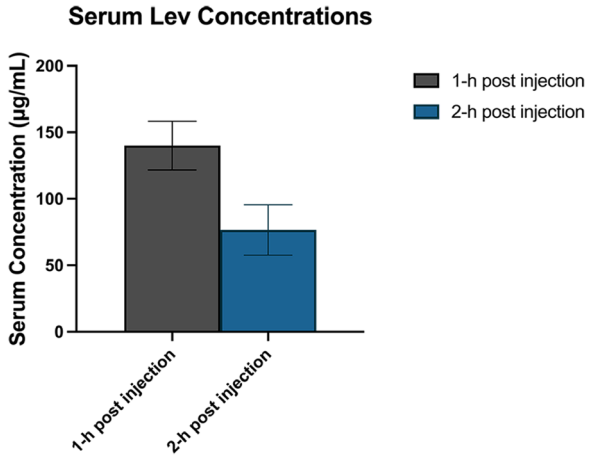

Figure 3. Serum levels of LEV 1 hour and 2 hours after intraperitoneal injection in kindling model. Data expressed as mean±SEM
LEV: Levetiracetam, SEM: Standard error of the mean

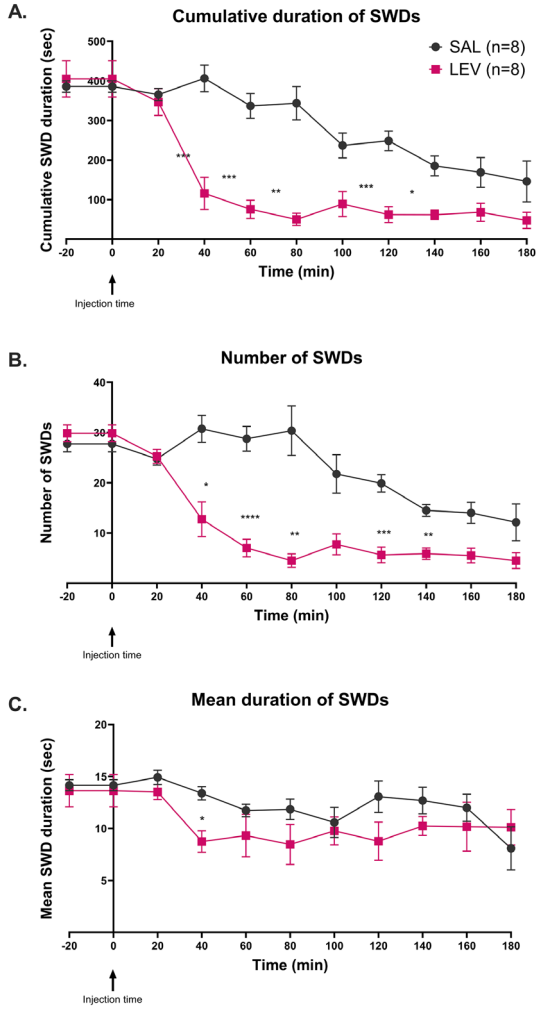

Figure 4. The effect of intraperitoneal 100 mg/kg LEV injection compared to saline injected control group on cumulative duration of SWDs **(A)**, number of SWDs **(B)**, mean duration of an individual SWDs **(C)**. Data expressed as mean±SEM
*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001, LEV: Levetiracetam, SEM: Standard error of the mean, SWDs: Spike-and-wave discharges, SAL: Saline

DISCUSSION

The findings from our study highlight the significant anti-seizure effects of LEV in two distinct animal models of epilepsy, providing valuable insights into its therapeutic potential. In amygdala-kindled rats, LEV administration led to a marked reduction in seizure severity and seizure duration compared to saline-treated animals. Specifically, the mean seizure stage of the LEV group was significantly lower than that of saline-treated kindled rats. Moreover, LEV significantly decreased the total seizure duration, which contrasts sharply with the control group.

In the GAERS model, administration of LEV, resulted in a substantial suppression of SWDs beginning approximately 40 minutes post-injection, with this anti-seizure effect persisting throughout the 2-hour EEG recording period. These results underscore LEV's efficacy in mitigating seizure severity and duration across different epilepsy types, suggesting its potential as a promising therapeutic agent for managing both focal and absence seizures.

The efficacy and safety of LEV have been studied in different animal models for different epilepsy types, with the kindling model being one of the first. The amygdala-kindling model, first characterized by Goddard et al.[9] includes most, if not all, of these characteristics of human TLE.[17] LEV exerts potent anticonvulsant effects in fully kindled rats and it also has potent antiepileptogenic effects during kindling development.[12,13] In our study, we showed that a single injection of 100 mg/kg LEV reversed the effects of kindling stimulation. No motor seizures were observed in the experimental group, while all the animals in the control group had stage 5 seizures according to Racine's scale. Additionally, LEV injection caused a statistically significant decrease in amygdala AD duration and total seizure duration compared to the control group. These observations correlated with the high plasma LEV levels measured at 1 h, and 2-h post-injection.

We also showed the anti-absence properties of LEV in adult GAERS in accordance with the study of Gower et al.[18] This previous study has shown that an i.p. injection of LEV at doses ranging from 5.4 to 170 mg/kg markedly reduced SWDs from 15 to 30% in a non-dose-dependent manner. Furthermore, SWD suppression exceeded 95% in one or two rats per group, at doses of 5.4-96.0 mg/kg, in a 2-hour EEG recording. The effect of LEV in absence epilepsy was investigated in another animal model of absence epilepsy, Wistar-Albino-Glaxo from Rijswijk rats, by Bouwman et al.[19] where they showed that both 50 mg/kg and 100 mg/kg LEV decreased the mean and cumulative duration of SWDs. They also showed LEV decreased the peak frequency of SWDs, like the GABA transaminase inhibitor vigabatrin, suggesting the same anti-absence mechanism for LEV. In our study, suppression in terms of cumulative SWD duration and number of SWDs started to be observed in all animals around 40 minutes after LEV injection, and continued until the end of the 2-hour EEG recording. In parallel, the LEV concentrations remained high in blood samples taken two hours after injection.

The options for the treatment of absence epilepsy are limited; ethosuximide, lamotrigine, and valproic acid alone or in combination are the first choice. However, pharmaco-resistant seizures are observed in 20% of patients.[20,21] The main mechanism of action of ethosuximide is the blockade of transient, low-threshold Ca^{2+} currents produced by T-type Ca^{2+} channels in thalamic neurons. Lamotrigine is a voltage-dependent sodium (Na^{+}) channel blocker. Unlike other Na^{+} channel-blocking agents, it must have additional mechanisms that explain its efficacy in generalized epilepsies; however, these mechanisms are not yet characterized. Valproic acid is a broad-spectrum anti-seizure medication that has multiple mechanisms of action, including raising GABA levels in the brain, blocking voltage-sensitive Na^{+} channels, and activating Ca^{2+} dependent potassium (K^{+}) conductance, but the specific mechanism of preventing absence seizures is unknown. Valproic acid is as effective as lamotrigine and ethosuximide in controlling absence seizures, but its use is limited due to the side effects.[22] It has been reported that many anti-seizure medications, such as carbamazepine and phenytoin, can exacerbate absence seizures. The mechanism of seizure aggravation is uncertain, but it is known that these drugs act on Na^{+} channels. There is an urgent need for more effective and well-tolerated treatments to be developed for absence epilepsy to prevent or reverse the epilepsy-related comorbidities.

In a multicenter, prospective, long-term, open-label treatment study evaluating efficacy, tolerability, and safety of LEV in 21 patients with absence epilepsy, at the 6-month evaluation, 11 patients became seizure free and one showed 'decreased' seizures (more than 50% reduction in seizures).[23] At the 12-month evaluation, 10 patients were completely seizure free and two were seizure free with some anomalies in EEG. In contrast to these findings, there are studies showing seizure aggravation with LEV treatment in patients with absence epilepsy. The decrease in LEV dose caused a gradual decrease in seizure aggravation in these patients, and they recovered after stopping LEV treatment.[6] In another study, LEV treatment was only effective in 2 absence epilepsy patients out of 11; the treatment failed in 9 patients.[24]

Here, we are not only demonstrating the anticonvulsive effect of LEV in the amygdala kindling model of TLE but also the possible anti-absence properties of LEV in the animal model of absence epilepsy, GAERS.

Study Limitations

Female GAERS and Wistar rats were not included in this study to minimize response variability caused by hormonal and metabolic factors.

CONCLUSION

This is the first study to demonstrate the comparative effectiveness of LEV in two different types of epilepsy at the same time, TLE and absence epilepsy, to determine whether LEV is effective in both convulsive and non-convulsive types of seizures. This was tested using the amygdala kindling model of TLE and the GAERS model for absence epilepsy, simultaneously. In the light of these findings, it is evident that a single and efficacious dose of LEV not only reversed the effects of amygdala-kindling in fully kindled Wistar rats, but also exhibited anti-absence features in adult GAERS. At the dose of 100 mg/kg, LEV decreased both the time spent in seizure and the number of seizures in GAERS, during a 2-hour EEG recording compared to control.

Since the main mechanism of LEV is thought to be through its interaction with the SV2A, additional mechanisms through the GABAergic system and the modulation of Ca^{2+} channels, may

contribute differently to its anti-seizure effects in TLE and absence epilepsy. Further studies exploring the drug's mechanisms of action, optimal dosing regimens, long-term effects, and safety profiles in each epilepsy type are warranted to fully elucidate its clinical implications and optimize its therapeutic use in epilepsy management.

Ethics

Ethics Committee Approval: The study was approved by the Acıbadem Mehmet Ali Aydınlar University Ethical Committee for Experimental Animals (approval no: 2024/43, date: 24.07.2024).

Informed Consent: Animal experiment.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.T.E., Concept: F.O., N.Ç., Design: F.O., N.Ç., Data Collection or Processing: E.T.E., Analysis or Interpretation: E.T.E., F.O., N.Ç., Literature Search: E.T.E., F.O., N.Ç., Writing: E.T.E., F.O., N.Ç.

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

Financial Disclosure: E.T.E. is a YÖK 100/2000 PhD scholar.

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Archives of Epilepsy

Original Article

The Effect of Anti-seizure Drugs on Visual Functions in Epilepsy Patients

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Abstract

Objective: In this study, we aimed to detect early signs of central nervous system involvement in patients with epilepsy, under anti-seizure drug monotherapy, using visual evoked potentials (VEPs), a non-invasive and easily applicable test, and to correlate these findings with clinical data.

Methods: Between June 10, 2023, and December 31, 2023, 64 patients with epilepsy aged 18 to 65 who had been receiving monotherapy for at least 6 months were included in the study. Additionally, 50 age- and gender-matched healthy individuals were included as a control group. Age, gender, anti-seizure medication, and duration of use, ophthalmologic and neurologic examination findings, and brain magnetic resonance imaging results were recorded. Informed consent was obtained from all participants. VEPs of both groups were studied.

Results: The mean age of the patients was 32.39±12.78 years; 51.6% were female, and 48.4% were male. The distribution of medications among the patients was as follows: 59.4% were using levetiracetam, 25% valproic acid, 10.9% lamotrigine, 3.2% carbamazepine, and 1.5% lacosamide. The N75 and P100 latencies and amplitudes in patients were significantly higher than those in the control group ($p<0.05$). P100 latency differences in levetiracetam, carbamazepine and lacosamide users were less pronounced compared to valproic acid and lamotrigine users; however, these differences were not statistically significant ($p>0.05$.).

Conclusion: In this study, levetiracetam, lacosamide, and carbamazepine were found to have less adverse effects on P100 latency, independent of the duration of treatment. For the early diagnosis and treatment of silent visual disturbances, epilepsy patients should undergo visual evoked potential and eye examinations at regular intervals.

Keywords: Levetiracetam, valproic acid, lamotrigine, P100, visual evoked potentials

INTRODUCTION

Visual disturbances are a common side effect of many anti-seizure drugs. Visual impairment in patients with epilepsy may arise from the disease itself or from the effects of the anti-seizure medications (ASMs) used in treatment.

Depending on the drug's properties, some ASMs may cause specific visual problems even at recommended daily doses. ASMs act through gamma-aminobutyric acid (GABA), sodium (Na), chlorine (Cl), and calcium pathways. They enhance inhibitory neurotransmission by increasing GABA-mediated Cl transmission, stimulating the glutamic acid decarboxylase enzyme, directly increasing GABA release, or inhibiting GABA reuptake. Valproic acid has a pronounced potentiating effect on GABA-ergic functions.[1] Although the exact mechanism of action of carbamazepine is not fully understood, it has been reported to exhibit anticonvulsant effects by blocking voltage-dependent Na channels.[2,3] Levetiracetam, a second-generation anti-seizure drug, is believed to act by binding to the synaptic vesicle protein synaptic vesicle glycoprotein 2A and interfering with neurotransmitter release from vesicles, while lamotrigine provides neuron stabilization by selectively blocking Na channels and suppressing glutamatergic release.[2,4-7]

GABA is the primary inhibitory neurotransmitter in the brain, affecting up to 70% of the neuronal network and up to 40% of retinal inhibition.[8,9] The GABA inhibitory network in the occipital cortex enhances the selectivity of cortical cells for finer stimuli. This network's role in shaping the visual response to spatial pattern stimuli has been demonstrated by visual evoked potentials (VEPs).[10]

VEPs are particularly useful for detecting clinically silent disorders, identifying lesions, confirming suspicious and ambiguous changes, and monitoring the course of some neurological diseases. They are sensitive, reproducible, non-invasive, and easy to perform.

In the literature, there are studies reporting prolonged P100 latencies after ASM use, as well as studies reporting no change.[11-13] Moreover, most of these studies focused on pediatric patients, leaving unclear the relationship between VEP parameters and ASMs in adults, especially with newer drugs.

The aim of this study was to prospectively detect early and silent signs of central nervous system involvement in patients with epilepsy under anti-seizure drug monotherapy using VEP, a non-invasive and easily applicable test. Additionally, the study aimed to correlate these findings with clinical data.

METHODS

Characteristics of the Patient and Control Groups

The study included 64 epilepsy patients aged 18-65 years, met the inclusion criteria and had been receiving monotherapy for at least 6 months according to the International League Against Epilepsy (ILAE) criteria in our epilepsy outpatient clinic between June 10, 2023 and December 31, 2023. Additionally, 50 age-gender-matched healthy individuals were included as controls.

Patients' age, gender, ASM type and duration, Mini-Mental State test (MMST) results, and brain magnetic resonance imaging (MRI) examinations were recorded.

Participants included in this study were individuals aged 18 and over, who had been diagnosed with epilepsy for at least six months according to the ILAE diagnostic criteria, were on monotherapy, and had normal neurological and visual examinations, as well as normal MMST and MRI results. Additionally, participants had not experienced a seizure in the three days prior to the measurement. Exclusion criteria included individuals with neurological, systemic, toxic, traumatic, autoimmune, endocrinological, syndromic, or metabolic diseases; those taking chronic medications affecting the central nervous system (e.g., antiepileptics, neuroleptics, psychostimulants, analgesics, steroids, sedative-hypnotics); individuals with significant eye damage (visual acuity between 0.9 and 1.0, including correction with glasses); individuals who were underweight [body mass index (BMI) <18.5 kg/m^2] or overweight (BMI ≥35 kg/m^2); those with head trauma, intracranial malformations, or space-occupying lesions; those with abnormal MRI findings; and individuals with a history of psychiatric illness. The control group consisted of healthy individuals aged 18 and over who had no neurological, psychiatric, or metabolic diseases, no history of drug, alcohol, or substance addiction, and normal MRI results.

Informed consent was obtained from all participants. The study was approved by the University of Health Sciences Türkiye, Adana City Training and Research Hospital Clinical Research Ethics Committee (decision no: 2629, date: 08.06.2023).

VEP procedure was conducted according to the International Federation of Clinical Neurophysiology guidelines.[14]

The VEP study was performed using the Cadwell Sierra Summit System (Cadwell Laboratories, Kennewick, Washington, USA).[15]

MAIN POINTS

- Anti-seizure medications (ASMs) affected visual evoked potential parameters, particularly causing a delay in P100 latency.
- Levetiracetam, lacosamide, and carbamazepine had a less negative effect on P100 latency, regardless of treatment duration.
- Information regarding the silent visual effects of ASMs in adult patients is still insufficient and more studies are needed in this area.

Silver cup electrodes were used for recording, with high-pass and low-pass filters set to 1 Hz and 100 Hz, respectively. Sensitivity and scan rate were set to 5 μV/division and 25 ms/division, respectively. The Oz and Fz points were marked according to the international 10-20 electroencephalography system, and electrodes were placed at the active Oz and reference Fz. VEP test impedances were <5 kΩ for all electrodes. For pattern-reversal VEP, a CBOX 18.5 LED monitor displaying a black and white checkerboard, with a red dot in the center was used, and the stimulus rate was set to 1 Hz.

N75, P100, and N145 waves were analyzed by setting the distance between the LED monitor and the participants' eyes to 100 cm and the control size to 51 minutes of arc (dimensions 8x8). VEP was applied to both eyes in a dark room. VEP waves were obtained by averaging at least 100 potentials twice, for each eye. P100 amplitudes were calculated by measuring from N75 to P100.

Statistical Analysis

Descriptive statistics included frequency, percentage, arithmetic mean, and standard deviation. The chi-square test was used for categorical variable comparisons. The independent sample t-test was used to compare values between the case and control groups. Kruskal-Wallis analysis, which is a non-parametric test, was performed due to the non-homogeneous distribution of the case group based on drug use. Spearman correlation analysis was used to evaluate the relationship between values in the case group. IBM Statistical Package for the Social Sciences 21.0 (IBM Co. Armonk, NewYork) package was used for statistical analysis of the data. A p-value below 0.05 was considered statistically significant.

RESULTS

Among the patients, 51.6% (33) were female and 48.4% (31) were male, with a mean age of 32.39±12.78 years. In the control group, 70% (35) were female and 30% (15) were male, with a mean age of 36.32±11.85 years. Forty five patients (70.3%) had generalized seizures, 15 patients (23.4%) had focal seizures without awareness, and 4 patients (6.25%) had focal seizures with preserved awareness (Table 1).

No statistically significant difference was found between the gender groups (χ^2=3.561; p=0.074) and average age (t=0.901; p=0.370) of the case and control groups.

Regarding medication usage among the patients, 59.4% (38) were using levetiracetam, 25% (16) were using valproic acid, 10.9% (7) were using lamotrigine, 3.2% (2) were using carbamazepine, and 1.5% (1) were using lacosamide.

N75 and P100 latencies, and amplitudes were found to be statistically significantly higher in the patient group compared to the control group (Table 2).

By excluding patients using lacosamide and carbamazepine in the analysis of the case group (because the number of patients in this group was small and disrupted the homogeneous distribution), no significant difference was detected between the type of drug used and VEP parameters (p>0.05) (Table 3).

Levetiracetam users (mean P100 latency: 3.60±3.07) had a shorter P100 latency compared to valproic acid (4.70±3.24) and

lamotrigine (4.03±3.20) users. However, these differences were not statistically significant (p>0.05) (Figure 1).

No significant correlation was found between VEP parameters and treatment duration in the patient group (Spearman's correlation analysis). There was no statistically significant difference in VEP latencies between different seizure types (p>0.05). Additionally, no significant difference was found among other parameters within the patient group concerning the type of drug used (p>0.05).

DISCUSSION

It is estimated that approximately 50 million people worldwide have epilepsy, and 4.9 million people will receive a new diagnosis of epilepsy each year.[16,17] When prescribing ASMs, the goal is to achieve maximum seizure control with minimal side effects.

