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RESEARCH ARTICLE

Prevalence and associated factors of drug-resistant epilepsy in an adult epilepsy population

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Abstract

Introduction: Approximately 65-70% of people with epilepsy respond to their first or second anti-seizure medication, while 15-40% are refractory to pharmacotherapy. Different epilepsy types have varying treatment approaches and prognoses and there could be significant early predictors of drug resistance. Patients with refractory epilepsy experience more adverse effects and diminished quality of life, making prompt identification of this state vital. This study aimed to assess the burden of drug resistance in a cohort of adult epilepsy patients, and compare resistance rates among different seizure types. It also sought to identify early predictors of drug resistance.

Methods: We analysed cross-sectional data from 445 patients with adult-onset epilepsy, categorising participants according to response to therapy to two primary groups: drug-resistant (DR) and adequate response (AR). We further categorised them according to the seizure type and evaluated for possible associated factors such as epilepsy type, febrile seizures, family history, electroencephalogram (EEG) and imaging abnormalities, and adverse events.

Results: The overall drug resistance rate was 36%, with epilepsy with focal motor onset seizures showing the highest rate at 48.4% and epilepsy with generalised non-motor seizures exhibiting zero resistance. Factors associated with higher drug resistance included motor onset seizures ($p=0.003$), positive imaging findings ($p=0.001$), and a history of status epilepticus ($p=0.02$). No significant differences were found regarding focal versus generalised seizures, family history, febrile seizures, or EEG abnormalities. Adverse consequences of seizures were more common in the DR group ($p< 0.001$), and the AR group required significantly fewer medications ($p< 0.00001$).

Conclusions: The study highlights a 36% drug resistance rate in a cohort of adult patients with epilepsy beginning after the age of 12 years. Early identification and tailored management strategies for these high-risk patients based on seizure type and predictors may help to control their epilepsy better.

KEYWORDS

Drug resistant epilepsy, focal onset, generalised onset, motor seizures, non-motor seizures

INTRODUCTION

Epilepsy is a chronic neurological disorder that affects approximately 1% of the global population.[1,2] A community-based study conducted in Sri Lanka in 1987 reported a prevalence rate of 9 per 1,000 people[3]. Despite the wide availability of epilepsy medication, refractory epilepsy is a common phenomenon. Approximately 65 to 70% of individuals with epilepsy respond adequately to their first or second anti-seizure medication.[4] Drug resistance or pharmaco-resistance is one of the important causes of refractory epilepsy and shows variable prevalence in different populations ranging from 15-40%.[5,6,7]

According to the International League Against Epilepsy (ILAE) 2010 classification, "drug-resistant epilepsy" is defined as the failure to achieve seizure freedom after appropriate trials of two or more tolerated first-line anti-epileptic drug regimens, either as monotherapy or in combination. Seizure freedom is characterised as a period without seizures lasting at least three times the longest pre-intervention inter-seizure interval (based on seizures occurring within the last 12 months) or 12 months, whichever is longer.[8] It is crucial to rule out factors such as incorrect diagnoses, inappropriate anti-seizure medication (ASM) choices or dosages, and seizure precipitants before concluding that a patient has drug-resistant epilepsy. Moreover, drug resistance is a dynamic condition, as some epilepsy types can develop resistance over time, such as juvenile myoclonic epilepsy and childhood absence seizures.[9]

Given the variability in treatment approaches and prognoses for different types of epilepsy, accurate identification and classification are essential. Furthermore, certain associated factors such as family history, febrile seizures, etc. might play an important role as predictors of drug resistance.[10] Patients with refractory epilepsy are known to have an increased risk of premature death, injuries, psychosocial dysfunction, and a reduced quality of life, compared to patients with a good response.[11]

Epilepsy surgeries such as lesionectomies, temporal lobe resection, corpus callosotomies, etc. can be promising in certain epilepsy cases and may achieve reasonable seizure freedom after the appropriately planned surgical interventions.[12,13] Therefore, prompt identification and treatment of patients with drug resistant epilepsy are critical.

This study aimed to determine the frequency of drug-resistant epilepsy among a cohort of adults with epilepsy attending the neurology clinics of Teaching Hospital Karapitiya and compare the frequencies among those with different epilepsy types. This study also aimed to describe the associated factors for drug resistant epilepsy.

METHODS

This cross-sectional descriptive study focused on an adult epilepsy population attending the Neurology clinics at Teaching Hospital Karapitiya, Sri Lanka, from June to November 2018. Ethical approval was granted by the Ethical Review Committee of the Faculty of Medicine, University of Ruhuna.

Participants included adult patients diagnosed with epilepsy, who experienced seizure onset at or above the age of 12 and were on stable doses of anti-seizure medication (ASM) for more than 12 months. Exclusion criteria included epilepsy secondary to acquired structural lesions such as head trauma, intracranial haemorrhages, and ongoing metabolic abnormalities, central nervous system (CNS) infections or inflammation, recently diagnosed epilepsy with less than 12 months of treatment, and individuals lacking proper clinical records.

The sample size was calculated to be 442 using the Lwanga Lamshaw formula, with a 99% confidence interval and 5% precision. Due to the absence of local data on drug resistance, a prevalence rate of 21% was adopted based on a study from Singapore that reflects an Asian population.[6] Out of 560 patients screened over six months, 445 were eligible for inclusion. Informed written consent was obtained from all participants after providing a detailed information sheet.

We obtained socio-demographic and relevant clinical data through an interviewer administered questionnaire and previously documented medical records. Seizure semiologies were recorded by direct questioning from the patient and or from eyewitnesses or from previous documentation in the clinic record. Patients with inadequate records or no eyewitness accounts were excluded from the study. This information was utilised to categorise the epilepsy type.

Electroencephalogram (EEG) and imaging findings were obtained by reviewing previous reports or documentation in clinic records. One or more appropriately reported interictal EEGs with or without EEG tracing were considered as adequate for evaluation. All the EEGs were reported by either a consultant neurophysiologist or a senior consultant neurologist. EEGs recorded as epileptiform activity / focal background changes / focal or generalised sharp waves, spikes, spikes and waves were considered positive changes. The seizure semiologies and EEG information were utilised to categorise the epilepsy type.

Either brain magnetic resonance imaging (MRI) (with or without gadolinium) and or contrast enhanced computed tomography (CT) of the brain were required as appropriate brain imaging. All the brain imaging were reported by a consultant radiologist.

Participants were categorised into three groups: “drug-resistant (DR)” and “adequate response (AR),” groups were identified

based on the ILAE criteria of drug-resistant epilepsy.[7] Cases with uncertain treatment responses, such as those with poor compliance, were classified into a third group labelled "uncertain response (UR)." All participants were further subcategorised based on their predominant seizure type according to the position paper of the ILAE commission for classification and terminology of seizures in 2017.[12] Patients with evolving epilepsy syndromes were categorised according to their most recent seizure type.

Groups were divided according to the seizure type, considering the onset as focal versus generalised, then whether the onset being motor or non-motor in each type, considering the first prominent sign or symptom of the seizure. (seizure symptoms considered in the classification were according to the expanded seizure types described in the ILAE 2017 operational classification of seizure types).[12]

Based on the semiological features at onset of seizures, the cohort was devided to have "focal onset motor", "focal onset non-motor", "generalised onset motor" and "generalised onset non-motor" seizures. Seizures which start with focal features and then become were considered as "focal to bilateral tonic-clonic". Patients with uncertain onset of seizures were categorised to the "unclassified" group. Details about awareness were obtained from the patients but not included in the categorisation of seizure types in this study.

Data analysis was performed using SPSS (version 16.0), with descriptive statistics expressed as mean and standard deviation (SD) or median and interquartile range (IQR). Categorical variables were reported as numbers and percentages. Comparisons between groups were conducted using t-tests, with a significance threshold set at $p<0.05$.

The overall prevalence of drug resistance within the entire cohort, as well as among specific epilepsy categories, were calculated. The proportion of patients in the DR group relative to all three groups in each category was reported. Additionally, the association between certain factors (e.g., epilepsy type, febrile seizures, family history, EEG and imaging abnormalities, and the timing of seizures) and drug resistance was evaluated. The occurrence of adverse consequences of seizures as reported by patients in the DR and AR groups was also assessed and compared. The number of current anti-seizure medications used by each individual was obtained and compared between the two groups.

RESULTS

In this study, retrospective data were collected from 445 adult patients diagnosed with epilepsy. The age range of the participants was between 16 and 78 years, with a mean age of 40 years (SD = 15.7). The gender distribution included 240 females (54%) and 205 males (46%). The baseline characteristics of the population are summarized in Table 1.