VEPs are a sensitive non-invasive method for evaluating the effects of ASMs on the central nervous system. The literature contains a limited number of studies on the impact of ASMs on VEPs, and the findings are often conflicting. This study is the first to examine the effects of multiple ASMs on visual function in a group of adult patients treated with more than three different ASMs concurrently.

Harding et al.[18] found results similar to the placebo after administering valproic acid to 10 volunteers for a maximum of 14 days, and stated that valproic acid had no effect on VEPs latencies. However, in subsequent studies, it was determined that there was no difference in VEPs latency and amplitude between the healthy group and the epileptic groups before the initiation of ASM. VEPs P100 latency was prolonged after treatment; this could be attributed to ASMs.[11,12] Therefore, we selected our study

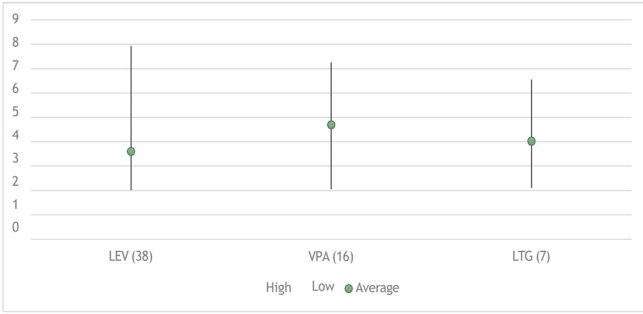

Figure 1. Right-left P100 latency differences
LEV: Levetiracetam, VPA: Valproic acid, LTG: Lamotrigine

Table 1. Homogeneity and descriptive characteristics of case and control groups

Groups	Gender		Age	
	Female n (%*)	Male n (%*)	x̄	SD
Control (50)	35 (70.0%)	15 (30.0%)	36.32	11.85
Case (64)	33 (61.6%)	31 (48.4%)	32.39	12.78
Test values	χ^2**=3.561, p=0.074		t***=0.901, p=0.370	

*Percentage of rows, **Chi-square test, ***Independent sample t-test, SD: Standard deviation

Table 2. Comparison of case and control groups

	Control (50)		Case (64)		Test values	
Variables	**x̄**	**SD**	**x̄**	**SD**	**t***	**p-value**
N75 right latency	54.30	7.19	57.97	13.10	-3.812	**0.000**
N75 left latency	55.40	7.38	63.61	43.34	-4.615	**0.000**
Right-left N75 latency difference	4.15	3.46	7.72	11.56	-6.547	**0.000**
P100 right & left latancy averages	86.65	6.32	101.33	13.64	-4.649	**0.000**
Right-left P100 latency difference	3.61	2.58	5.25	3.66	-5.836	**0.000**
N145 right	128.99	18.22	130.26	16.75	-1.294	**0.075**
N145 left	130.38	16.31	132.22	22.13	-1.008	**0.082**
Right-left N145 latency difference	5.86	3.94	6.95	7.29	-4.551	**0.000**
N75/P100 amplitude difference	1.31	1.26	2.18	1.97	-6.640	**0.000**

*Independent sample t-test, SD: Standard deviation

Table 3. Evaluation of the drug type used in the case group according to parameters

Variables	Levetiracetam (38)		Valproic acid (16)		Lamotrigine (7)		p-value*
	x̄	SD	x̄	SD	x̄	SD	
Right-left N75 latency difference	7.28	9.42	7.26	8.91	8.18	6.24	0.710
Right-left P100 latency difference	3.60	3.07	4.70	3.24	4.03	3.20	0.862
Rigt-left N145 latency difference	7.60	2.21	6.75	6.21	7.14	4.18	0.258
N75-P100 amplitude difference	2.60	1.83	2.06	1.27	2.28	1.49	0.057

*One-way analysis of variance note: in the lacosamide and carbamazepine (3) group, right-left N75 latency difference was (7.01±7.33), right-left P100 latency difference (3.45±2.51), right-left N145 latency difference (6.29±3.31), N75-P100 amplitude difference (3.00±1.11) was determined.
SD: Standard deviations

population from patients under effective ASM treatment. The study group consisted of these patients, while healthy volunteers with a homogeneous distribution constituted the control group.

Verrotti et al.[11] compared two groups: 58 children with epilepsy who were treated with carbamazepine, valproic acid, and phenobarbital for one year, and 50 controls. They found P100 latency prolongation in those treated with carbamazepine and valproic acid. Another study involving 53 patients using carbamazepine, valproic acid, and levetiracetam, along with 20 controls, found significant P100 latency prolongation in the ASM group compared to controls. It was noted that levetiracetam had a lesser impact on P100 latencies in epileptic patients, compared to valproic acid and carbamazepine.[19] Two recent studies with patients using only levetiracetam reported no significant difference in P100 latencies compared to the control group; however, these studies involved very small sample sizes.[20,21]

In this study, we observed a statistically significant prolongation of VEPs latencies (N75, P100) in epileptic patients using ASM compared to the control group ($p<0.05$).[11,19] However, there was no difference between the types of drugs used in terms of prolongation of VEP latencies ($p>0.05$) (Table 3).

Although lamotrigine is a broad-spectrum, new-generation ASM frequently preferred for women of childbearing age and during pregnancy, we did not find any previous studies on lamotrigine's effects. Although our study did not reach statistical significance, it found that P100 latency prolongation in lamotrigine users is similar to that in valproic acid users.

Additionally, we observed a significant increase in amplitudes in the patient group compared to the control group ($p<0.05$). A study reported higher VEP amplitudes in the right and left eyes of 18 pediatric patients using levetiracetam compared to 24 healthy children.[20] However, it is evident that more work is needed on this subject.

Finally, our study found no significant effect of treatment duration on VEP latencies.[20]

As can be seen, no consistently accepted conclusion has yet been reached in the literature on this subject. These inconsistencies may be partly due to differences in research techniques (flash or pattern VEPs) and patient population, as well as the possible effects of anticonvulsant drugs and the nature of the underlying cause.

Study Limitations

Although we selected both our study group and control group, by excluding those with conditions that could affect VEPs findings, the most important limitation of our study is the absence of VEPs findings in our patients before treatment. However, there were also similar sample selections reported in the literature.[19-21] Although our sample is larger than many studies, larger scale and longer follow-up studies are needed to make a detailed assessment.

CONCLUSION

We found that ASMs affected VEPs parameters, particularly P100 latency. Levetiracetam had a less negative effect on P100 latency, although the difference did not reach statistical significance. Most studies in the literature have focused on pediatric patients, with a limited number of studies including adults. Our study provides important information about the effects of ASMs on VEPs parameters in adult patients. We recommend that these findings be considered when choosing treatment options and that regular (at least annual) VEPs and eye examinations be conducted in epilepsy patients using ASMs. This may help in early diagnosis and treatment of silent visual disturbances.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Türkiye, Adana City Training and Research Hospital Clinical Research Ethics Committee (decision no: 2629, date: 08.06.2023).

Informed Consent: Informed consent was obtained from all participants.

Footnotes

Authorship Contributions

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

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

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Archives of Epilepsy

Original Article

The Social and Demographic Characteristics of Neurosurgical Patients with Drug-resistant Temporal Lobe Epilepsy

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Abstract

Objective: In this study, our objective was to investigate the sociodemographic characteristics of patients with drug-resistant temporal lobe epilepsy (DR-TLE) undergoing neurosurgical management.

Methods: The single-center, non-randomized, retrospective, parallel-group study was conducted in 2022-2023. The subject temporal DR-TLE. The object social and demographic indicators of neurosurgical patients. One hundred patients with DR-TLE after neurosurgical management were classified into two groups according to the type of surgical procedure.

Results: Seventy-eight patients underwent resective surgery in group 1; twenty-two patients underwent destructive surgery in group 2. The mean age of the cohort was 32.3±8.18 years, with 53% of the patients being men and 47% women. The level of education in the cohort was characterised by a predominance of vocational qualifications (41%) compared to secondary education (24%) and tertiary education (34%). In group 1, the majority of patients had secondary vocational education; in group 2, patients with tertiary education predominated. There were twice as many unemployed people as employed people in the cohort, 64% and 31% respectively, indicating a difference between the groups. The percentage of patients with disabilities was 59%, indicating a predominance of patients with disabilities in group 1 and a predominance of patients without disabilities in group 2. The family situation was characterized by a low marital status (38%) and a mean age of 32.3±8.18 years, with no significant differences between the groups. Despite the reproductive age of the patients, the family situation and parental status were characterised by low rates of marriage and a low birth rate of 18%, with no differences between the groups.

Conclusion: The group of neurosurgical patients was socially maladjusted: two-thirds were disabled and unemployed and only a quarter had a university degree. The trend toward late surgical management of drug-resistant temporal epilepsy continues. It is necessary to educate physicians and patients about the current possibilities of epilepsy surgery.

Keywords: Drug-resistant epilepsy, surgery, destructive surgery, resective surgery, social functioning

INTRODUCTION

The current phase of epileptology development is characterized by an increasing interest worldwide in surgical treatments for epilepsy, as well as the updating of basic definitions and classifications.[1] At the 15th European Epilepsy Congress, held in Rome, Italy from 7-11 September 2024, it became evident that numerous sections were devoted to the various aspects of the surgical treatment of epilepsy. The changing stance of the International League Against Epilepsy on terminology to describe management has also contributed to the increasing use of surgical treatment for epilepsy. Experts believe that the term "antiepileptic" is reserved for treatment options that have been shown to have a direct impact on the course of epilepsy, the likelihood of developing epilepsy, or the likelihood of developing more severe epilepsy. Surgical treatments are included in these options.[2] In the history of epilepsy surgery, three main phases are distinguished: the clinical, neurophysiological, and epileptogenic lesion era.[3] The third phase, the era of neuroimaging, has improved the ability to diagnose structural lesions as the cause of epilepsy, which has increased the indications for surgical treatment of epilepsy.[4]

The change in the organizational model of medical care, which is based on the principles of the four Ps: predictive, preventive, personalized, and participatory, requires the use of modern diagnostic technologies.[5] This has led to the development of functional neurosurgery, which uses different types of destruction and stimulation of target brain structures.[6] Minimally invasive surgical techniques expand the possibilities of neurosurgery application and reduce economic losses for the state and disability for patients.[7] Improved diagnostic and treatment methods will enhance patient socialization and minimize disease-related labor losses.[8-10]

The emerging transformation in epilepsy management tactics demands an increase in theoretical and practical research in this area. Indications must be developed, risks of complications must be stratified, and surgical effectiveness must be predicted using new methodologies.[11,12] Choosing an optimal surgical management approach based on the etiology of the disease and predicting outcomes in patients with drug-resistant structural epilepsy, is an important initiative that characterizes the current level of development of the epilepsy surgical management issue.[13-15]

Mesial temporal lobe epilepsy is one of the most frequently surgically treated forms of epilepsy with the highest success rates. However, the structural features and functional importance of the mesial structures also determine the high rate of cognitive complications in surgical treatment, mainly memory impairment.[5] This has led to the development of actively destructive treatment methods in addition to classical resective methods of surgical treatment of mesial temporal epilepsy.[4]

Understanding the problems of epilepsy surgery and developing ways to improve medical care requires an assessment of the social burden of the disease and the demographics of the patients. However, the social and demographic characteristics of neurosurgical patients with drug-resistant epilepsy are poorly studied.

In this study, our purpose was to determine the sociodemographic characteristics of patients with drug-resistant temporal lobe epilepsy (DR-TLE) who underwent neurosurgical treatment.

METHODS

Study Design

The study design was single-center, non-randomized, retrospective, in parallel groups. It was carried out at Polenov Neurosurgical Institute, a branch of Almazov National Research Centre, in 2022-2023.

The study was part of the state assignment commissioned by the Ministry of Health of the Russian Federation (topic no: 123021000127-7: "Development of a New Technology for Neurorehabilitation of Patients After Surgical Management of Drug-resistant Epilepsy").

The subject of the study was DR-TLE. The subject of the study was the social and demographic indicators of neurosurgical patients.

MAIN POINTS

- The development of epileptology is characterised by a growing worldwide interest in surgical treatments for epilepsy.
- Improved epilepsy management will improve the socialisation of patients and minimise sickness-related absence from work.
- Social functioning was assessed on the basis of social activity and family functioning.
- Indicators of social functioning were educational level, employment and degree of disability.
- Family life was assessed on the basis of marital status and the birth index.

Overview of the Groups

The study is based on the results of the examination and treatment of 100 patients, after neurosurgical management of epilepsy, with DR-TLE at Polenov Neurosurgical Institute.

The diagnosis of DR-TLE was based on the definitions and classifications developed and approved by the International League Against Epilepsy: Definition of epilepsy, drug resistance, status epilepticus, classification of epilepsy, and epileptic seizures of 2017.

Inclusion criteria:

1. Signed informed consent.
2. Focal temporal lobe epilepsies.
3. Male and female patients aged 18 to 70 years inclusive at the time of signing the informed consent form.
4. Lesional and non-lesional epilepsy of more than 2 years of duration.
5. Proven diagnosis of drug-resistant epilepsy.
6. Surgical treatment of DR-TLE at Polenov Neurosurgical Institute.
7. Availability of a catamnesis after surgical management.
8. Ability to answer the questionnaire satisfactorily.

Non-inclusion criteria:

1. Type of surgical procedure-neurostimulation, electrode implantation.
2. Extratemporal focal epilepsy.
3. Presence of somatic pathology that aggravates the patient's condition and worsens the overall prognosis.
4. Patients less than 18 years of age.

Exclusion criteria:

1. Generalized forms of epilepsy.
2. Patients who cannot understand the questionnaires.
3. Refusal of any communicative action by the patient, discontinuation of communication.
4. Severe psychiatric comorbidity.

All patients underwent the necessary screening to ensure that they met the inclusion/exclusion criteria. The inclusion/exclusion criteria were chosen to ensure the safety of the patients and the validity of the data obtained.

The patients were divided into 2 groups according to the type of surgical procedure. Group 1 underwent resective surgery, group 2 underwent destructive surgery.

Data on disease onset, disease progression, and treatment were obtained from discharge summaries, from hospitals where the patients had previously been treated, and from history taken from interviews with patients and their relatives. All patients underwent the necessary checks to ensure that they met the inclusion/exclusion criteria. The inclusion/exclusion criteria were chosen to ensure patient safety and validity of the data obtained.

Ethical Aspects

The study was carried out according to the standards of relevant clinical practice and the principles of the Declaration of Helsinki. All patients signed an informed consent form. Approval was obtained from the Ethics Committee of Almazov National Medical Research Centre (date: 18.04.2022, approval no: 2304-22).

Statistical Analysis

Statistical analysis was performed using International Business Machines® Statistical Package for the Social Science® Amos™ 23 (United States of America: Armonk, New York State). For indicators with an approximate normal distribution, the results were presented as the arithmetic mean (M), the standard error of the mean (m), and the sample size (n); in other cases, the results were presented as median and quartiles. The criterion of significance was set at the level of $p<0.05$. Correlations between pairs of quantitative variables were assessed using the non-parametric Spearman criterion. Different types of analysis of variance were used to detect differences between subgroups for single variables, including parametric (ANOVA) and non-parametric (Mann-Whitney U test, Kruskal-Wallis H-test).

RESULTS

The patients were divided into 2 groups according to the type of surgical procedures; group 1 underwent resective surgery, 78 patients (78%). Destructive surgery was performed on group 2-22 patients (22%).

Clinical and Demographic Indicators

The mean age in the cohort was 32.3±8.18 years, with a minimum of 19 years and a maximum of 54 years. Distribution by gender: 53% male, 47% female; male to female ratio 1:1.[13]

The demographic characteristics of the patients are presented in Table 1. Demographic data did not differ between groups.

Clinical Features

The mean duration of epilepsy in the cohort was 20.09±9.24 years, with no differences between the groups (p=0.3).

In the cohort, all patients had mesial temporal lobe epilepsy with proven drug resistance and uncontrolled seizures. The clinical picture of epilepsy is shown in Table 2.

Patients were categorized into four groups depending on how long they had had the disease: three to five years, six to ten years, eleven to twenty years, and more than twenty years of drug-resistant epilepsy (Figure 1).

Social Functioning

Social functioning was assessed based on social activity and family functioning. Indicators of social functioning were educational

Table 1. Social and demographic characteristics in groups and cohort

Baseline characteristics	Group 1 (n=78)		Group 2 (n=22)		Cohort (n=100)		p-value
	Number	Percent	Number	Percent	Number	Percent	
Gender distribution							
Male	44	56	9	41	53	53	0.2
Female	34	44	13	59	47	47	0.18
Age distribution (in years)							
Mean age	32.64±8.19		31.09±8.21		32.3±8.18		0.2
Minimum	19		20		19		
Maximum	54		46		54		-

Table 2. Clinical features of drug-resistant epilepsy in neurosurgical patients

Baseline characteristics	Group 1 (n=78)	Group 2 (n=22)	Cohort (n=100)	p-value
	Years	Years	Years	
Duration of epilepsy				
Mean duration	20.68±8.94	18±10.18	20.09±9.24	0.3
Minimum	4	4	4	-
Maximum	41	42	42	-
Age at the onset of epilepsy				
Mean duration	12.18±8.94	13.09±6.96	12.38±8.52	0.4
Minimum	0.25	4	0.167	-
Maximum	52	27	52	-

background, employment, and disability rates. Family functioning was assessed by marital status and childbirth index. The social characteristics of the patients are shown in Table 3.

The level of education in the cohort was characterized by a predominance of vocational qualifications, 41% compared to secondary education, 24%, and higher education, 34%. In group 1, the majority of patients had vocational secondary education. In group 2, patients with tertiary education prevailed. There were twice as many unemployed as employed in the cohort, 64% and 31% respectively. Additionally, 4.2% were studying. These numbers show a clear distinction between the groups. The number of patients with disabilities was 59%. Patients with disabilities predominate in group 1, while patients without disabilities predominate in group 2. The family situation was characterized by a low marital status (40%). There were no significant differences between the groups, with a mean age of 32.3±8.18 years. Parental status was characterized by a low childbearing rate (18%), with no significant difference between the groups, despite the reproductive age of men and women.

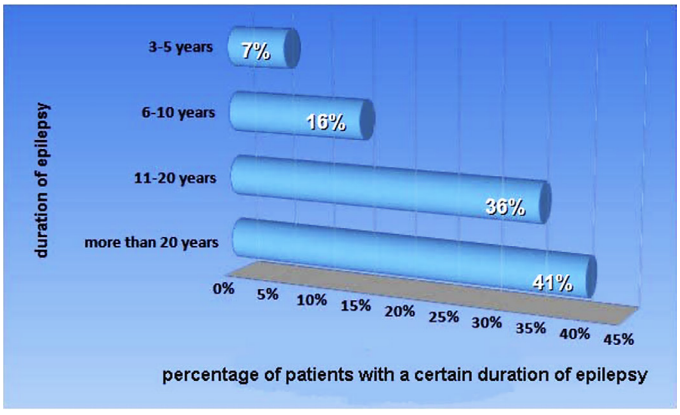

Figure 1. Distribution of patients according to the specific duration of epilepsy

The level of education in the cohort was characterized by a predominance of vocational qualifications (41%), compared to secondary education (24%) and higher education (34%). In group 1, the majority of patients had vocational secondary education; in group 2, patients with tertiary education prevailed. There were twice as many unemployed as employed in the cohort, 64% and 31%, and 4% were studying, showing no difference between the groups. The number of patients with disabilities was 59%, patients with disabilities predominate in group 1, while patients without disabilities predominate in group 2. The family situation was characterized by a low percentage of individuals who were married (39%) and showed no significant differences between the groups; the mean age was 32.3±8.18 years. Parental status was characterized by a low childbearing rate (18%), with no significant difference between the groups despite the reproductive age of men and women.