Classification was done up to the level of seizure type according to the ILAE 2017, multi-level classification and identified; 324 (73%) patients with epilepsies with generalised onset motor seizures, 12 (3%) with generalised onset non motor seizures, 39 (9%) with focal to bilateral tonic clonic seizures, 31 (7%) with focal onset motor seizures, 28 (6%) with focal onset non motor and 11 (2%) with unclassified seizures.

The study revealed a drug resistance rate of 36%, with 57% of patients being responders and 7% classified as having an uncertain state of drug resistance.

Among the different epilepsy subcategories, the epilepsy with focal onset motor seizures group exhibited the highest drug resistance rate at 48.4%. This was followed by the focal to bilateral tonic-clonic seizure group at 41%, epilepsy with generalised onset motor seizures at 36.4%, and unclassified epilepsy at 36.3%. Notably, focal non-motor epilepsy demonstrated a resistance rate of only 25%, while the generalised non-motor epilepsy group showed zero resistance (Figure 1).

In this group, 18.64% of patients reported a positive family history of epilepsy, and 12.83% had experienced febrile seizures in childhood. All participants underwent one or more interictal EEGs after their diagnosis, and 23% exhibited EEG abnormalities at least once. The entire cohort underwent brain imaging with either MRI or contrast CT at least once and only 6.78% had showed abnormalities presumably related to epilepsy.

Chi-square tests of independence was performed to evaluate the relationship between various factors (family history, history of febrile seizures, EEG abnormalities, imaging abnormalities) and drug resistance (Table 2). The analysis showed a significant relationship between positive imaging findings and drug resistance ($p=0.001$), indicating that patients with structural abnormalities were more resistant to medical treatments. Additionally, a history of status epilepticus was positively correlated with drug resistance ($p=0.02$). However, other variables, including family history ($p=0.27$), history of febrile seizures ($p=0.17$), and EEG abnormalities ($p=0.31$), did not show statistically significant relationships with drug resistance.

The Chi-square test also revealed a significant relationship between motor seizures and drug resistance ($p=0.003$), suggesting that epilepsies with motor seizures were more associated with drug resistance compared to epilepsies with non-motor seizures. However, no statistically significant difference was found in the rate of drug resistance among patients with epilepsy with focal onset and generalised onset seizures ($p=0.58$).

TABLE 1 **Baseline characteristics of adults with epilepsy (n=445)**

Character		Total (%)	DR	AR	UR	p value
Mean age (SD)		40 (15.7)	41(14.7)	38 (16.8)	44 (9.7)	0.96
Gender	Male	205 (46%)	71 (44.4%)	121 (47.8%)	13 (40.6%)	0.64
	Female	240 (54%)	89 (55.6%)	132 (55.25%)	19 (59.4%)	
Education	Illiterate	4	4 (2.5%)	0 (0%)	0 (0%)	
	< Grade 8	132	51 (31.9%)	70 (27.7%)	11 (34%)	
	Up to Ordinary Level	216	78 (48.8%)	120 (47.4%)	18 (56%)	
	Up to Advanced Level	84	20 (12.5%)	61 (24.1%)	3 (9.4%)	
	Graduate	9	7 (4.4%)	2 (.8%)	0	
Seizure type	GM	334 (73%)	118 (73.5%)	184 (72.8%)	22 (68.8%)	
	GNM	12 (2.7%)	0 (0)	12 (4.8%)	0 (0)	
	FM	31 (7%)	15 (9.3%)	10 (4%)	6 (18.8%)	
	FNM	28 (6.2%)	7 (4.4%)	21 (8.3%)	0 (0)	
	FBTC	39 (8.7%)	16 (10%)	19 (7.5%)	4 (12.5%)	
	UC	11 (2.4%)	4 (2.5%)	7 (2.8%)	0	
Years since diagnosis mean (SD)		15.1 (12.8)	15.4 (12.8)	14 (12.6)	23 (12.7)	
Timing of seizure occurrence	Day	262 (58.8%)	86 (32.8%)	164 (62.5%)	12 (4.5%)	0.917
	Night	119 (26.7%)	49 (41%)	54 (45.3%)	16 (13.4%)	
	Both	64 (14.3%)	25 (39%)	35 (54.6%)	4 (6.2%)	
Number of anti-seizure medications	1	238 (53.5%)	39 (24%)	171 (67.55%)	28 (87.5%)	<0.0001
	2	137 (30.8%)	69 (43%)	68 (27%)	0	
	>3	70 (15.7%)	52 (32.5%)	14 (5.5%)	4 (12.5%)	<0.0001
Adverse consequences of epilepsy		172 (38.6%)	87 (54.5%)	62 (24.5%)	23 (72%)	<0.0001

GM – Generalised onset Motor, GNM – Generalised onset Non-motor, FM – Focal onset Motor, FNM – Focal onset Non-motor, FBTC – Focal to Bilateral Tonic Clonic, UC – Unclassified

TABLE 2 Comparison of possible predictors for drug resistance

		Total	DR	AR	p value
Family history of epilepsy					0.27
	Present	77 (18.64%)	34 (44.16%)	43 (55.84%)	
	Absent	336	126 (37.5%)	210 (62.5%)	
History of febrile seizures					0.17
	Present	53 (12.83%)	16 (30.19%)	37 (69.81%)	
	Absent	360	144 (40%)	216 (60%)	
EEG abnormalities					0.31
	Present	95 (23%)	41 (43.16%)	54 (56.84%)	
	Absent	318	119 (37.42%)	199 (62.58%)	
Imaging abnormalities					0.001
	Present	28 (6.78%)	19 (67.86%)	9 (32.14%)	
	Absent	385	141 (36.62%)	244 (63.38%)	
History of status epilepticus					0.02
	Present	31 (7.5%)	18 (58.06%)	13 (41.94%)	
	Absent	382	142 (37.17%)	240 (62.83%)	
Seizure onset (focal generalised)					0.58
	Generalised	314 (76%)	118 (37.58%)	196 (62.42%)	
	Focal	88	38 (43.18%)	50 (56.81%)	
Seizure type (motor / non motor)					0.003
	Motor	362 (87.65%)	149 (41.16%)	213 (58.84%)	
	Non motor	40	7 (17.50%)	33 (82.50%)	

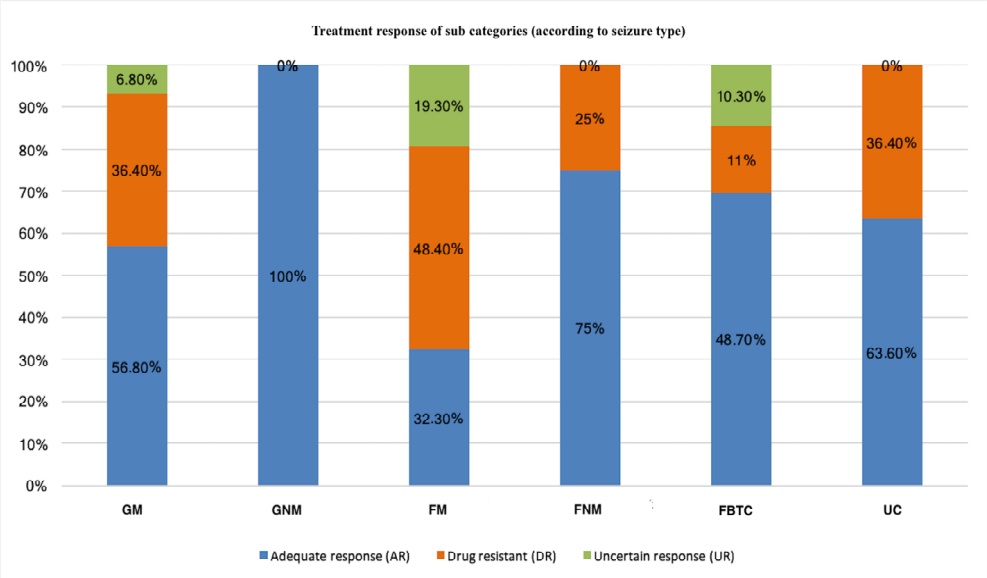

FIGURE 1 Response to treatment among individual subgroups of epilepsy according to seizure type.