Disability (p=0.01) or lack thereof (p=0.05), employment status (p=0.01), being married (p=0.03), and childlessness (p=0.01) influenced the decision in favour of surgical treatment of DR-TLE. Educational level and being unmarried were not statistically significant (p=0.2).

The socio-demographic profile of patients who underwent surgery for DR-TLE thus reflects the negative impact of disease duration on social functioning.

Table 3. Social and demographic characteristics in groups and cohort

Variable	Group 1 (n=78)		Group 2 (n=22)		Cohort (n=100)		p-value
	Number	Percent	Number	Percent	Number	Percent	
Disability							
Disabled	49	50	9	9	58	58	0.011*
Not disabled	29	28	13	13	42	42	0.05*
Employment							
Employed	17	24	5	7	22	31	0.011*
Not employed	38	53	8	11	46	64	0.015*
Students	2	3	1	1	3	4	0.1
Seniors	1	1	0	0	1	1	0.15
Level of education							
Secondary education	21	21	3	3	24	24	0.5
Vocational secondary education	33	33	8	8	41	41	0.08
Tertiary education	23	23	11	11	34	34	0.2
Family status							
Single	44	45	12	12	56	58	0.2
Married	30	31	8	8	38	39	0.03*
Living in cohabitation	3	3	0	0	3	3	0.5
Parental status							
Have children	13	17	5	22	18	18	0.5
Have no children	20	26	17	78	37	37	0.01*

DISCUSSION

The sociodemographic characteristics of neurosurgical patients with DR-TLE reflected the social problems of epilepsy: the predominance of young people of working age and the social maladjustment of patients with a long course of disease.[13] The duration of epilepsy before referral to a neurosurgical clinic not only worsened the social functioning of patients with epilepsy, but also inhibited the application of modern surgical treatment methods.[4] The preponderance of patients in group 1 who underwent resective surgery was due to several reasons. In the past, resective techniques were the main surgical management for drug-resistant epilepsy. Destructive techniques are modern methods and have not yet become established in clinical practice. The rate of destructive methods is higher in patients with a short course of epilepsy.

Consequently, destructive surgical techniques have become the methods of choice for the treatment of DR-TLE with a shorter disease duration. The phenomenon of late referral for surgical treatment of epilepsy played a negative role in the development of destructive methods.[3]

The efficacy of destructive techniques was higher in patients with a short duration of epilepsy.[4,5] However, late referral for surgical management reduced efficacy and limited the use of the technique.[3] The duration of the disease contributed to epileptogenesis and the formation of the epileptic system,[12] but also to suicidal behavior in patients.[16]

In the Department of Functional Neurosurgery No. 2 of Polenov Neurosurgical Institute, radiofrequency ablation of the epileptic focus has been used since 2017. Late recourse to neurosurgical management of epilepsy, plays a negative role in the application of destructive methods. The late use of surgical methods reduces efficacy rates and limits their implementation. The lack of significant differences between groups in terms of demographics and disease duration in our study reflected the current state of the problem.

At the same time, our previous studies have shown that the expressed willingness to undergo surgical management was three times higher than the actual willingness.[14] A study of comorbid anxiety and depression in patients with DR-TLE in a neurosurgical clinic found no significant impairment, suggesting a conscious decision.[15]

It is important to consider the impact of disability and unemployment on the decision to surgically manage for DRE. The presence of seizures may play a role in decision making, particularly in relation to employment opportunities for people with vocational training.

Thus, social awareness currently lags behind surgical management options for DR-TLE, negatively impacting the social functioning of people with epilepsy and increasing the social burden of the disease.

Study Limitation

It is a prospective study with a limited sample size.

CONCLUSION

The trend toward late neurosurgical management of drug-resistant epilepsy continues. The group of neurosurgical patients was socially maladjusted: two-thirds were disabled and unemployed, and only a quarter had a university degree.

It is necessary to educate physicians and patients about the current possibilities of epilepsy surgery.

Ethics

Ethics Committee Approval: Approval was obtained from the Ethics Committee of Almazov National Medical Research Centre (date: 18.04.2022, approval no: 2304-22).

Informed Consent: All patients signed an informed consent form.

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.O., N.I., V.N., Concept: G.O., N.I., V.N., N.D., Design: G.O., V.N., N.D., Data Collection or Processing: N.I., N.D., Analysis or Interpretation: G.O., N.I., V.N., N.D., Literature Search: G.O., N.D., Writing: G.O., N.I., V.N., N.D.

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

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Archives of Epilepsy

Original Article

Quality of Life in Children with Epilepsy: A Bibliometric Analysis

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Abstract

Objective: The aim of this study was to explore research related to the quality of life (QOL) of children with epilepsy using bibliometric analysis.

Methods: This study used the Web of Science Core Collection database. Articles in this widely used globally database were searched on February 14, 2024, using the following keywords: ("epilepsy" or "seizure" or "convulsion" or "epileptic" or "status epilepticus") and ["quality of life" or "QOL" or "life quality" or "health related quality of life (HRQOL)" or "health-related quality of life" or "HRQOL"] and ("children" or "child" or "childhood" or "infant" or "adolescent").

Results: This study, conducted in 1991, on the QOL of children with epilepsy, revealed that 1,810 articles in English had been published in this domain. Examination of citations of research in this field revealed that the most cited article was "Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the International League Against Epilepsy Commission on Therapeutic Strategies". Examination of inter-country collaborations in studies on the subject revealed that the United Kingdom and the United States of America (USA) engaged in the most collaborations. Specifically, the United Kingdom collaborated most with the USA (n=69), followed by Italy (n=31), France (n=30), Germany (n=29), and the Netherlands (n=28).

Conclusion: Our scan of the literature revealed no previous bibliometric studies in which the subject of QOL in pediatric epilepsy patients was addressed. This bibliometric study analyzed sources, authors, researchers, institutions, links, countries, keywords, topics, and themes, investigating epileptic children's QOL.

Keywords: Epilepsy, seizure, convulsion, quality of life, children, adolescent, bibliometric analysis

INTRODUCTION

Epilepsy is a common neurological condition marked by seizures. It affects individuals from diverse age groups and cultural backgrounds. The fourth highest contributor to disability among 220 separate health issues, severe epilepsy can be devastating. Its adverse consequences extend to the social and professional spheres, and to physical and mental well-being.[1] Quality of life (QOL) is highly important in chronic conditions such as epilepsy. The World Health Organization characterizes QOL as "a condition of holistic health encompassing physical, mental, and social well-being, rather than just the absence of illness or weakness".[2] QOL is a multifaceted construct that encapsulates both the positive and negative facets of an individual's life, reflecting overall well-being. From that perspective, QOL extends beyond the mere assessment of physical health to encompass diverse areas such as family dynamics, educational attainment, work status, financial prosperity, personal freedoms, environmental considerations, and security in both the personal and financial spheres.[3,4] Variables affecting QOL include age, place of residence, socioeconomic status, maternal educational background, seizure characteristics such as type and frequency, and the quantity of antiepileptic medications used.[5] Health-related QOL (HRQOL) is also a multifaceted concept involving aspects of social, emotional, and physical functioning or well-being, which are related to the individual's health status.[6] There are also studies showing that QOL is adversely affected in children with epilepsy.[7-9]

The bibliometric analysis employed in this study is a highly comprehensive quantitative method. Such analysis makes it possible to determine the authors of studies on a specific topic, the institutions and countries where those authors work, the most cited publications, and the keywords used. Bibliometric analysis serves as an important tool not only for understanding previous research but also as a guide to future studies by identifying potential areas of investigation.[10]

Our review of the relevant literature revealed that while bibliometric analyses have been conducted on research focusing on children with epilepsy, there has been no bibliometric analysis specifically addressing these children's QOL.[11-13] The purpose of this research was to examine studies on the QOL of such children from a bibliometric perspective and to determine missing elements, along with data concerning life and treatment, that have not previously been investigated.

The aim of this study was, therefore, to explore research related to the QOL of children with epilepsy using bibliometric analysis. The investigation was structured around the following questions:

1. What patterns emerge in terms of publication output, country distribution, journal sources, and authorship within this field of research?

2. Which topics and subjects generate the most extensive investigation into QOL among children diagnosed with epilepsy?

3. What gaps or under-explored areas currently exist in the study of the QOL of children living with epilepsy?

METHODS

Data Collection

This study used the Web of Science (WOS) Core Collection database. Articles in this widely used database were searched on February 14, 2024, using the following keywords: topic search (TS) = ("epilepsy" or "seizure" or "convulsion" or "epileptic" or "status epilepticus") and TS = ("quality of life" or "QOL" or "life quality" or "health related quality of life" or "health-related quality of life" or "HRQOL") and TS = ("children" or "child" or "childhood" or "infant" or "adolescent"). Original research articles published in English between 1991 and 2024 in the Social Sciences Citation Index (SSCI) and the Science Citation Index Expanded (SCI-EXPANDED) were selected.

When the keywords were entered into WOS, 2,987 results were initially obtained. When the article was selected as the document type, with SSCI and the SCI-EXPANDED as the WOS index, and with English as the language, the results were narrowed down to 1,810. BibTeX and Tab Delimited File formats were downloaded from the WOS export section, and analyses were conducted on these files.

Statistical Analysis

This research used R software to analyze and present bibliometric data sourced from the WOS database. While several software options are available for conducting bibliometric analysis and visualization, the selection hinges on the particular analysis requirements.[14] Bibliometrix is a commonly used tool among bibliometricians due to its R programming capabilities. Bibliometrix offers several advantages, such as rapid updates and seamless compatibility with other statistical R-packages.[15] It streamlines the tasks of importing and converting data into R data frames and its integration with WOS facilitates the automatic retrieval of metadata for the entire scientific output of academics.[14,15] Biblioshiny is employed for bibliometric analysis, including science mapping and performance evaluation. Serving as a web interface for bibliometrix (https://www.bibliometrix.org), Biblioshiny simplifies various tasks, such as importing data, converting these into data frames, filtering data, conducting analytics, and generating plots related to sources, authors, and documents.[16] This research also used VOSviewer for its analyses. VOSviewer employs both mapping and clustering methods to visualize connections among terms present in research. This software groups cited words together and exhibits them using different colors, with circle sizes indicating how frequently the information appears.[17]

MAIN POINTS

- This bibliometric study analyzed sources, researchers, institutions, countries, and keywords in the context of investigating the quality of life (QOL) in epileptic children.
- Studies of epileptic children's QOL were most frequently conducted in the United States of America, Canada, and the United Kingdom.
- The journals producing the most publications were Epilepsy and Behavior, Epilepsia, and Seizure-European Journal of Epilepsy.

RESULTS

Main Information

Since 1991, our investigation into the QOL of children with epilepsy revealed that 1,810 articles in English had been published in this domain; cataloged within both SSCI and SCI-EXPANDED, with a total of 7,993 authors involved (Table 1).

General Trend

A linear increase was observed when analyzing the distribution of QOL research concerning children with epilepsy over various years, with the highest number of publications in this field occurring in 2021 (n=164). Since the analyses in the present study were conducted in the first quarter of 2024, the data for that year were not included (Figure 1).

Figure 2, in which keywords, countries, and institutions, where the publications were produced, shows that publications in this field appear to be most frequent in the United States of America (USA), Canada, and the United Kingdom. Keywords such as children, QOL, and childhood epilepsy are predominantly featured.

Table 1. Data information

Main information about data	
Timespan	1991/2024
Sources (journals, books, etc)	384
Documents	1,810
Average years from publication	9.33
Average citations per documents	9.23
Average citations per year per doc	29.92
References	41.808
Document contents	
Keywords plus (Id)	2.809
Author's keywords (De)	3.151
Authors	
Authors	7.993
Authors of single-authored docs	63
Authors collaboration	
Single-authored docs	75
Co-authors per doc	6.15
International co-authorships %	21.6

Journals

Publications concerning QOL in children with epilepsy appeared most frequently in the following journals: Epilepsy and Behavior (n=449), Epilepsia (n=158), Seizure: European Journal of Epilepsy (n=98), Epilepsy Research (n=58), Pediatric Neurology (n=38), and the Journal of Child Neurology (n=35) (Figure 3). Examination of the performance of the journals with the highest numbers of publications in this field shows that the understanding of the importance of QOL in these children has increased since 2007.

We used Bradford's law to examine the journals in which studies on the QOL in children with epilepsy had been published. This demonstrates how research on a particular topic is spread across different journals. According to Bradford's law, zone 1 represents the most prolific area, zone 3 is less productive, and zone 2 falls between the two.[18] Analysis of influential journals focused on the QOL in children with epilepsy showed that the journals Epilepsy and Behavior and Epilepsia lie in zone 1. Articles from other journals within this field were in zones 2 and 3 (Figure 3a).

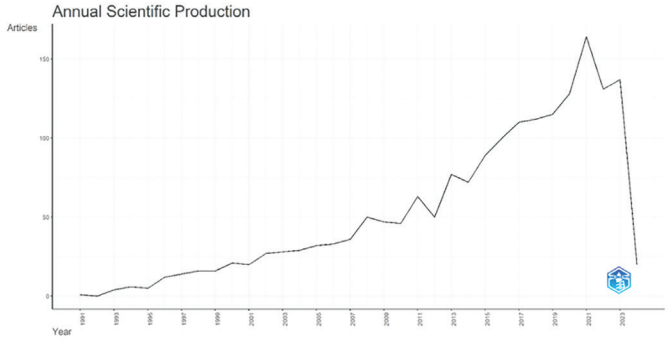

Figure 1. Annual scientific production

Examination of citations of research related to QOL in children with epilepsy revealed that the most cited articles were "Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the International League Against Epilepsy (ILAE) Commission on Therapeutic Strategies (Kwan et al.[19])", "cost of disorders of the brain in Europe (Gustavsson et al.[20])", and "everolimus for subependymal giant-cell astrocytomas in tuberous sclerosis (Krueger et al.[21])" (Table 2).

Authors, Institutions and Countries

This part of the study examined the authors of articles about QOL in children with epilepsy published in English, on WOS, specifically in SSCI and SCI-EXPANDED. Professor Mary Lou Smith from the Department of Psychology at the University of Toronto in Canada emerged as the most prolific researcher in this field. Associate Professor Mark A Ferro, affiliated with the School of Public Health Sciences at the University of Waterloo, emerged as the second most prolific author, followed by Professor Kathy N Speechley from the Department of Paediatrics at the University of Western Ontario (Table 3, Figure 4).

Lotka's law sub-analysis was also employed in this study. According to this law, which defines the productivity of authors in a particular research field, 60% of authors publish only one article, 15% publish two articles, and 7% publish three articles.[22] Analysis of articles related to the QOL of children with epilepsy using Lotka's law revealed that 81.2% of authors contributed only one article (n=6,546), while 10.6% produced two articles (n=851), and 0.35% produced three (n=279) (Figure 4a). The distribution of authors in the study deviated from Lotka's law.

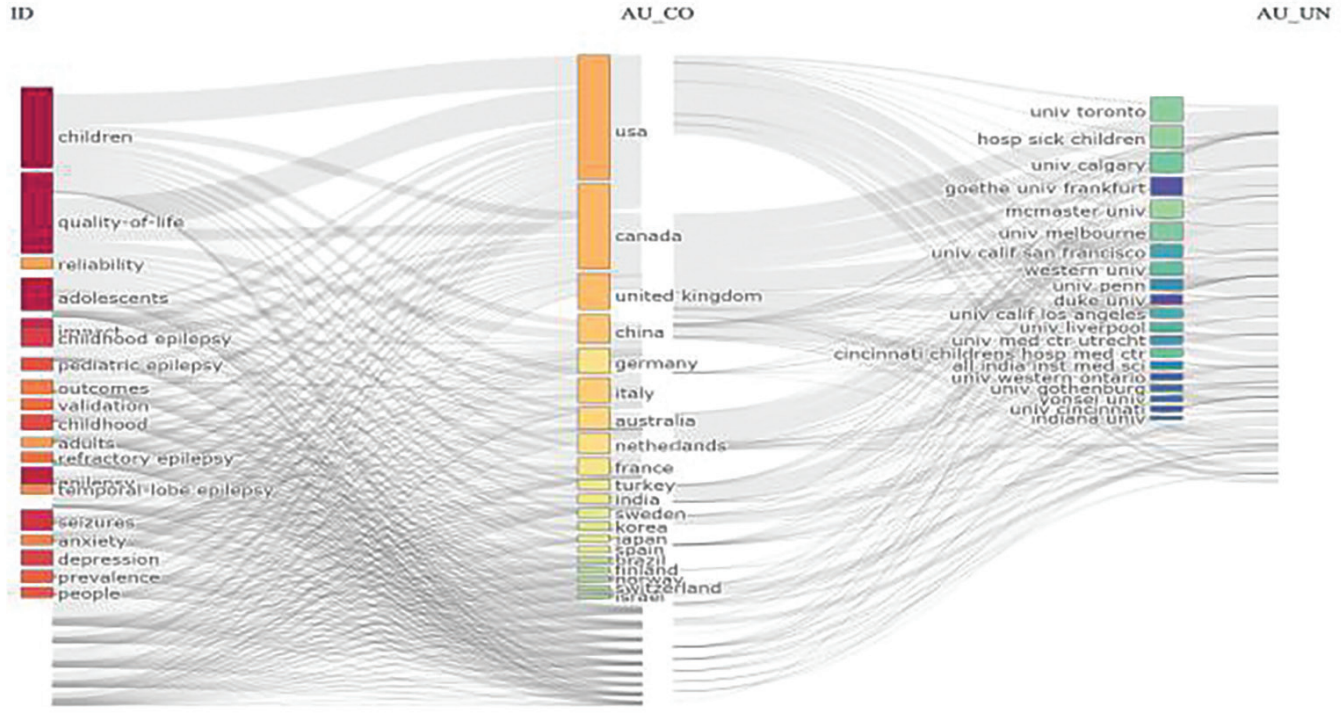

Figure 2. Triple analysis

In terms of the researchers' affiliations, the prime position was occupied by McMaster University, followed by The Hospital for Sick Children in second place, and the University of Toronto in third (Figure 4b).

Analysis of scientific publications by nations identified the leading 10 countries as the USA (n=2,669), Canada (n=1,085), the United Kingdom (n=787), China (n=648), Italy (n=588), Australia (n=471), the Netherlands (n=464), Germany (n=459), France (n=352), and India (n=201) (Figure 4c).

Examination of inter-country collaborations in studies related to the QOL of children with epilepsy revealed that the United Kingdom and the USA engaged in the most activity. Specifically, the United Kingdom collaborated most with the USA (n=69), followed by Italy (n=31), France (n=30), Germany (n=29), and the Netherlands (n=28). Collaborations also occurred between the USA and Canada (n=65); between Italy and France (n=27); and between the USA and Australia (n=25), France (n=24), and Italy (n=22) (Figure 4d).

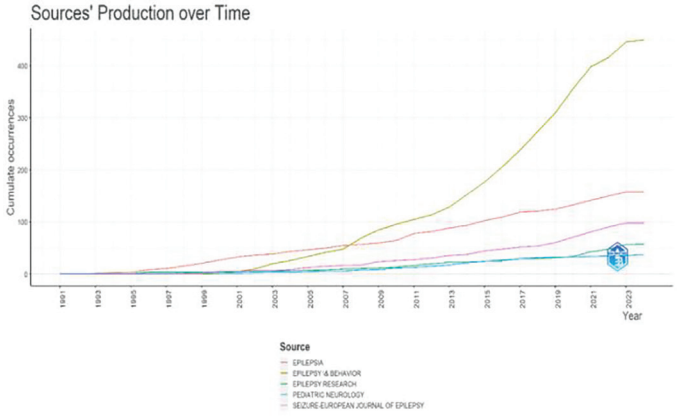

Figure 3. Sources growth

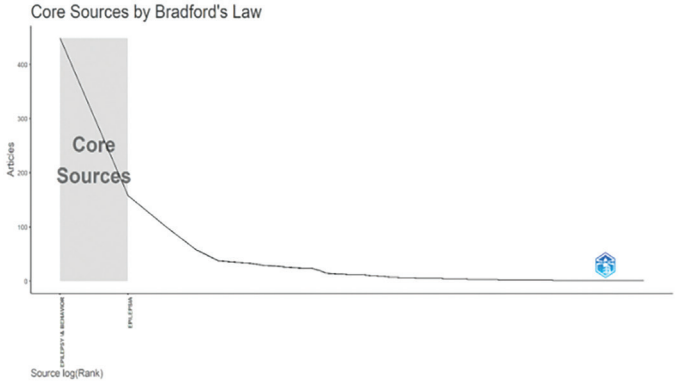

Figure 3. (a) Bradford's law core sources

Table 3. Most relevant authors and authors local impact

Author	h_index	g_index	TC	NP	PY start
Smith ML	19	30	958	38	2000
Ferro MA	16	26	723	37	2010
Speechley KN	15	26	685	31	2008
Modi AC	15	27	745	30	2009
Austin JK	17	22	1,312	22	1994
Ronen GM	14	22	743	22	1999
Reilly C	9	17	314	22	2014
Cross JH	9	21	1,131	21	2009
Widjaja E	9	16	261	21	2013
Baker GA	16	18	1,017	18	1996

PY: Publication year, TC: Total citations, NP: Number of publications

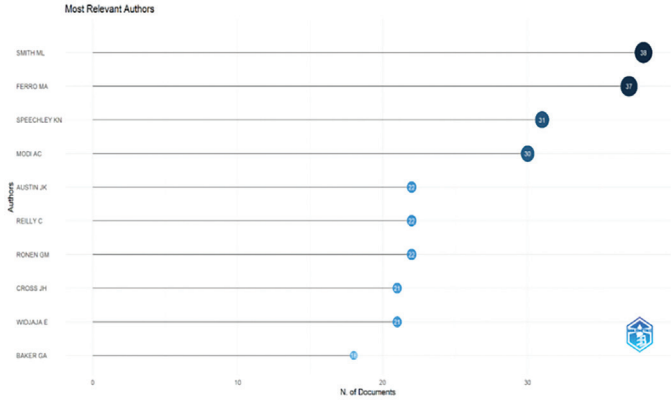

Figure 4. Most relevant authors

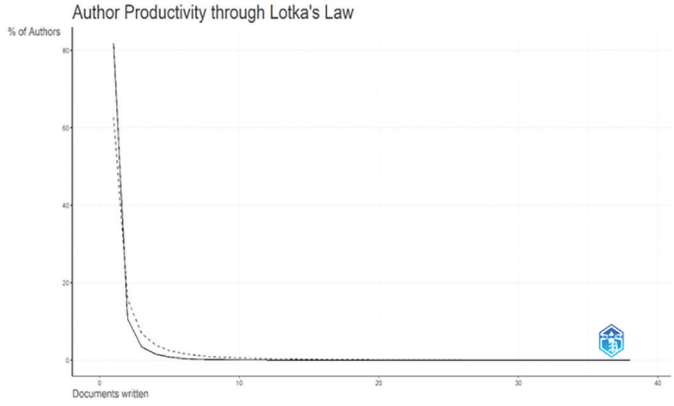

Figure 4. (a) Lotka's law

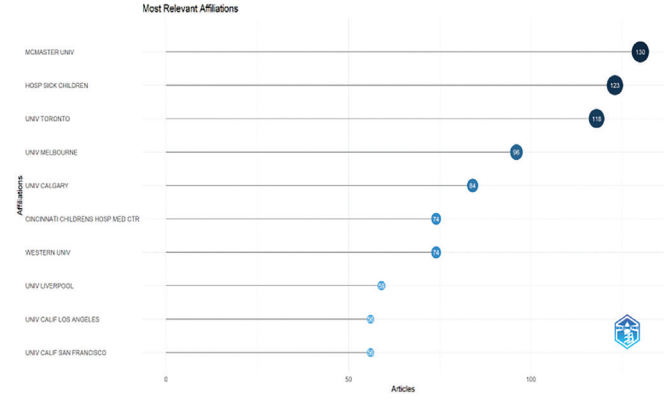

Figure 4. (b) Most relevant affiliations

Keyword and Trend Topic Analyses

This study primarily focuses on subjects related to children, QOL, adolescents, epilepsy, impact, seizures, and childhood epilepsy (Figures 5 and 5a).

Factor analysis of keyword clusters was conducted using multiple correspondence analysis. Four clusters were identified in the selected analysis. In the large group, words such as seizure, epilepsy, parents, QOL, and risk factors were collected. In the second group, terms such as intractable epilepsy, efficacy, long-term, and therapy were grouped together. Measurement evaluation-related words such as questionnaire, scale, validity, and reliability were clustered in the third group. Words such as depression, anxiety, and disorders were grouped together in the fourth group (Figure 5b).

The authors' chosen terms were examined using VOSviewer. From the visual depiction, the colors of the boxes represent both the distribution of keywords and the extent of collaboration between researchers using them. The words in the figure are most closely associated with: "epilepsy" followed by "quality of life" in second place and "children" in third (Figure 5c).

This study also investigated the trend in words used over the years in studies of QOL in children with epilepsy. This revealed that the concepts employed varied over time (Figure 5d).

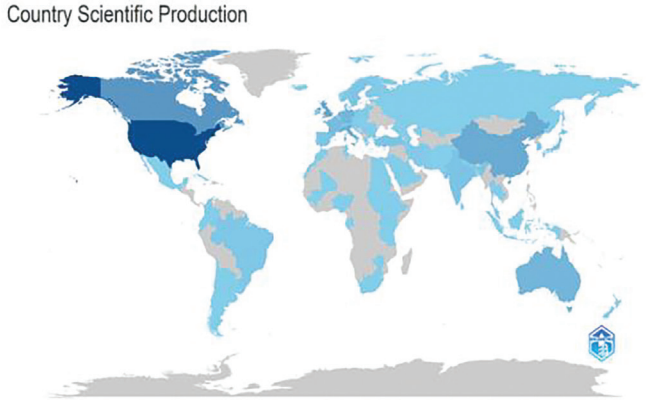

Figure 4. (c) Country scientific map

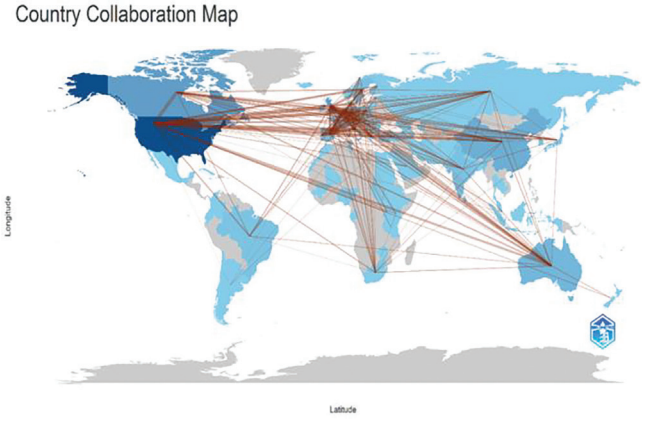

Figure 4. (d) Country collaboration map

Ethical Approval

The study was conducted as a bibliometric analysis. All data sources were available on the internet, and no animal or human subjects were involved. Ethical committee permission and consent was not required, therefore.

DISCUSSION

Data published over a period of 33 years related to pediatric epilepsy patients and their QOL, including authors, international institutions, journals in the field, references attracting citations, and up-to-date keywords on the subject, were were evaluated in this study using bibliometric-based analysis. The purpose of the research was to achieve a comprehensive understanding of the evolution of the scientific literature concerning the QOL of such children and to evaluate the impact of publications on the scientific community.

Children with epilepsy are affected in the physical, cognitive, psychological, emotional, and social spheres. These effects can best be evaluated by determining the patient's self-reported QOL.[5] The research findings showed that studies of the QOL of children with epilepsy increased from 1991 onward, and that, in terms of annual distributions, the largest number was performed in 2021. Considering that studies published in 2021 were initiated in 2020, we attribute this to the difficulties imposed on children with epilepsy by the COVID-19 pandemic. In addition, the number of studies on the subject decreased rapidly as of 2022 with the end of the pandemic. It may, therefore, be concluded from this study that epilepsy should not be considered solely from the physiological or clinical perspectives. The increase in studies involving children with epilepsy supports the idea that a holistic approach toward the disease is required.

Studies of the QOL of children with epilepsy were most frequently conducted in the USA, Canada, and the United Kingdom. Examination of the distribution of publications showed that developed countries were particularly productive. Countries' economic status has been linked to academic publication productivity in numerous studies.[23] Developing countries among the top 20 nations in terms of publication productivity were Türkiye, India, and Brazil.

Analysis showed that the greatest research collaboration was among developed countries such as the United Kingdom, the USA, Italy, Germany, France, the Netherlands, and Canada. Developed countries possess more research institutions, systematic data systems, and resources for research, and conduct more comprehensive epidemiological studies than less developed ones.[24] It may therefore be expected that the numbers of studies of QOL in children with epilepsy, and collaboration between countries will be higher in developed and more prosperous countries.

The findings of this study show that more than half of the scientific documents published between 1991 and 2024 were original research and review papers. The journals producing the most publications were in descending order, Epilepsy and Behavior, Epilepsia, Seizure-European Journal of Epilepsy, Epilepsy Research, Pediatric Neurology, and the Journal of Child Neurology. All these are competent in their field and publish studies on seizures and epilepsy based on experimental and clinical

Figure 5. Treemap

Figure 5. (a) Wordcloud

research. Unsurprisingly, the majority of the top six sources were neurological journals focusing on epilepsy. As shown by resource alignment analysis and a comparison of the H index, Epilepsy and Behavior, is also the fastest-growing and highest-impact resource.[25] Bradford's law identified Epilepsy and Behavior as the principal basic resource.[26] This finding shows that authors who wish to publish on the subject of QOL of individuals with epilepsy should consider submitting their work to that particular journal.

Analysis of the number of yearly citations in the different journals, showed that the most frequent, in descending order of frequency, were: Epilepsia, European Neuropsychopharmacology, The New England Journal of Medicine, and Nature Reviews: Disease Primers. Interestingly, with the exception of Epilepsia, the journals with the most publications in this field and those with the most citations were not one and the same. We believe that this may be attributable to the journals' different content distributions.

The study with the highest total number of citations was Kwan et al.[19] 2010 paper "Definition of drug-resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies," which was published in Epilepsia.[19] In that study, the ILAE appointed a working group to produce a common definition of drug-resistant epilepsy for the purpose of improving patient care and facilitating clinical research. The general framework of this definition has two hierarchical levels. The logic behind the definition and the principles guiding correct use were discussed, and examples of its application in clinical practice were provided.[19] Although epilepsy is treatable, 30% of patients with the condition develop drug resistance, resulting in uncontrolled seizures that further compromise their QOL.[27] The frequency of seizures also has a significant impact on the QOL of patients with epilepsy. When seizures are well controlled in epileptic individuals, their QOL scores have been found to be similar to those of the general population.[28] That article also emerged as the most effective in terms of average annual citation numbers.[19] Patients with epilepsy are exposed to a range of HRQOL issues, irrespective of whether their seizures are well controlled, including limitations in employment and social opportunities, perceived stigma, psychological pathologies including anxiety and depression, problems with marriage and family life, memory problems, and other cognitive impairments.[29] The paper receiving the second highest number of total citations was Gustavsson et al.[20] study "Cost of Disorders of the Brain in Europe 2010" published in European Neuropsychopharmacology. That study emphasized that the cost of brain disorders in 27 European Union countries, as well as Norway, Iceland, and Switzerland, was 798 billion Euros per year, and that the cost burden corresponded to 25% of direct health spending.[20] Epilepsy is more frequently seen in low- and middle-income countries.[30] Access to epilepsy care in such countries is problematic due to constraints in both the supply and demand sides