GM= generalised onset motor, GNM= generalised onset non motor, FM= focal onset motor, FNM= focal onset non motor, FBTC= focal to bilateral tonic clonic, UC= unclassified, DR= drug resistant, AR= adequate response, UR= uncertain response

Regarding the use of medications, 24% of the drug-resistant (DR) group and 67.5% of the adequate responders (AR) group were using only a single drug. In the DR group, 43% were on two drugs, while 32.5% used three or more drugs; in contrast, only 5.5% of the AR group used three or more drugs, with a significant difference observed between the two groups ($p< 0.00001$).

In terms of adverse effects, 38.6% of the total cohort reported at least one adverse consequence related to their epilepsy. 54.5% of individuals in the DR group and 24.5% in the AR group had experienced one or more adverse consequences. The Chi-square test indicated a significant increase in adverse consequences in the DR group ($p< 0.001$).

DISCUSSION

The primary objective of this study was to assess the burden of drug resistance in epilepsy and to explore its relationship with specific seizure types and other associated factors, aiming to guide the next level of treatment.

We specifically included patients whose first seizure occurred after the age of 12 years. This age cutoff was established to exclude most neonatal onset genetic, metabolic and other childhood developmental and epileptic encephalopathies while including "idiopathic generalised epilepsies" (also known as "genetic generalised epilepsies"). This presumably common entity is known to peak around 14 to 17 years of age, except for childhood absence epilepsy which usually begins before 12 years of age.[16]

Utilising the 2017 International League Against Epilepsy (ILAE) classification of seizure and epilepsy types,[10] we categorised our population into; epilepsies with focal onset motor seizures, focal onset non-motor seizures, generalised onset motor seizures, generalised onset non-motor seizures, focal to bilateral tonic-clonic seizures, combined seizures and unclassified seizures when the semiology is uncertain to decide whether motor versus non-motor or focal versus generalised. We believe these categories are more descriptive and better understandable. According to the ILAE operational task force, this non-hierarchical seizure classification helps to describe the seizure characteristics for better communication in clinical, teaching and research settings.[12] We stopped our classification at seizure level as this aids our analysis which is based on seizure semiology. Establishment of epilepsy syndrome was not attempted due to the limitation of accessing initial data and advanced investigations. Our findings indicated that a significant majority (73%) of our cohort experienced generalised onset motor seizures, whereas generalised onset non-motor and unclassified seizures were seen in only 3% and 2% of the population, respectively.

In contrast to available data, the majority of our cohort had generalized epilepsy. This discrepancy can be attributed to several methodological considerations such as differences in classification methodologies, exclusion of childhood epilepsies, which likely constitute a significant proportion of focal epilepsies, and exclusion of acquired symptomatic epilepsies such as intracranial haemorrhages, space occupying lesions, traumatic brain injuries, large infarcts, previous brain surgeries etc. In addition, limitations in documentation when collecting retrospective data from previous clinic records, patients and eyewitnesses can lead to significant recall and documentation biases. We maintained direct, structured questioning to evaluate focal and generalised seizure symptoms to minimise those biases, but we acknowledge that some information bias can still be present. This possible over rating of epilepsies with generalised onset motor seizures is a potential limitation of our study. To validate our findings, future studies should aim at prospective collection of first-hand and comprehensive data.

Our findings align with existing literature indicating drug resistance rates ranging from 15% to 40%.[10, 15] We observed an overall drug-resistant rate of 36%, with notable variability among epilepsy types, ranging from 0% to 48%. Specifically, epilepsies with focal motor seizures exhibited the highest resistance rate at 48%, followed by epilepsies with focal to bilateral tonic-clonic seizures at 41%. Epilepsies with generalised motor seizures (36.4%) and unclassified epilepsy (36.3%) displayed slightly lower resistance rates, while epilepsies with focal non-motor seizures had a significantly lower rate (25%). Notably, epilepsy with generalised non-motor seizures, particularly absence seizures, showed no instances of drug resistance, suggesting that these patients were likely diagnosed with "Juvenile absence epilepsy" or Childhood absence with late diagnosis. These idiopathic generalised epilepsies are known to respond well to appropriate anti-seizure medication.[16, 17] The highest resistance seen among patients with focal motor seizures suggests potential compatibility with surgical interventions, warranting further evaluation of these patients for possible surgical options.