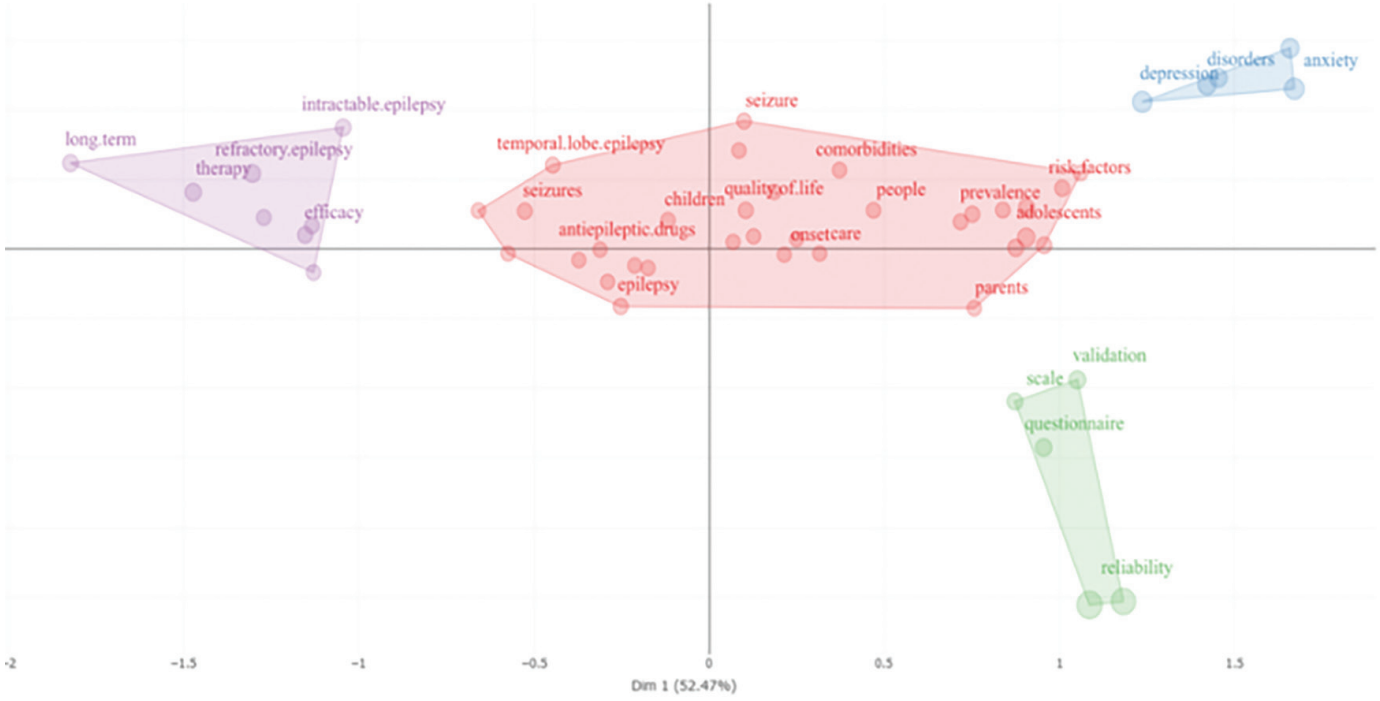

Figure 5. (b) Keyword plus conceptual structure map of publications

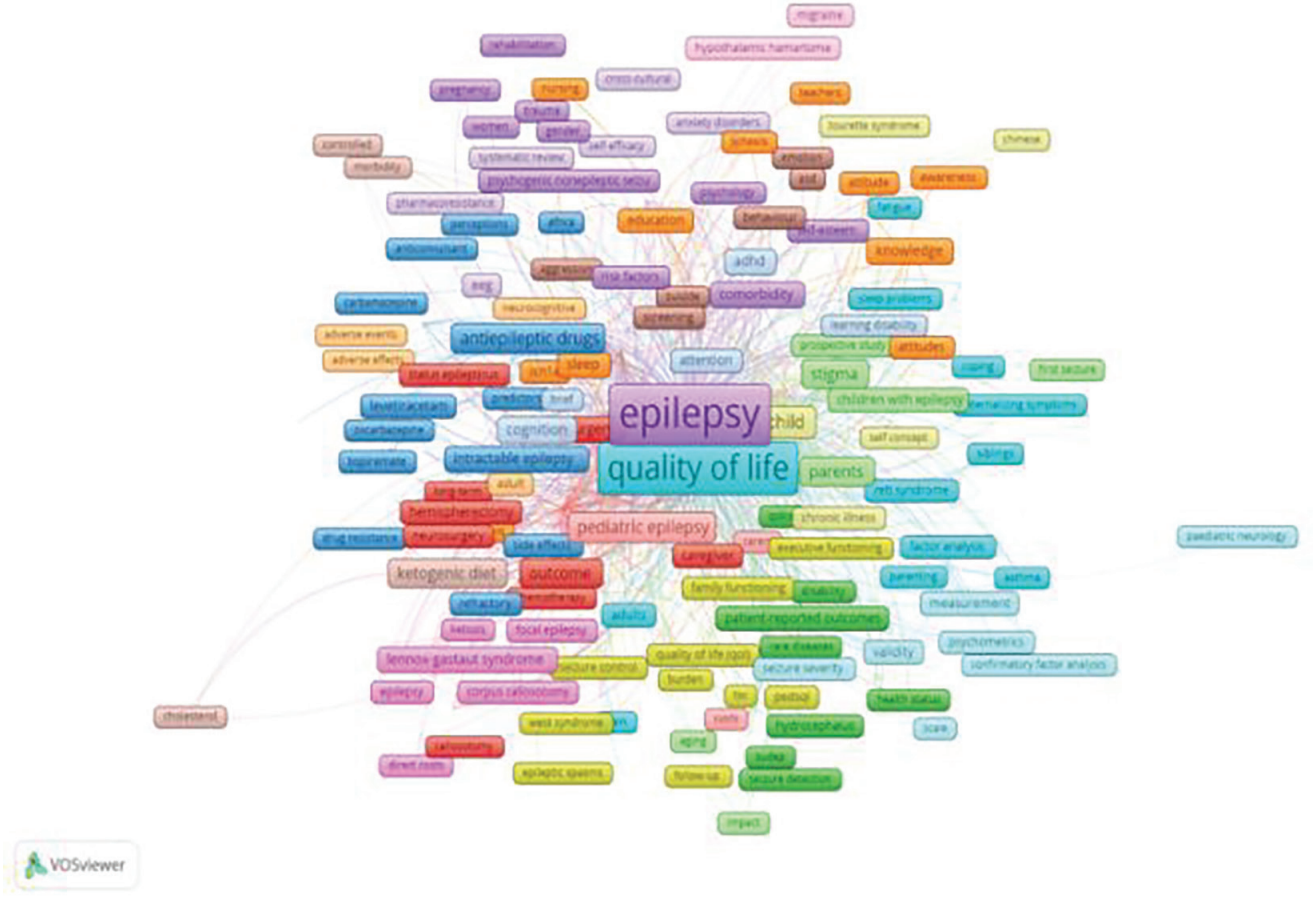

Figure 5. (c) Authors' keywords collaboration

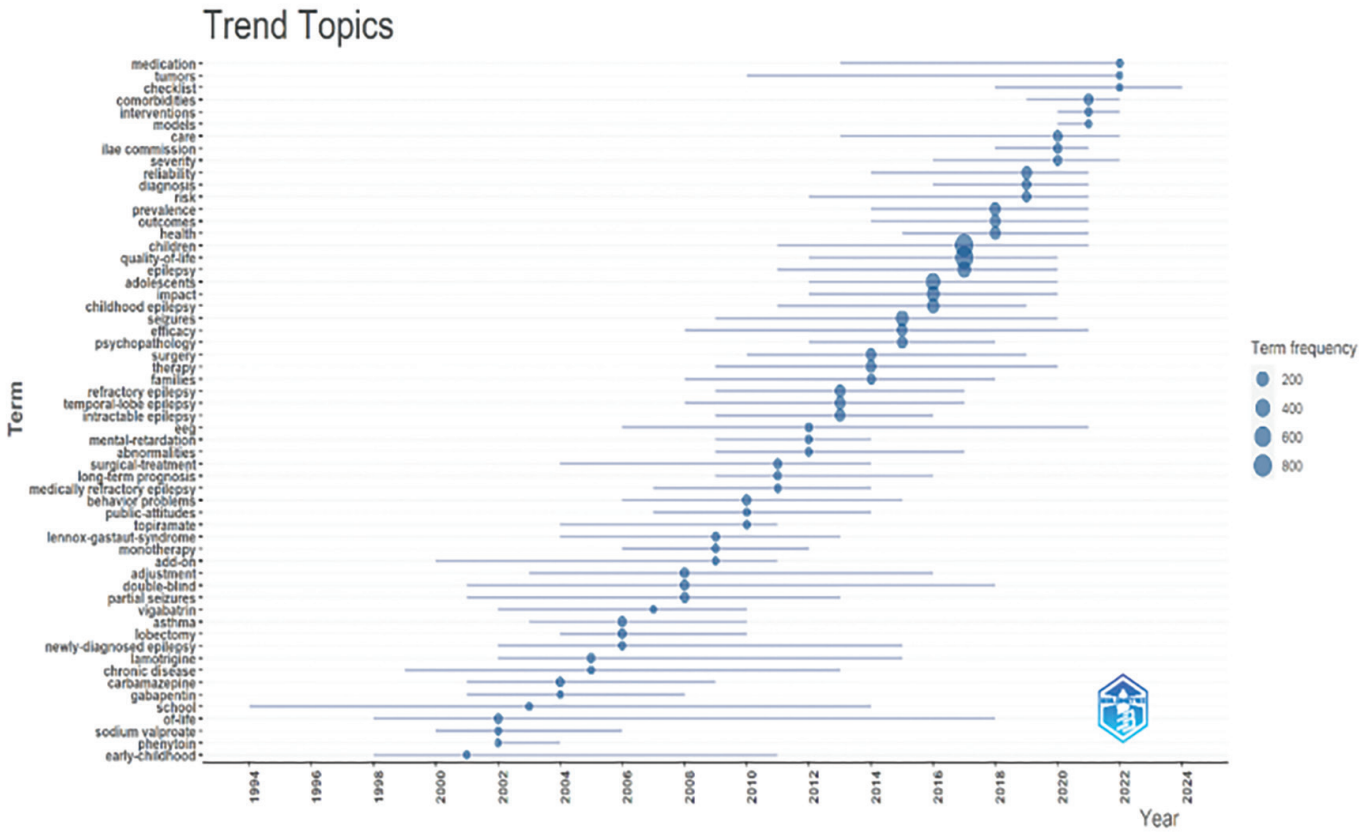

Figure 5. (d) Trend topics

(distances to healthcare facilities, lack of medical care; shortages of antiepileptic drugs, cultural beliefs concerning epilepsy and traditional treatments, and treatment costs). In addition to these factors, the condition can also lead to psychological stress and low self-esteem, resulting in non-compliance with epilepsy treatment. Lack of adherence to treatment results in recurrence of seizures, status epilepticus, hospital admissions, and increased health care utilization, which can impact significantly on QOL.[31-33] This study further highlights the multifaceted effects of epilepsy on human life, especially its relationship to the economic burden on society. However, examination of the keywords in the studies evaluated in this research shows the breadth of the perspective toward epilepsy, including treatment, comorbidity, prognosis and etiology. Evaluation of the distribution of keywords in this research, using factor analysis, showed that the largest keyword factors were types of epilepsy, seizure, risk factors, QOL, parents, and children and adolescents. QOL is a complex and multi-dimensional concept that determines the individual's general state of well-being. In addition to physical health, this concept contains numerous elements such as education, work, wealth, freedom, and environmental aspects, and evaluates numerous elements such as personal and financial security.[34] An association has been observed between the QOL of children with epilepsy and the presence of comorbidities. Children with comorbidities exhibit significantly lower QOL in the areas of physical and social functioning, psychosocial health, and school/educational functioning.[35] Examination of other factors highlights that psychiatric disorders such as depression and anxiety are grouped in a single group. Irrespective of their age, patients with epilepsy are known to suffer from depression and anxiety.[36] Epilepsy poses a severe burden on patients, parents, and society. Disease-specific restrictions can impact areas such as the individual's self-efficacy and mobility. Additionally, epilepsy has been linked to a decreased QOL and increased depression scores.[34] The psychiatric comorbidities experienced by children with epilepsy include attention deficit hyperactivity disorder, as well as anxiety and depression. The co-presence of neurodevelopmental disorders can make it difficult to diagnose psychiatric comorbidities in children with epilepsy.[37] Regular assessments of psychiatric problems associated with epilepsy can enhance the efficacy of therapeutic processes. The early identification of such problems will improve the likelihood of intervention.

Trend and content analysis of studies on the QOL of children with epilepsy showed that the most frequently employed words were "children" and "adolescents". This indicates that epilepsy is an important disease affecting the QOL of children and adolescents. The third most commonly employed keyword in research was "quality of life." The use of that term increased continuously since 2012. Other frequently used keywords included "epilepsy" and "seizures". Terms such as "comorbidities" and "psychopathology" show that psychiatric problems seen together with epilepsy have been the subject of considerable research. It has been stated that the quality of life of children with epilepsy is mostly affected by social support and depressive mood. In this context, knowing this information can help children and their families achieve a better quality of life.[38] The keywords "outcomes" and "efficacy" reveal

how the therapeutic process in epilepsy and the effectiveness thereof affects QOL. It is important to consider QOL in pediatric epilepsy cases from that perspective and to adopt a transdisciplinary and multidisciplinary approach. It is important for health professionals who focus on children to adopt a holistic approach toward children with epilepsy by participating actively in the treatment process. Including QOL evaluations in treatment planning may help children better understand their general condition. Examining the factors impacting QOL may contribute to improving the therapeutic process. Considering QOL evaluations in treatment planning can also contribute to improving the efficacy of treatment. Monitoring the general development of children with epilepsy, implementing supportive intervention programs, and increasing training for parents and teachers can also improve the QOL of such children.

Study Limitations

The principal limitations of this research are the inability to screen databases such as Scopus, EMBASE, PubMed, Google Scholar, and Dimensions, and the exclusive use of English search terms, which prevented a comprehensive evaluation using terms in other languages.

CONCLUSION

Our scan of the literature revealed no previous bibliometric studies in which the subject of QOL in pediatric epilepsy patients was addressed by itself. The present bibliometric study analyzed sources, authors, researchers, institutions, links, countries, keywords, topics, and themes investigating the QOL in epileptic children. Research over the last two decades has reported significant advances in QOL for children with epilepsy, as well as in the process of obtaining information directly from these children and their families. We hope that this article will serve as a useful guide for both physicians and pediatric epilepsy patients and their families concerning the global interactions between pediatric epilepsy and QOL. This will enable researchers to plan new investigations into QOL in children with epilepsy by examining existing literature. Studies of the QOL of children with epilepsy have made important contributions to the relevant literature, although there are also some gaps or inadequately addressed issues. For example, difficulties in the field of education experienced by children with epilepsy affect their QOL both directly and indirectly. From that perspective, more research is needed into difficulties experienced in school life and the measures that can be adopted to overcome them. Although psychiatric comorbidities have been investigated, it will be useful for further studies to address areas such as social relationships, family and peer relationships, and stigmatization. Comparative studies may also yield a better understanding of the effects of therapeutic methods on QOL. The scarcity of studies on the subject of physical functionality, an important component of QOL, was particularly striking. Finally, further research is needed into physical functioning and activity, to understand which also affect the QOL of children with epilepsy.

Table 2. Most cited articles[19,20,21,39-55]

No	Paper (DOI)	Author	PY	Journal	Total citations	TC per year
1	Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies (10.1111/j.1528-1167.2009.02397.x)	Kwan et al.[19]	2010	Epilepsia	2908	193.87
2	Cost of disorders of the brain in Europe 2010 (10.1016/j.euroneuro.2011.08.008)	Gustavsson et al.[20]	2011	European Neuropsychopharmacology	1101	78.64
3	Everolimus for subependymal giant-cell astrocytomas in tuberous sclerosis (10.1056/NEJMoa1001671)	Krueger et al.[21]	2010	The New England Journal of Medicine	717	47.80
4	Effect of cannabidiol on drop seizures in the Lennox-Gastaut syndrome (10.1056/NEJMoa1714631)	Devinsky et al.[39]	2018	The New England Journal of Medicine	550	78.57
5	The proxy problem: child report versus parent report in health-related quality of life research (10.1023/A:1008801802877)	Theunissen et al.[40]	1998	Quality of Life Research	507	18.78
6	Cerebral palsy (Primer) (10.1038/nrdp.2015.82)	Graham et al.[41]	2016	Nature Reviews: Disease Primers	429	47.67
7	A comparative study of impairment of quality of life in children with skin disease and children with other chronic childhood diseases (10.1111/j.1365-2133.2006.07185.x)	Beattie and Lewis-Jones[42]	2006	British Journal of Dermatology	369	19.42
8	Cerebral palsy (10.1016/S0140-6736(13)61835-8)	Colver et al.[43]	2014	Lancet (London, England)	338	30.73
9	Surgery for drug-resistant epilepsy in children (10.1056/NEJMoa1615335)	Dwivedi et al.[44]	2017	New England Journal of Medicine	336	42.00
10	Prevalence and health impact of developmental disabilities in US children (Not available)	Boyle et al.[45]	1994	Pediatrics	325	10.48
11	The impact of epilepsy from the patient's perspective I. Descriptions and subjective perceptions (10.1016/S0920-1211(00)00126-1)	Fisher et al.[46]	2000	Epilepsy Research	321	12.84

Table 2. Continued

No	Paper (doi)	Author	PY	Journal	Total citations	TC per year
12	Uncovering the neurobehavioural comorbidities of epilepsy over the lifespan (10.1016/S0140-6736(12)61455-X)	Lin et al.[47]	2012	The Lancet	313	24.08
13	Efficacy of felbamate in childhood epileptic encephalopathy (Lennox-Gastaut syndrome) (10.1056/NEJM199301073280105)	Felbamate Study Group[48]	1993	New England Journal of Medicine	305	9.53
14	Neuro-QOL: quality of life item banks for adults with neurological disorders: item development and calibrations based upon clinical and general population testing (10.1007/s11136-011-9958-8)	Gershon et al.[49]	2012	Quality of Life Research	246	18.92
15	International consensus clinical practice statements for the treatment of neuropsychiatric conditions associated with epilepsy (10.1111/j.1528-1167.2011.03276.x)	Kerr et al.[50]	2011	Epilepsia	243	17.36
16	Successful surgery for epilepsy due to early brain lesions despite generalized EEG findings (10.1212/01.wnl.0000266386.55715.3f)	Wyllie et al.[51]	2007	Neurology	241	13.39
17	Depression and anxiety disorders in pediatric epilepsy (10.1111/j.1528-1167.2005.43604.x)	Caplan et al.[52]	2005	Epilepsia	239	11.95
18	Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy (10.1016/j.yebeh.2013.08.037)	Porter and Jacobson[53]	2013	Epilepsy and Behavior	230	19.17
19	Evidence-based guideline update: vagus nerve stimulation for the treatment of epilepsy (10.1212/WNL.0b013e3182a393d1)	Morris et al.[54]	2013	Neurology	217	18.08
20	The treatment of epilepsy in developing countries: where do we go from here? (Not available)	Scott et al.[55]	2001	Bulletin of the World Health Organization	214	8.92

PY: Publication year, TC: Total citations

Ethics

Ethics Committee Approval: The study was conducted as a bibliometric analysis. All data sources were available on the internet, and no animal or human subjects were involved. Ethical committee permission was not required, therefore.

Informed Consent: Patient consent is not required.

Footnotes

Authorship Contributions

Concept: K.M.K., H.A., Design: K.M.K., H.A., Data Collection or Processing: K.M.K., Analysis or Interpretation: K.M.K., Literature Search: K.M.K., H.A., Writing: K.M.K., H.A.

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

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

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Archives of Epilepsy

Original Article

A Forty-year Bibliometric Analysis on the Stigma in Children with Epilepsy

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Abstract

Objective: Stigma in children with epilepsy is an important issue that negatively affects children with epilepsy and their immediate environment. However, examining the relevant literature revealed that systematic reviews on this subject were limited, and there was no bibliometric study. The aim of this study is to conduct a bibliometric analysis of the studies conducted over the past 40 years on stigma in children with epilepsy.

Methods: This study used the Web of Science Core Collection database. Articles in this widely used globally database were searched on August 14, 2024, using the following keywords: topic search (TS) = ("epilepsy" or "seizure" or "convulsion" or "epileptic" or "status epilepticus") and TS = ("stigma*" or "social stigma*" or "stereotyping" or "discriminat*" or "prejudice" or "social exclusion" or "social cohesion") and TS = ("child*" or "adolescent*" or "pediatric" or "preschool"). Original research articles published in English between 1980 and 2024 in the Social Sciences Citation Index, the Science Citation Index Expanded, and the Emerging Sources Citation Index were selected.

Results: In this study, a total of 883 articles in the Web of Science database were examined and analyzed. Studies on stigma in children with epilepsy have been increasing since the 1980s. Eight hundred eighty-three articles were published in 333 different journals, among which 47 included three or more related publications. The journals in which the relevant publications were published were Epilepsy and Behavior (n=221), Epilepsia (n=54), Seizure-European Journal of Epilepsy (n=41).

Conclusion: The number of published articles increased over the years, with more studies conducted in developed countries. In recent years, it has been observed that stigma in children with epilepsy has focused on topics such as quality of life and intervention. This study will guide researchers who will publish on stigma in children with epilepsy.

Keywords: Epilepsy, stigma, children, bibliometric study

INTRODUCTION

Epilepsy is a chronic neurological disorder, usually diagnosed during childhood and adolescence, that causes abnormal electrical activity in the brain and predisposes the individual to recurrent seizures.[1] The word epilepsy is derived from the Greek word epilepsia and can be divided into two separate words, epi (on) and lepsis (to hold or have a seizure).[2]

Epilepsy affects approximately 50 million people worldwide. Approximately 50% of epilepsy diagnoses are made during childhood and adolescence, affecting the lives of 10.5 million children under the age of 15.[3] The lifetime prevalence rate of epilepsy in children is 7.2 per 1,000 individuals. Approximately 5% of these individuals will have at least one epileptic seizure during their lifetime.[4] In recent studies, the prevalence of epilepsy has been reported as 139/100,000 in underdeveloped and developing countries and 49/100,000 in developed countries. Four out of five of individuals with epilepsy live in underdeveloped and developing countries.[3] Individuals with epilepsy in disadvantaged areas often do not receive treatment due to lack of access, which negatively affects both their physical and psychological health.[5]

Epilepsy and seizures are caused by genetic, structural, metabolic, infectious, immune, and unknown causes. These causes are not hierarchical and epilepsy can result from multiple causes.[6] Antiepileptic drugs are effective in epilepsy and can control the symptoms. The symptoms observed are effectively managed in 7/10 of individuals with epilepsy when using appropriate antiepileptic drugs.[3] Individuals with epilepsy and their families face difficulties. Discrimination and stigmatization are among the challenges faced by individuals with epilepsy.

Stigma is defined as a discrediting attitude towards those who deviate from the norms of society. It can be a source of social rejection, isolation and discrimination.[7] Stigmatization experienced by individuals with epilepsy is a global problem that negatively affects quality of life.[8,9] Stigma comes from ancient Greek and means "to carve, mark as a sign of shame, punishment or disgrace".[10] People with epilepsy may feel embarrassed and ashamed if they have seizures in public due to symptoms such as limb tremors, staring, chewing, and urinary or bowel incontinence.[11] Uncontrolled seizures in people with epilepsy can be very debilitating. People may even be afraid to go out of their homes unaccompanied. They may fear what people will think of them if they have a seizure in public. For these and similar reasons, epilepsy has been a culturally devalued condition throughout the world and throughout history.[12]

Stigma in epilepsy, is defined in two ways: felt by individuals and applied to them. Applied stigma refers to discriminatory behavior against individuals with epilepsy, which is also observable externally. Felt stigma, on the other hand, consists of the emotions that individuals associate with epilepsy. These emotions include shame, embarrassment and fear.[13] Stigma in epilepsy may lead to increased anxiety and depressive symptoms and decreased quality of life in individuals with epilepsy.[14]

In light of the above, this study aims to address the issue of stigma in children with epilepsy from a bibliometric perspective.

Bibliometric analysis is a systematic study of the scientific literature to identify patterns, trends and influences in a particular field. The major steps include collecting data from relevant databases, cleaning and refining the data, and subjecting the data to various bibliometric methods to produce meaningful knowledge. Bibliometric analysis is an increasingly popular and comprehensive technique for examining and evaluating large amounts of scientific data increasingly used in research.[15] It is reported that studies utilizing bibliometric analysis are more advantageous than traditional review studies. In addition to analyzing a large number of studies on the topic, it brings together the relevant literature in a systematic and comprehensive manner.[16] Traditional review studies can be based on the subjective understanding of the academics who conduct these reviews.[17]

There is no bibliometric study focusing on the concept of stigma in children with epilepsy in the relevant literature. This study aims to address the issue of stigma in children with epilepsy from a bibliometric perspective. Specifically, we focus on: (1) identifying the general trend of studies on stigma in children with epilepsy; (2) identifying studies on stigma in children with epilepsy by topics, articles, journals, countries, etc.; (3) identifying trending topics and gaps in studies on stigma in children with epilepsy. By examining the studies on stigma in children with epilepsy in the last 40 years, this study will pave the way for new research by guiding researchers on this topic.

MAIN POINTS

- Stigmatization experienced by individuals with epilepsy is a global problem that negatively affects quality of life.
- This study aims to address the issue of stigma in children with epilepsy from a bibliometric perspective.
- Specifically, we focus on: (1) identifying the general trend of studies on stigma in children with epilepsy (2) identifying studies on stigma in children with epilepsy by topics, articles, journals, and countries (3) identifying trending topics and gaps in studies on stigma in children with epilepsy.

METHODS

The aim of this study is to examine how the studies on stigma in children with epilepsy have developed since 1980 and to assess the current situation. For this purpose, the articles published on this subject, authors, institutions, country collaborations, number of citations, and trending topics are analyzed.

Data Collection

This study used the Web of Science (WOS) Core Collection database. Articles in this globally widely used database were searched on August 14, 2024, using the following keywords: topic search (TS) = ("epilepsy" or "seizure" or "convulsion" or "epileptic" or "status epilepticus") and TS = ("stigma*" or "social stigma*" or "streotyping" or "discriminat*" or "prejudice" or "social exclusion" or "social cohesion") and TS = ("child*" or "adolescent*" or "pediatric" or "preschool"). Original research articles published in English between 1980 and 2024 in the Social Sciences Citation Index (SSCI), the Science Citation Index Expanded (SCI-EXPANDED) and the Emerging Sources Citation Index (ESCI) were selected.

When keywords were entered into WOS, there were no restrictions on the type of literature, and 1,174 results were initially obtained. Two researchers independently assessed each publication and selected article as the document type, SSCI, SCI-EXPANDED and ESCI as the WOS index, and English as the language. Only articles were included in this study. Document types such as editorial material, meeting abstract, proceeding paper, and book chapter were not included. BibTeX and Tab Delimited File formats were downloaded from the WOS export section and analyses were performed on these files. In this study, a total of 883 articles were included in the analysis.

Statistical Analysis

We used the bibliometrix R open source package for quantitative research in bibliometrics to perform bibliometric analyses on the entire collection number.[18] As part of the bibliometric analysis in our study, we used biblioshiny to perform science mapping and performance analyses. Biblioshiny is a Web interface for bibliometrix that supports data import (www.bibliometrix.org/Biblioshiny.html), transformation into a data frame, data filtering, analysis and plots for sources, authors, and documents.[19,20]

VOSviewer, used in this study, is a software tool that allows creating maps based on network data and the visualization and analysis of these maps.[21]

Ethical Approval

The study was conducted as a bibliometric analysis. All data sources were available on the internet, and no animal or human subjects were involved. Ethics committee permission was not, therefore, required.

RESULTS

Main Information About Data

Our investigation into the stigma in children with epilepsy from 1980 revealed that 883 articles in English had been published in this domain cataloged within the SSCI, the SCI-EXPANDED, and the ESCI, with a total of 3,940 authors involved. The annual growth rate is 8.12% and the number of citations per study is 26.41 (Table 1).

Studies on stigma in children with epilepsy have been increasing since the 1980s, with fluctuations in some years. In general, there is a trend from the 1980s to the present day. While the number of publications was 2 in 1980, it increased to 10 in 2000, 28 in 2012, and 74 in 2021 (Figure 1). Although publications on stigma in children with epilepsy have increased over the years, the number remains insufficient relative to the total 883 articles published.

Table 1. Data information

Main information about data	
Timespan	1980:2024
Sources (journals, books, etc.)	333
Documents	883
Annual growth rate %	8.12
Document Average Age	9.3
Average citations per doc	26.41
References	24,299
Document contents	
Keywords Plus (ID)	1,848
Author's Keywords (DE)	2,084
Authors	
Authors	3,940
Authors of single-authored docs	48
Authors collaboration	
Single-authored docs	51
Co-authors per doc	5.41
International co-authorships %	27.63
Document types	
Article	763
Article; early access	8
Article; proceedings paper	14
Review	98

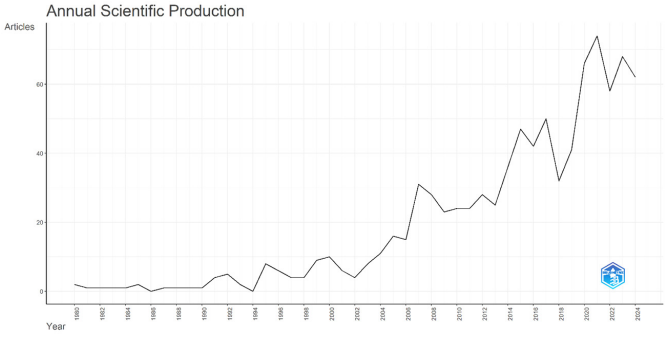

Figure 1. Annual scientific production

Bibliometric Analysis of Journals and Articles

In our study, we used Bradford's law to evaluate the journals in which publications on stigma in children with epilepsy were published. Bradford's law is a principle in bibliometrics. This law defines the distribution of scientific contributions in a field. It consists of the most cited first region, a less cited second region, and an even less cited third region. In essence, it identifies the key journals that contribute significantly to a particular field and allows researchers and information professionals to focus their attention on these key sources.[22] Epilepsy and Behavior, Epilepsia, and Seizure-European Journal of Epilepsy were found to be in zone 1 (Figure 2).

Epilepsy and Behavior is the leading journal for publications on epilepsy and seizures, focusing on clinical neurology, neurosurgery, neuropsychiatry, neuropsychology, neurophysiology, neuropharmacology, and neuroimaging. Epilepsia is a leading journal that publishes current clinical and research results on all aspects of epilepsy, focusing on clinical neurology, neurophysiology, molecular biology, neuroimaging, neurochemistry, and therapeutic trials. Seizure-European Journal of Epilepsy is a journal that publishes articles on all topics related to epilepsy and seizure disorders. The journal reflects on the social and psychological burden and impact of the condition on people with epilepsy, their families, and society at large, and methods and ideas that can help alleviate the disability and stigma that the condition can cause.

The most cited articles on stigma in children with epilepsy are "the global burden and stigma of epilepsy (de Boer et al.[12])," "epilepsy and social identity: stigmatization of a chronic neurological disorder (Jacoby et al.[23])", and "refractory epilepsy and treatment outcomes (Laxer et al.[24]) (Table 2).

Bibliometric Analysis of Authors, Institutions and Countries

The publications by authors on stigma in children with epilepsy were analyzed. The authors of the publications in the SSCI, the SCI-EXPANDED, and the ESCI databases in WOS were examined. A total of 3,940 authors wrote and published 883 articles, including 38 authors who published 5 or more related articles.

The author who published the most on stigma in children with epilepsy was Joan K Austin from Indiana University Faculty of Nursing. The second most published author is Gretchen L Birbeck from the University of Rochester. The third most published author was Ann Jacoby from the University of Liverpool (Figure 3).

Lotka's law reveals the quantitative distribution of the publications of authors contributing to the literature on a particular subject in that field. This is a study to examine the scientific productivity of the authors. Lotka's law predicts that 70% of the authors who publish on a subject contribute to the subject with one publication, 15% with two publications, and 7% with three publications.[25] Analysis of articles on stigma in children with epilepsy using Lotka's law revealed that 87.5% of the authors contributed only one article (n=3,446), 0.86% produced two articles (n=340), and 0.21% produced three articles (n=81). It was observed that the distribution of authors in the study did not follow Lotka's law (Figure 4).

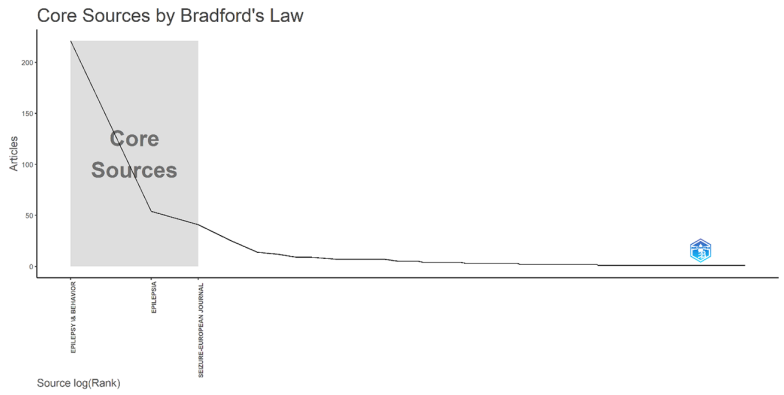

Figure 2. Bradford's law

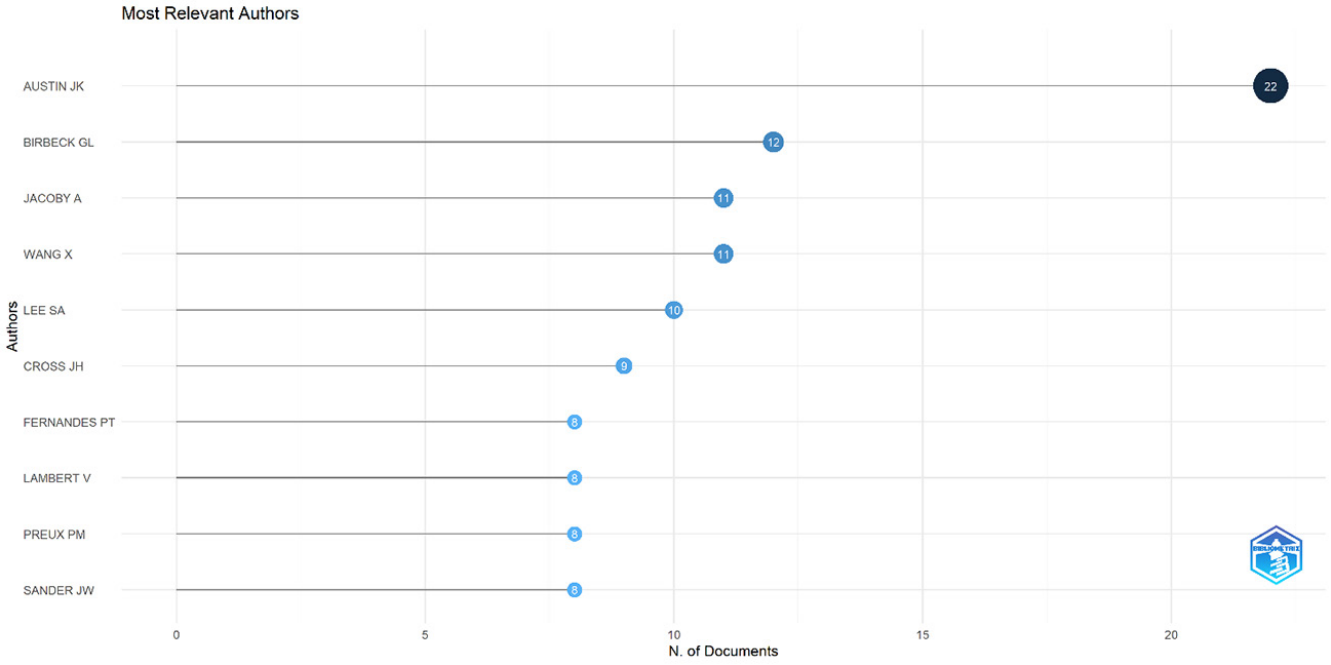

Figure 3. Most relevant authors

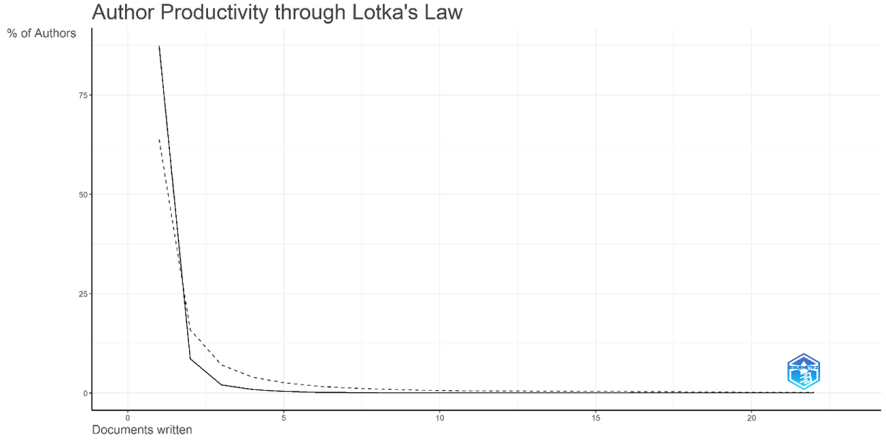

Figure 4. Author productivity through Lotka's law

When most relevant affiliations were analyzed (Figure 5), the University of Liverpool (n=46) was at the top. This was followed by Makerere University (n=35), All India Institute of Medical Sciences (n=34), Indiana University (n=34), University of California, Los Angeles (n=31), and Harvard Medical School (n=29).

Analysis of scientific publications by country showed that the leading 10 countries (Figure 6) were: the United States of America (USA) (n=189), United Kingdom (n=71), Canada (n=64), China (n=36), Netherlands (n=31), India (n=28), France (n=25), Germany (n=25), Italy (n=25), Australia (n=25).

When inter-country cooperation on stigma in children with epilepsy was analyzed, it was observed that the greatest cooperation was between the USA and the United Kingdom (n=33), followed by USA-Canada (n=19), United Kingdom-Netherlands (n=16), USA-Zambia (n=13), Netherlands-Belgium (n=11), United Kingdom-Italy (n=11), United Kingdom-Kenya (n=11), USA-Uganda (n=11), USA-Ireland (n=10), United Kingdom-Brazil (n=9) (Figure 7).

Bibliometric Analysis of Keyword and Trend Topic Analyses

The most frequently used words in this study were children (n=307), stigma (n=199), quality of life (n=136), people (n=124), adolescents (n=119), knowledge (n=107), epilepsy (n=94), impact (n=91), attitudes (n=77), prevalence (n=73). Factor analysis of the keywords used in publications on stigma in children with epilepsy was performed. In the selected analysis, two clusters were identified, and words such as stigma, perceived stigma, quality of life, perceptions, childhood epilepsy, knowledge, risk factors, seizures, epilepsy, management, public awareness, and public attitudes formed the large group. In the second small group, the words seizure, disorders, anxiety, and depression came together (Figure 8).

In this study, the keywords in multiple studies on stigma in children with epilepsy were analyzed with VOSviewer. When the color and distribution of the boxes in this figure were examined, it was seen that such as anxiety, depression, childhood, risk factors, communication, and family were grouped together with the keyword epilepsy. In blue, words like discrimination, perceived stigma, disclosure, social supports, and parents were grouped together with the keyword stigma (Figure 9). This study also investigated the trend in the words used in stigma studies in children with epilepsy over the years. This revealed that the concepts used have changed over time (Figure 10).

DISCUSSION

In this study, it was observed that publications on stigma in children with epilepsy increased over the years from 1980 to 2024, with an annual growth rate of 8.12%. It was noteworthy that only 48 of the articles published by 3,940 researchers were single-authored, while the others were multi-authored. The fact that the number of citations of each of the studies in this study was 26.41 shows the scientific value of the studies. Although the number of articles published on stigma in children with epilepsy has increased over the years, it was also noteworthy that the number of publications was not high enough, considering the importance of the subject.

Epilepsy affects 50 million people worldwide, of which approximately 20% are children. Three scientific publications by country were analyzed, it was noteworthy that most publications were made in developed countries, and only India was among the top 10 countries from underdeveloped or developing countries. When the relevant literature was examined, it was reported that the prevalence of epilepsy was higher in underdeveloped and developing countries than in developed countries.[3] The examination of the findings in this study necessitates more research on this subject in underdeveloped or developing countries. One of the pleasing results obtained in this study is the increase in cooperation between developed and developing countries, indicated by the countries of the co-authors.

In this study, the most frequently used words were children, stigma, quality of life, people, adolescents, knowledge, epilepsy, impact, attitudes, and prevalence. Stigma negatively affects the quality of life in individuals with epilepsy.[8,9,14,26,27] The World Health