Moreover, when comparing the two main groups (DR and AR) with similar baseline characteristics, as detailed in Table 1, we identified that motor onset epilepsies were significantly more likely to exhibit drug resistance compared to non-motor types. Furthermore, the presence of structural abnormalities and positive history of status epilepticus were positively correlated with drug resistance. Conversely, factors such as family history of seizures, history of febrile seizures, interictal EEG abnormalities, and the distinction between focal versus generalised onset did not exhibit significant correlations. These findings suggest that EEG abnormalities and family history may not serve as significant predictors of drug resistance in this patient population. Our results are different from existing literature that traditionally considers these factors as significant risk factors for drug-resistance in epilepsy. While the underlying cause of this discrepancy remains unclear, one plausible explanation would be methodological limitations of

our study, such as potential recording bias in previous EEG assessments or inaccuracies in patients' self-reported family history. Further studies with careful EEG assessments and comprehensive history taking would help to clarify this.

This finding indicates that EEG abnormalities and family history may not be as relevant in predicting drug resistance in this population. However, these findings are against the existing knowledge. We are not certain about the reason for this discrepancy. One possibility is reporting bias of previously recorded EEGs and patients' provision of the history.

All participants in the study underwent either contrast-enhanced CT, MRI, or both at various stages of their epilepsy. Notably, 6.8% of the population exhibited imaging abnormalities, that are likely to be epileptogenic. Among the 28 patients with abnormal imaging, seven underwent MRI with epilepsy protocol while the remaining patients received a standard MRI brain protocol. The abnormalities identified included mesial temporal sclerosis, focal cortical dysplasia, and congenital malformations. However, only a limited number of patients were subjected to an MRI using a dedicated epilepsy protocol in this cohort. We believe that dedicated epilepsy MRI would have significantly enhanced the detection of structural abnormalities associated with epilepsy, which was a limitation of this study.

Furthermore, we observed a significant increase in adverse consequences associated with epilepsy, including major injuries resulting from seizures, emotional or psychological challenges, and learning difficulties such as frequent school absences and disturbed study patterns to avoid seizure precipitation in the DR group compared to the AR group ($p<0.001$). Here we only considered symptoms subjectively reported by patients and their families. Acknowledging the patient's perception of adverse effects are significant, we did not perform objective assessments in this study. Learning difficulties and psychological issues were directly related to seizures and long-term complications like learning disabilities and severe depression were not included in our analysis.

The DR group also demonstrated a markedly higher requirement for polypharmacy, with a substantial portion using three or more medications, while only a minor fraction of the AR group required a third medication ($p<0.00001$). This highlights the limited efficacy of adding third drugs for effective seizure control. A percentage of 24% of the DR group who are still on a single medication had been switched to the current medication due to complete failure of one or two medications before.

We used the latest multi-level classification of epilepsy proposed by the ILAE in 2017 to categorise our cohort based on seizure type. We find this classification to be more descriptive and useful in clinical practice. It also helped us to categorise them based on certain seizure semiological characteristics. However, we did not attempt to categorise patients further into epilepsy types or syndromes due to information bias inherent in this retrospective analysis of a long-standing disease and also limited access to prolonged EEGs and monitoring facilities and advanced imaging investigations. Despite an adequate sample size, the patient numbers within certain subcategories of epilepsy were limited, thus limiting the generalisability of our findings.

CONCLUSION

Our study population, primarily consisting of adults with generalised onset motor seizures, exhibited a 36% prevalence of drug resistance. Notably, there was considerable variability in drug resistance rates among epilepsies with different seizure types, with epilepsy with focal motor seizures exhibiting the highest rates, and focal non-motor seizures demonstrating no cases of drug resistance. The findings indicate a significant association between drug resistance and factors such as motor seizures, structural abnormalities in imaging studies, and a history of status epilepticus. Conversely, factors like family history of epilepsy, interictal EEG abnormalities, and febrile seizures did not show a correlation with drug resistance in this study. Moreover, patients in the drug-resistant (DR) group experienced a greater burden of adverse consequences of epilepsy compared to those in the adequately responsive (AR) group. The low utilisation of a third anti-seizure medication in the AR group suggests limited efficacy in controlling seizures with additional pharmacotherapy. To enhance our understanding of this patient population, future research should focus on evaluation of potential surgical interventions, management of comorbid conditions, and deeper investigation into specific subcategories of epilepsy. Conducting studies with larger sample sizes across various epilepsy groups would provide invaluable insights and contribute to more effective treatment strategies.

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