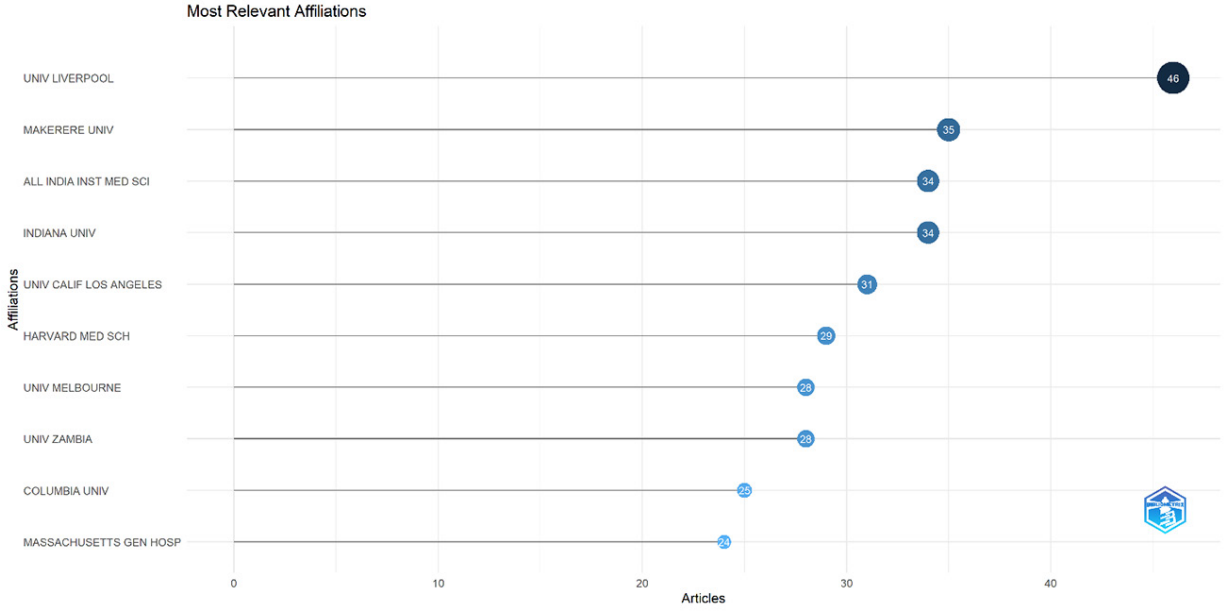

Figure 5. Most relevant affiliations

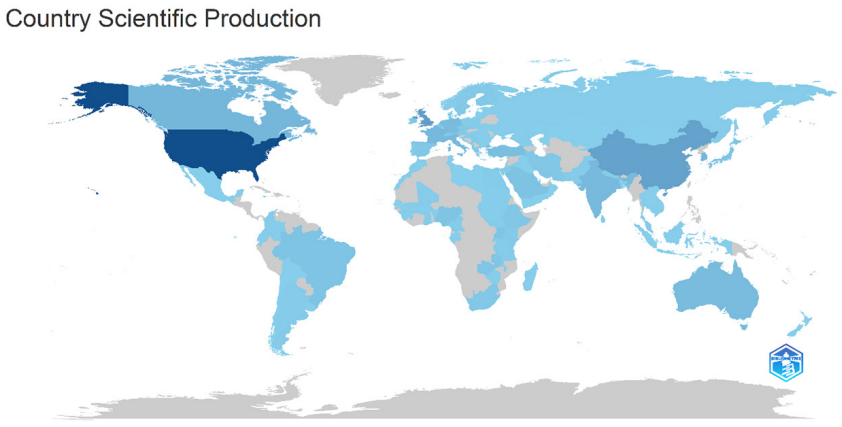

Figure 6. Country scientific production

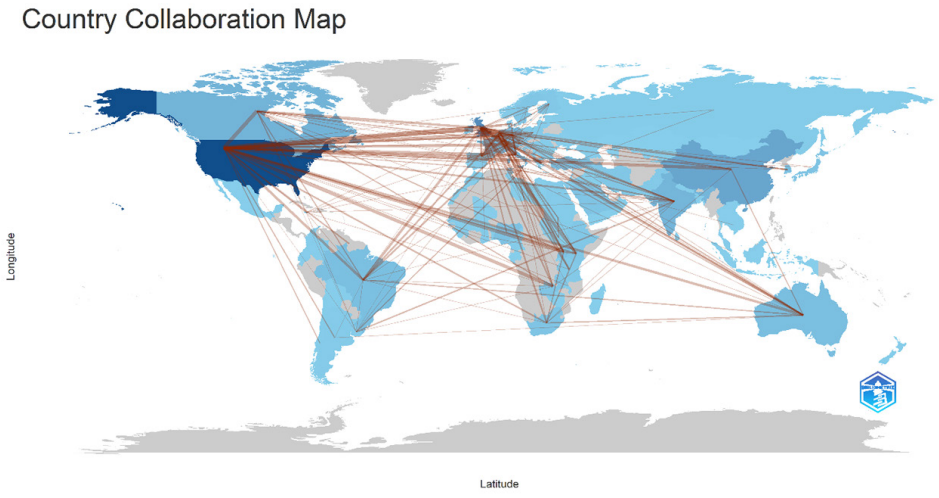

Figure 7. Country collaboration map

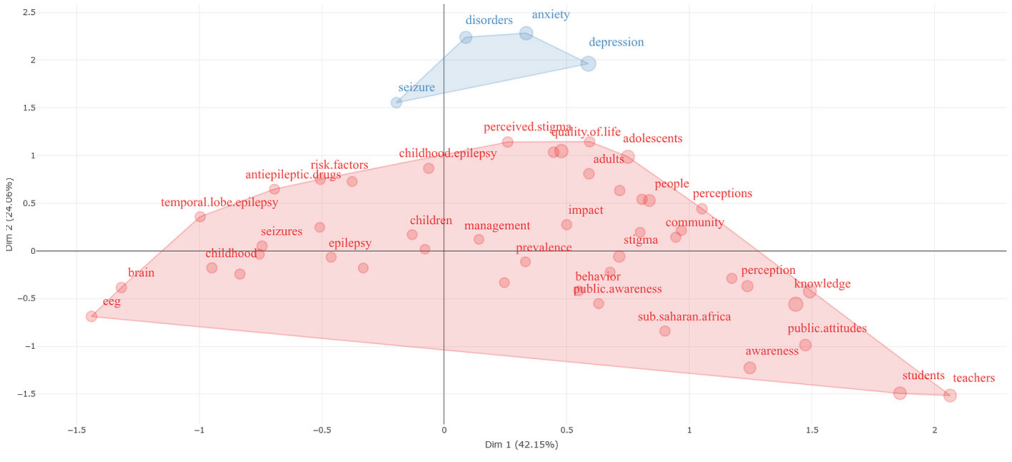

Figure 8. Keyword plus conceptual structure map of keywords

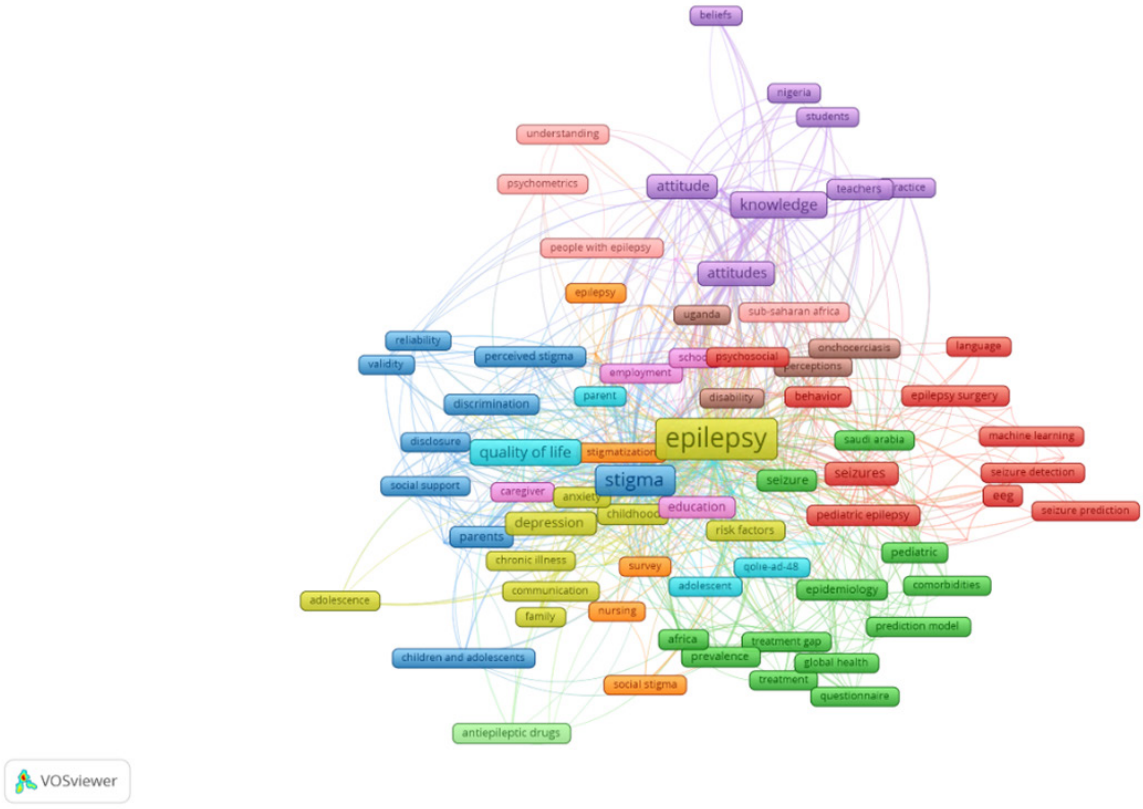

Figure 9. Authors keywords collaboration

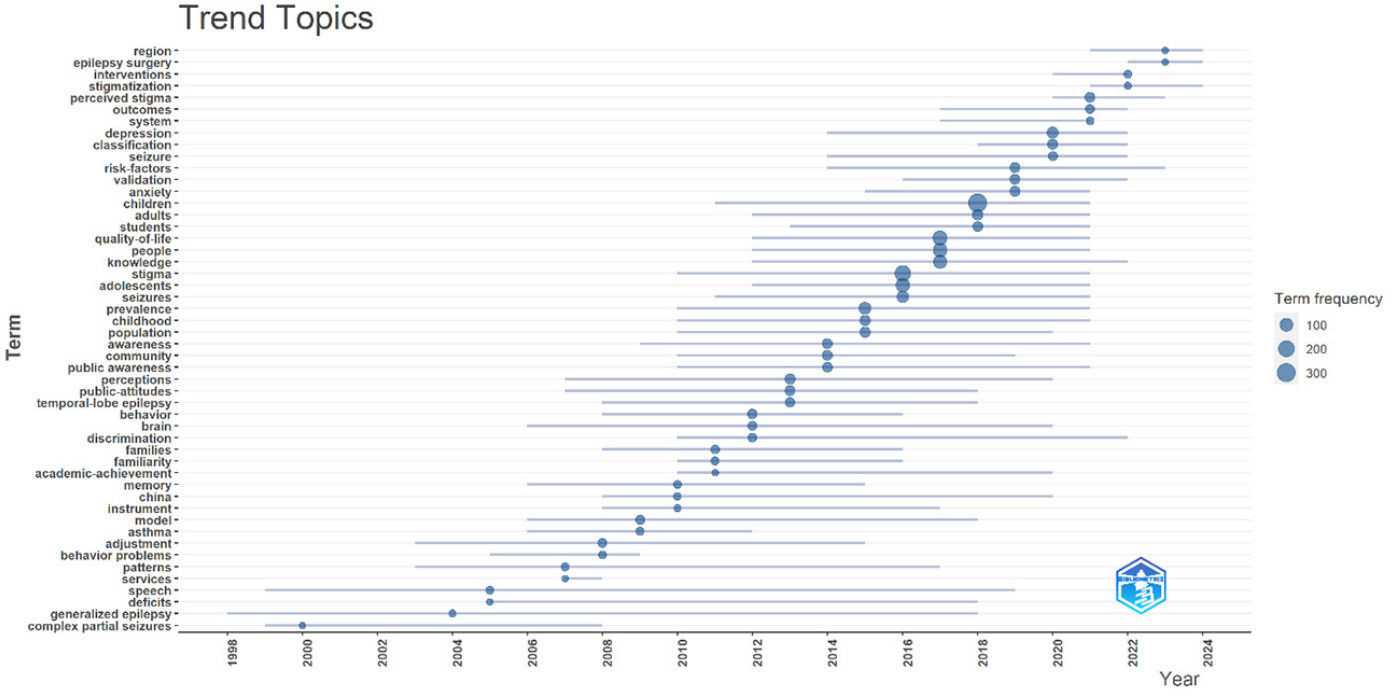

Figure 10. Trend topics

Organization defined quality of life as a state of complete physical, mental, and social well-being, not just the absence of disease or disability.[28] It states that quality of life in individuals with epilepsy depends on factors such as the type of epilepsy, frequency of seizures, whether seizures are controlled, antiepileptic drugs, as well as personal, social, or environmental factors.[29]

Children with epilepsy face low academic performance and school dropout due to bullying, alienation, and stigmatization.[30] The presence of stigma in children with epilepsy has negative consequences for both children and their families. Reducing stigma is important for successful epilepsy treatments.[31]

When the relevant literature is reviewed, difficulties such as educational barriers, stigma, and lack of access to treatment have been reported in many parts of the world for years. Efforts have been made to increase access to epilepsy treatment, especially in underdeveloped and developing countries where access to treatment is more limited. Difficulty in accessing treatment in epilepsy is not only a problem in low-income and developing countries. Difficulties in accessing treatment can also be seen in individuals with epilepsy living in developed countries.[32] Lack of knowledge about epilepsy negatively affects individuals with epilepsy and their families more significantly. The attitudes of the individuals who make up the society, consisting of erroneous thoughts, feelings and behaviors about epilepsy, increase the burden of stigma on individuals with epilepsy and their families.[33]

There is a comorbidity observed in individuals with epilepsy. Internalizing problems such as anxiety and depression, and psychiatric disorders such as autism spectrum disorder, and attention deficit hyperactivity disorder, are more common in children with epilepsy than previously thought. Although the common pathophysiology is not easily explained, these psychiatric disorders seen in children with epilepsy cause the picture to become more complex and may complicate treatment.[34]

Lack of accurate knowledge about epilepsy is associated with superstitions (e.g., madness and demons) in various civilizations.[35] Such devaluations often lead to stigmatization of people with epilepsy and carry a psychosocial burden.[12] The unpredictable nature of seizures can cause feelings of unhappiness, loneliness, hopelessness, low self-esteem and self-blame in people with epilepsy, which can lead to social isolation and stigmatization.[36]

It is known that individuals with advantageous social support cope better with difficulties.[37] It has been observed that the stigma felt in individuals with epilepsy has a negative relationship with the self-efficacy level. Identifying and strengthening the self-efficacy of children with epilepsy will facilitate the management of the disease.[38]

High levels of self-efficacy and social support are needed to achieve positive results in the treatment and management of epilepsy. In this way, their quality of life can be enhanced through positive effects in their academic and social lives. The stigma associated with epilepsy can be an obstacle for individuals with epilepsy to access treatment. Therefore, providing training aimed at increasing social awareness that epilepsy is a medical syndrome and that it is a treatable disease can help eliminate the factors that negatively affect the treatment of epilepsy.[39]

Table 2. Most cited articles[12,23,24,40-46]

No	Paper (DOI)	Author	PY	Journal	Total citations	TC per year
1	The global burden and stigma of epilepsy (10.1016/j.yebeh.2007.12.019)	De Boer et al.[12]	2008	Epilepsy and Behavior	573	33.71
2	The consequences of refractory epilepsy and its treatment (10.1016/j.yebeh.2014.05.031)	Laxer et al.[24]	2014	Epilepsy and Behavior	464	42.18
3	Epilepsy and social identity: the stigma of a chronic neurological disorder (10.1016/S1474-4422(05)01014-8)	Jacoby et al.[23]	2005	The Lancet Neurology	363	18.15
4	Global disparities in the epilepsy treatment gap: a systematic review (10.2471/BLT.09.064147)	Meyer et al.[40]	2010	Bulletin of the World Health Organization	307	20.46
5	A multivariate approach for patient-specific EEG seizure detection using empirical wavelet transform (10.1109/TBME.2017.2650259)	Bhattacharyya and Pachori[41]	2017	EEE Transactions on Biomedical Engineering	295	36.875
6	Periventricular heterotopia: an X-linked dominant epilepsy locus causing aberrant cerebral cortical development (10.1016/S0896-6273(00)80025-2)	Ekşioğlu et al.[42]	1996	Neuron	255	8.79
7	PI3K/AKT pathway mutations cause a spectrum of brain malformations from megalencephaly to focal cortical dysplasia (10.1093/brain/awv045)	Jansen et al.[43]	2015	Brain	251	25.1
8	Working, declarative and procedural memory in specific language impairment (10.1016/j.cortex.2011.06.001)	Lum et al.[44]	2012	Cortex	236	18.15
9	The treatment of epilepsy in developing countries: where do we go from here? (N/A)	Scott et al.[45]	2001	Bulletin of the World Health Organization	219	9.12
10	The fra(X) syndrome - neurological, electrophysiological, and neuropathological abnormalities (10.1002/ajmg.1320380267)	Wisniewski et al.[46]	1991	American Journal of Medical Genetics	203	5.97

Study Limitations

The principal limitations of this research are that databases such as Scopus, EMBASE, PubMed, Google Scholar, and Dimensions were not screened. Additionally, because the search terms were applied in English, a more comprehensive evaluation was not possible.

CONCLUSION

In this study, in which the issue of stigma in children with epilepsy was examined by bibliometric analysis, the fact that terms such as stigma and quality of life have been included more in studies since 2010 indicates that epilepsy, which is a neurological disease, should be handled with a holistic approach in both childhood and adolescence. Decreased stigma related to epilepsy, increased self-efficacy, and social support increase the quality of life. It is clear that increased knowledge and awareness of the child, family, friends, school, teachers, and other people about epilepsy facilitates epilepsy treatment.

When the relevant literature was examined, it was observed that researchers from underdeveloped or developing countries published fewer on stigma in children with epilepsy. Although there is a need for more publications on this subject in these countries, it is also noteworthy that more comparative studies involving individuals from different cultures are necessary. In addition, it is thought that comparative studies on stigma in girls and boys with epilepsy would be useful in the context of gender. In this study, it was observed that intervention for stigma in children with epilepsy has been researched in recent years, and there is a need for further study in the future.

Ethics

Ethics Committee Approval: No ethics committee permission was required for bibliometric analysis.

Informed Consent: Patient consent was not required.

Footnotes

Authorship Contributions

Concept: K.M.K., H.A., Design: K.M.K., H.A., Data Collection or Processing: K.M.K., Analysis or Interpretation: K.M.K., Literature Search: K.M.K., H.A., Writing: K.M.K., H.A.

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Original Article

Vagus Nerve Stimulation in Drug-resistant Epilepsy: A Single-center Experience

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Abstract

Objective: Vagus nerve stimulation (VNS) has been increasingly used in recent years as an alternative treatment method for drug-resistant epilepsy (DRE). In this study, we aimed to analyze the data of patients diagnosed with DRE and treated with VNS, who are being followed up at the Muğla Sıtkı Koçman University Faculty of Medicine, Department of Neurology, and to review our experience.

Methods: This is a study including patients who were still under follow-up as of October 31, 2024, and had undergone VNS implantation at least one year prior. Demographic characteristics, epilepsy history, and VNS-related data were collected and recorded in the follow-up form. The effectiveness of VNS was evaluated according to the McHugh classification, based on changes in seizure duration, severity, and frequency.

Results: Of the 40 patients, 42.5% (n=17) were female and 57.5% (n=23) were male. The mean age was 37.2±11.2 years. The average duration of epilepsy was 24.7±10.7 years. The median seizure frequency prior to VNS implantation was 20 per month (minimum: 1 to maximum: 600). The median values for VNS output current and VNS magnet current were 1.50 and 1.75 milliamperes, respectively. The median values for VNS duty cycle, VNS OFF time (minutes), and VNS ON time (seconds) were 10, 5, and 30, respectively. According to the McHugh classification, 22.5% (n=9) were classified as class 1A, 30% (n=12) as class 2A, 10% (n=4) as class 2B, 17.5% (n=7) as class 3A, 7.5% (n=3) as class 3B, and 12.5% (n=5) as class 5.

Conclusion: Following VNS implantation, more than 50% reduction in epileptic seizures was observed in 62.5% of patients, while less than 50% reduction was seen in 25% of patients. VNS is an important treatment option for patients with DRE.

Keywords: Epilepsy treatment, seizure, seizure frequency

INTRODUCTION

The definition of drug-resistant epilepsy (DRE) was published by the International League Against Epilepsy in 2010: failure to suppress seizure activity or persistence of seizures for more than 12 months or for a period three times the longest inter-seizure interval reported previously, despite effective use of two or more appropriately selected anti-seizure drugs in monotherapy, alternating monotherapy or in combination, at therapeutic doses.[1] The etiology of DRE can often include mesial-temporal sclerosis, tuberous sclerosis, Sturge-Weber syndrome, cerebral tumors, hamartomas, arteriovenous malformations, structural malformations, cerebral infection sequelae, or trauma. Various diets, such as the ketogenic diet, the medium-chain triglyceride diet, the modified Atkins diet, and the low glycemic index diet, are used in its treatment. Surgical treatments, such as focal resection, corpus callosotomy, or hemispherectomy, are among the options for patients with partial or multifocal epilepsy. Stimulation methods are another treatment option for patients who do not respond to medical treatment or are not suitable for surgical treatment. Vagal nerve stimulation (VNS), deep brain stimulation of the anterior nucleus of the thalamus, and responsive neurostimulation can be applied to these patients.[2-4]

VNS, one of the methods used in the treatment of DRE, was first implanted as a device in a human in 1988. VNS, which was approved for use in focal-onset DRE in patients over 12 years of age in Europe in 1994 and in the United States of America (USA) in 1997, has become

increasingly popular in recent years.[5,6] With the development of technology and accumulation of clinical experience, VNS has been actively used in many epilepsy centers. The expected results included a decrease in seizure frequency, severity, and duration in patients.

In this study, we aimed to examine the data of patients with VNS at our center.

METHODS

This study was planned according to the Declaration of Helsinki. Approval was obtained from Muğla Sıtkı Koçman University Faculty of Medicine Clinical Research Ethics Committee (no: 13/XI, date: 07.09.2022). The study included patients over the age of 18 years who were diagnosed with DRE and underwent VNS; who applied to the outpatient clinic of the Muğla Sıtkı Koçman University Faculty of Medicine, Department of Neurology, between September 1, 2022, and October 31, 2024; who were still being followed up in our clinic on October 31, 2024; and who had at least one year after VNS implantation.

All patients included in the study were systematically evaluated by a psychiatrist prior to VNS implantation. During this assessment, the individuals' mental health status, capacity for treatment adherence, and psychiatric suitability for the interventional procedure were comprehensively evaluated. The presence of an active psychotic episode, uncontrolled mood disorder, or acute suicidal ideation was considered a temporary contraindication for VNS, and psychiatric stabilization was ensured before proceeding with the intervention in such cases. Aside from these conditions, the presence of stable severe psychiatric disorders (e.g., schizophrenia, bipolar disorder) or intellectual disability was not considered a barrier to accessing treatment. This approach was adopted in line with the principle that individuals with epilepsy have a fundamental right to access effective and evidence-based treatment options. The evaluation process was carried out by a multidisciplinary team composed of neurologists, neurosurgeons, and psychiatrists, allowing for a holistic assessment of each patient's medical, surgical, and psychiatric suitability.

VNS surgeries were performed at the same hospital and the department of neurosurgery. The surgical procedures for all patients were performed on the left vagus nerve using the surgical technique described by Reid.[7] The incision point is the midway between the chin and the sternal notch, with 1/3 of the incision lying medial to the sternocleidomastoid muscle (SCM) and 2/3 remaining lateral to the SCM transversely. The head is fixed with extension, kept straight, or rotated 15 degrees towards the opposite side for surgery by using intraoperative ultrasonography for identifying the best vagus nerve position inside the carotid sheath. After the VNS leads were placed on the left vagus nerve microsurgically, the system was connected with a VNS generator placed in a pocket opened approximately 5 cm inferior to the left clavicle. Generator replacements were performed from the previous incision over the generator and involved using a full power battery. The age, sex, occupation, marital status, education level, history of epilepsy, medications used, VNS application time and duration, VNS battery status, post-VNS utilization status, seizure frequency, seizure severity and duration, and VNS device setting information of the patients were collected and recorded in the follow-up form. The battery operating cycle, duty cycle, current intensity, stimulus frequency, pulse width, and battery impedance values were recorded under the VNS device setting information title. The effectiveness of VNS was evaluated according to the McHugh classification, using changes in seizure duration, severity, and number. Data from 45 patients were examined in this study. Four of the 45 patients continued their follow-up in different cities, and one patient exited for other reasons than epilepsy. The data from 40 patients were statistically evaluated, and in the light of these data, our VNS experience at the Muğla Sıtkı Koçman University Faculty of Medicine, Department of Neurology, was reviewed and discussed.

MAIN POINTS

- Following vagus nerve stimulation (VNS) implantation, a reduction in epileptic seizures greater than 50% was observed in 62.5% of patients.
- VNS is an important treatment option for patients with drug-resistant epilepsy.
- No side effects were observed after VNS implantation in most patients.
- Epilepsy patients who receive VNS can cope with several VNS side effects, as these side effects are tolerable compared to the benefits.

Statistical Analysis

The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Descriptive statistics for continuous variables were presented as mean±standard deviation or median [minimum (min)-maximum (max)] values, depending on the distribution. Categorical variables were summarized using frequencies (n) and percentages (%). All statistical analyses were performed using RStudio version 2024.09.0 (Posit Software, Public Benefit Corporation, Boston, Massachusetts, USA).

RESULTS

The data of 40 patients, who visited the outpatient clinic of our center between September 1, 2022, and October 31, 2024, and who were implanted with VNS due to the diagnosis of DRE, were statistically evaluated (Tables 1, 2). Of the 40 patients included in the study, 42.5% (n=17) were female and 57.5% (n=23) were male. The mean age was 37.2±11.2 years. 70% (28) of the patients were single, and 30% (12) were married. When the educational levels of the patients were examined, 25% (10) were illiterate, 27.5% (11) were primary school graduates, 25% (10) were high school graduates, and 22.5% (9) were university graduates. Of the 40 patients, 60% (n=24) were unemployed, 27.5% (n=11) worked in the service sector, 5% (n=2) worked as farmers, 5% (n=2) worked as teachers, and 2.5% (n=1) worked as civil servants. 25% (10) of patients were illiterate, 27.5% (11) were primary school graduates, 25% (10) were high school graduates, and 22.5% (9) were university graduates. Focal-onset epileptic seizures were observed in 82.5% (33) of the patients, while 17.5% (7) had multifocal-onset seizures. The median age at the onset of epilepsy was 8 years (range, 0-46 years). The mean duration of epilepsy was 24.7±10.7 years. Our patients used 16 different anti-seizure drugs. Levetiracetam was a preferred anti-seizure drug in 72.5% (29) of patients, carbamazepine in 57.5% (23) of patients, and another drug in 40% (16) as shown in Table 3. The median seizure frequency of the patients before VNS implantation was 20 seizures per month (min: 1, max: 600). The median age at VNS implantation

Table 1. Descriptive statistics of categorical variables

Variable name	n (%)
Marital status	
Single	28 (70)
Married	12 (30)
Occupation	
Farmer	2 (5)
Service sector	11 (27.5)
Unemployed	24 (60)
Civil servant	1 (2.5)
Teacher	2 (5)
Education level	
Illiterate	10 (25)
Primary school	11 (27.5)
High school	10 (25)
University	9 (22.5)
VNS battery percentage	
18-25	1 (2.5)
25-50	9 (22.5)
50-75	8 (20)
75-100	22 (55)
Epilepsy onset	
Focal	33 (82.5)
Multifocal	7 (17.5)
McHugh classification	
1A	9 (22.5)
2A	12 (30)
2B	4 (10)
3A	7 (17.5)
3B	3 (7.5)
V	5 (12.5)

VNS: Vagus nerve stimulation

Table 2. Descriptive statistics of numerical variables

Variable	Value
VNS implantation duration (years)	2.50 (1.00-4.00)
VNS output current (mA)	1.50 (0.75-2.25)
VNS magnet current (mA)	1.75 (1.00-2.50)
VNS impedance	2,569.88±387.14
Duty cycle	10 (10-35)
On time (sec)	30 (21-30)
Off time (min)	5 (1.10-5.00)
Age at epilepsy onset	8 (0-46)
Duration of epilepsy	24.73±10.76
Number of seizures in 1 month pre-VNS	20 (1-600)
Avg. reduction in seizure frequency	50 (0-100)
Avg. reduction in seizure severity	50 (0-100)
Avg. reduction in seizure duration	50 (0-100)
Age at VNS implantation	32 (26-39.75)

Descriptive statistics are shown as mean±standard deviation or median (minimum-maximum).
Avg: Average, mA: Milliampere, Min: Minutes, Sec: Seconds, VNS: Vagus nerve stimulation

in our patients with follow-up was 32 years (range: 26 to 39.75). The median time since implantation was 2.50 years (min: 1, max: 12 years). When the VNS settings of our patients were examined, the median of VNS output current and VNS magnet current were 1.50-1.75 milliamperes (mA). The median VNS duty cycle, VNS off time (minutes), and VNS on time (seconds) were 10, 5, and 30, respectively. After VNS implantation, the median decrease in seizure frequency, seizure duration, and seizure severity was determined to be 50%. The results related to patients' epileptic seizures after VNS implantation were evaluated according to the McHugh classification. Of the patients, 22.5% (9) were classified as class 1A, 30% (12) as class 2A, 10% (4) as class 2B, 17.5% (7) as class 3A, 7.5% (3) as class 3B, and 12.5% (5) as class 5. No side effects were observed after VNS in 70% of the patients (28). Fourteen side effects were observed in 12 patients, with some patients developing more than one side effect (Table 4). The

Table 3. Frequency and percentage distribution of medications used

Medication	n (%)
LEV	29 (72.5)
CBZ	23 (57.5)
LTG	16 (40)
VPA	14 (35)
LCM	13 (32.5)
ZNS	12 (30)
CLZ	11 (27.5)
TPM	9 (22.5)
PRG	4 (10)
OXC	4 (10)
PB	4 (10)
GBP	4 (10)
CLB	3 (7.5)
PRM	2 (5)
PHB	1 (2.5)
ETX	1(2.5)

The second column shows the number (n) and percentage (%) of patients using each medication among the 40 patients. Since patients used multiple drugs, the total percentage exceeds 100%.
CBZ: Carbamazepine, CLB: Clobazam, CLZ: Clonazepam, ETX: Ethosuximide, GBP: Gabapentin, LCM: Lacosamide, LEV: Levetiracetam, LTG: Lamotrigine, OXC: Oxcarbazepine, PB: Phenobarbital, PHB: Phenytoin, PRG: Pregabalin, PRM: Primidone, TPM: Topiramate, VPA: Valproic Acid, ZNS: Zonisamide

Table 4. Frequency and percentage distribution of side effects

Side effects	Total patients (n, %)	Patients with side effects (n, %)
None	28 (70.00)	-
Paresthesia	4 (10.00)	4 (28.57)
Dyspnea	2 (5.00)	2 (14.29)
Pain	1 (2.50)	1 (7.14)
Hoarseness	3 (7.50)	3 (21.43)
Hypotension	1 (2.50)	1 (7.14)
Delayed wound healing	3 (7.50)	3 (21.43)

The distribution of observed side effects is shown both across the total sample of 40 patients, (multiple side effects allowed, total percentage >100%) and among the 14 patients who reported side effects

most common side effect after VNS implantation was paresthesia occurring in 4 patients, while hoarseness was observed in 3 patients. In addition, 3 patients experienced delayed healing of the surgical wound after VNS implantation.

DISCUSSION

In recent years, VNS has been increasingly used as an alternative treatment for DRE that does not respond to medical treatment. The idea that seizures can be stopped by stimulating the vagal nerve was first proposed by Leonard Corning in the 1880s. In the 1980s, Zabara[8] performed VNS in a dog and demonstrated that seizures could be stopped. VNS implantation in humans was first attempted in 1988 and the first results were presented at the annual meeting of the American Epilepsy Society in 1989. This study was published by Penry and Dean[5] in 1990, and VNS was proposed as a new treatment option for patients with focal-onset epilepsy who were resistant to medication.[9,10] VNS was approved for clinical use in Europe in 1994. In 1997, VNS was approved by the Food and Drug Administration for use in focal-onset DRE patients over the age of 12.[6]

VNS is a neuromodulatory therapy used in addition to anti-seizure medications to manage DRE. The synergistic effects of VNS and anti-seizure medication combinations are used to achieve seizure control and improve quality of life. A recent study has shown that the use of VNS in combination with anti-seizure medications, especially with synaptic vesicle glycoprotein 2A (SV2A) modulators and slow sodium channel inhibitors, provides higher success rates in seizure control. These combinations have been shown to be effective in reducing seizure frequency (64.0% and 61.8%, respectively) and even in achieving seizure freedom (19.8% and 19.7%).[11] In another study, the combined use of VNS and SV2A modulators significantly enhanced HrQoL and reduced depression scores, indicating favorable synergistic effects of these combinations.[12] When the most frequently used drugs by our patients were examined, it was seen that the 5 most frequently used drugs, consistent with the literature, were levetiracetam, carbamazepine, lamotrigine, valproic acid, and lacosamide.

When evaluating the treatment efficacy of VNS, the primary goal was to determine a decrease in seizure frequency and severity. Reducing in anti-seizure drug use, decreasing in the frequency of interictal epileptiform discharges, and increasing in quality of life are seen as secondary goals. In a study by Vonck et al.,[13] 195 patients were followed up for 33 months, and a 55% decrease in seizure numbers was shown with VNS. A study conducted by Spanaki et al.[14] reported that the reduction rate in the number of seizures was 72%. A study conducted in Türkiye showed that 52.9% of patients had a reduction in seizures of more than 50%, while 35.3% had less than 50% reduction.[15] VNS had positive effects not only on seizure frequency but also on seizure duration, seizure severity, and postictal period. In a study of 48 patients, a decrease in seizure or postictal period severity was observed in 19 patients. This situation reveals that in addition to the number of seizures, seizure duration, severity, and postictal period characteristics should be taken into consideration when evaluating efficacy. The McHugh et al.[16] classification is frequently used to measure efficacy according to these criteria. In this practical classification, an 80-100% decrease in seizure frequency is classified as class 1, a 50-80% decrease as class 2, and a decrease below 50% is classified as class 3. An improvement in ictal or postictal activity is marked with suffix A, and its absence is marked with suffix B. Benefits with magnets alone are class 4, and no benefit is observed in class 5. Of the patients, 22.5% (9) were in class 1A, 30% (12) in class 2A, 10% (4) in class 2B, 17.5% (7) in class 3A, 7.5% (3) in class 3B, and 12.5% (5) in class 5 (Figure 1). In other words, a more than 50% decrease in epileptic seizures was observed in 62.5% of the patients, whereas a less than 50% decrease was observed in 25% of the patients. No change was observed in epileptic seizures in 12.5% of the patients.

After implantation, the VNS was adjusted according to the principle of min. side effects and maximum benefit for the patient. The most commonly used working principle is a 30-second operation (VNS on time) and a 5-minute break (VNS off time), and the duty cycle value is 10%. Duty cycle is calculated with the following formula: [on time+2×(2 sec triangular ramps)] / [on time+(off time×60)]×100%. If the patient's seizure control cannot be achieved in the current working order of VNS, the duty cycle value can be increased by shortening the off-time period.[17] The pulse width is usually 500 µs. The current frequency was typically determined to be 30 hertz (Hz). The current intensity can start at 0.25 mA and gradually increase to 3.5 mA. Magnet-induced stimulation is usually 0.25 mA more intense than continuous stimulation.[18] In our clinic, 2 weeks after the implantation surgery, VNS is activated with the VNS output current set at 0.75 mA and the VNS magnet current at 1.00 mA; then, they are increased to 1.00 mA and 1.25 mA, respectively, on the same day. Then, in the following check-ups, battery settings are adjusted according to the patient's seizure control and tolerance. When the VNS settings of the patients we followed in our clinic were examined, the median values of VNS output current and VNS magnet current were determined as between 1.50-1.75 mA, in accordance with the literature. In addition, the median values of the VNS duty cycle, VNS off time (minutes), and VNS on time (seconds) were found to be 5-10 min and 30 s, respectively, in accordance with the literature.

The battery life depends on many parameters. Stimulation settings, magnet usage, and battery model affect battery life. Depending on the battery model used, the period varied between four and twelve years. During follow-up, five of our patients had their VNS batteries depleted and therefore had their batteries replaced.

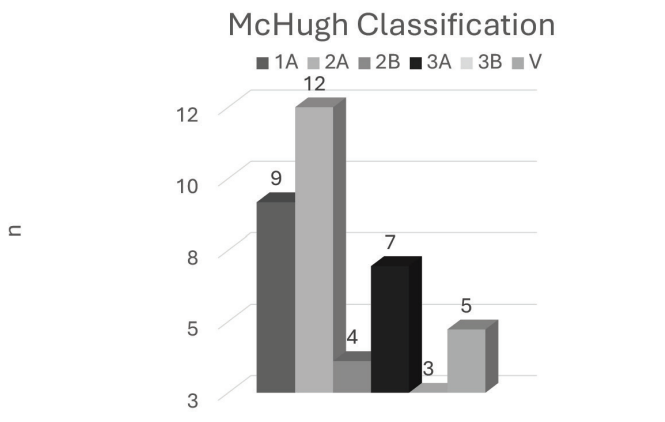

Figure 1. Bar plot for McHugh classification distribution

During implantation, patients may develop intraoperative complications. The most common of these are vocal cord injury, peritracheal hematoma development due to damage to vascular structures, clavicle or esophageal injury, pneumothorax, and vagal nerve injury.[19] VNS implantation was performed in 39 of our patients at our center, and delayed wound healing was observed in 3 patients. No additional surgical complications were noted. The side effects that occur due to stimulation in working VNS include hoarseness, episodes of coughing, paresthesia in the neck region, dyspnea, chest pain, burning sensation in the throat, numbness in the jaw, sore throat, and difficulty swallowing. The cause of cough, hoarseness, and dyspnea is laryngopharyngeal dysfunction due to stimulation of the inferior laryngeal nerve. Side effects, such as earache, headache, weight gain, or weight loss, are less commonly seen due to VNS. While these side effects are more common in the first period of VNS implantation, they are expected to decrease over time. Cardiac arrhythmias are among the complications that can be observed in the long term after VNS implantation. Electrode breakage was the most common complication associated with the equipment used. It usually develops years after surgery because of deformities that form over time. Migration of the electrode from the vagus nerve is also a common equipment-related complication.[9,20] Epilepsy patients who receive VNS can cope with many of the side effects of VNS, and these side effects are tolerable compared to the benefits experienced by the patients. No side effects were observed after VNS implantation in most patients. However, paresthesia was observed in four patients, hoarseness in three patients, dyspnea in two patients, and pain and hypotension episodes in one patient (Figure 2). In our patients, side effects such as paresthesia, hoarseness, dyspnea, and pain were observed in accordance with the literature and were tolerated by the patients. Their effects decreased over time. The use of VNS for blood pressure regulation in patients with resistant hypertension has been investigated recently but remains promising for future development.[20] However, the blood pressure-lowering effect of VNS has been reported in different animal studies.[21,22] In the literature, hypotension is not frequently reported as a side effect in epileptic patients receiving VNS. The hypotension episodes that occurred in our patient were rare.

Although implanted metallic devices are a relative contraindication to magnetic resonance imaging (MRI) scanning, 1.5 or 3.0 Tesla MRI scans can be performed under certain conditions in a patient implanted with a VNS.[23] During the follow-up of 3 of our patients, MRI was required. In these patients, the battery settings were checked and noted before the MRI scan. Subsequently, the patients' VNS settings were set to output current (mA); 0.0, magnet current (mA) 0.0, and MRI scans were performed. After the MRI scan, the patients' battery settings were adjusted to be the same as those before the MRI scan. No side effects or complications occurred in any patient during the procedure.

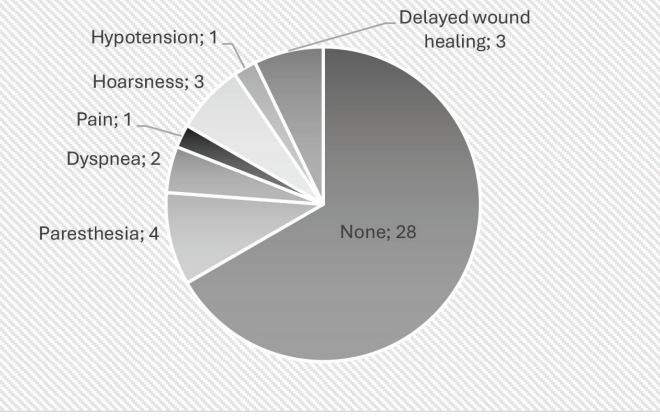

Figure 2. Pie plot for adverse effect distribution

Certain procedures must be performed prior to the planned surgical procedures in patients with VNS implants. It is generally considered safer to deactivate the VNS before elective surgical procedures to avoid possible complications. It is recommended that bipolar electrocautery devices be used instead of monopolar electrocautery devices during surgery. It is also recommended to place the electrosurgical electrodes as far away from the VNS generator and cables as possible.[24] Two of our patients underwent surgery during their follow-up. Before the surgery, the patients' VNS settings were set to output current (mA): 0.0, magnet current (mA): 0.0. In other words, the VNS was deactivated. Electrocautery was avoided if possible during surgery, and if electrocautery was necessary, bipolar electrocautery devices were used. After surgery, the VNS settings were adjusted to match the pre-surgery settings. No side effects or complications occurred in any patient during the procedure.

Polytherapy in pregnant women with DRE may affect maternal and fetal health. However, studies examining the effects of VNS on maternal and fetal health are limited and include small sample sizes. In a mini-review, a total of 44 pregnancies in 38 patients were examined; two pregnancies (2/44, 4.5%) resulted in miscarriage, and congenital malformations in two pregnancies (2/42, 4.8%) were attributed to polytherapy. The rest of the pregnant women reported no postpartum complications or unhealthy fetuses.[25] One of our patients became pregnant during the follow-up period after VNS implantation. The VNS device was monitored openly throughout her pregnancy, and it was turned off during the cesarean section due to the surgical procedure. No complications occurred in our patient or in her baby during or after delivery.

Study Limitations

One of the limitations of this study is the small sample size due to the limited number of patients who underwent VNS implantation. In addition, having our patients were over 18 years of age limited our ability to evaluate the effects of VNS implantation in different age groups.

CONCLUSION

In this study, we investigated the effectiveness of VNS in 40 adult patients were under regular follow-up, and reviewed our VNS experience. VNS, which is widely used in many epilepsy centers with the development of technology and the accumulation of clinical experience, is an effective treatment method for DRE. The frequency and duration of VNS side effects are tolerable for patients.

Ethics

Ethics Committee Approval: Approval was obtained from Muğla Sıtkı Koçman University Faculty of Medicine Clinical Research Ethics Committee (no: 13/XI, date: 07.09.2022).

Informed Consent: Written informed consent was obtained from all participants.

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Footnotes

Author Contributions: Surgical and Medical Practices: İ.Ö., G.G., D.M.Ş., S.B., G.K. Concept: İ.Ö., M.B.Ç., T.A.Ç., G.G., G.K. Design: İ.Ö., E.D., D.M.Ş., F.C.T., S.B., Data Collection or Processing: İ.Ö., M.B.Ç., T.A.Ç., E.D., F.C.T., Analysis or Interpretation: İ.Ö., F.C.T., Literature Search: İ.Ö., M.B.Ç., V.S.B., G.K. Writing: İ.Ö., M.B.Ç., T.A.Ç., E.D., G.G., D.M.Ş., F.C.T., S.B., G.K.

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