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REVIEW ARTICLE **OPEN ACCESS**

FACTORS INFLUENCING THE INCIDENCE OF REFRACTORY EPILEPSY: A SCOPING REVIEW

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ABSTRACT

Background: Epilepsy affects around 50 million people worldwide, with an incidence of 100 cases per 100,000 people annually in developing countries where access to adequate treatment is limited. Refractory epilepsy occurs in 20-40% of cases of patients whose seizures remain uncontrolled despite 1-2 years of adequate anti-seizure medication (ASM) therapy with good adherence. This condition poses significant challenges for management.
Objective: This scoping review aimed to systematically identify the factors associated with refractory epilepsy.
Methods: A scoping review was conducted in accordance with the PRISMA-ScR guidelines and the PEO/PET framework. A systematic PubMed search identified studies published between 2020 and 2025 on factors influencing refractory epilepsy. Eligible studies underwent a three-phase screening process (title, abstract, and full-text review).
Results: Twenty studies met the inclusion criteria, comprising seven review articles and thirteen clinical studies, most of which were observational. Recurrent associations between refractory epilepsy and several factors were identified, such as one large cohort of 5,794 patients reporting seizure onset within the first year of life to be the strongest predictor of refractory epilepsy, while another study showed that structural etiology increased the odds more than threefold (OR 3.47; 95% CI: 1.15-10.43). Psychiatric comorbidities, developmental delay, abnormal EEG or neuroimaging findings, and systemic contributors such as inflammation and metabolic disorders were also found to be commonly associated with refractory epilepsy.
Conclusion: The most frequently reported factors for developing refractory epilepsy across studies were younger age at first seizure, structural etiology, and genetic factors.

Keywords: DRE, drug-resistant epilepsy, refractory epilepsy, risk factors

Introduction

Epilepsy is a chronic neurological disorder affecting approximately 50 million individuals worldwide across all ages.[35] The incidence of epilepsy amounts to 100 cases per 100,000 people annually in developing countries where access to adequate treatment is limited.[18] The International League Against Epilepsy defines drug-resistant epilepsy (DRE) as failure of adequate trials of two tolerated and appropriately chosen and used anti-seizure medication (ASM) schedules (as monotherapies or in combination) to achieve sustained seizure freedom. DRE is often used interchangeably with medically refractory, medically intractable, or pharmacoresistant epilepsy. This scoping review uses “refractory epilepsy” as the primary term. The prevalence of refractory epilepsy has been estimated at 1.36 per 1,000 individuals in Western Europe. Among these patients, approximately 32% experience more than one seizure

per week.[32] Approximately one-third of people with epilepsy suffer from refractory epilepsy.[1]

Treatment failure in epilepsy can result in significant adverse effects, including increased risks of psychosocial, psychiatric, and medical morbidity, as well as a poorer quality of life. Epilepsy is a progressive condition that causes damage to the central nervous system, contributes to additional comorbidities such as fractures and head injuries, and elevates mortality risk (including suicide, accidents, and sudden unexpected death in epilepsy). Furthermore, psychological disorders (such as depression and anxiety), social stigma, driving restrictions, and occupational consequences often accompany the condition.[2]

The risk factors associated with refractory epilepsy are varied, with modifiable and non-modifiable factors. These include: mental retardation, neurological abnormalities, younger onset age, symptomatic etiology, high-frequency seizures, non-response to the initial drugs, and abnormal electroencephalography (EEG) findings. These include: (1) mental retardation; (2) neurological abnormalities; (3) younger onset age; (4) symptomatic etiology; (5) high-frequency seizures; (6) non-response to the initial drugs; and (7) abnormal electroencephalography (EEG) findings.[1] Additional factors that may be linked to treatment failure include abnormalities in brain imaging, the presence of neuropsychiatric comorbidities, intellectual disability, early seizure onset, status epilepticus (SE), and abnormalities on electroencephalography (EEG).[11] Recent advancements in neuroimaging and genetic research have also introduced new insights, such as the role of specific biomarkers and genetic mutations (e.g., SCN1A), which can predict treatment response and guide personalized management strategies, including the consideration of surgical options.[33]

Although many studies have examined risk factors for refractory epilepsy, the available evidence is still dispersed across varying designs, populations, and underlying causes. An updated and comprehensive synthesis is required to clarify the most relevant determinants. Accordingly, this scoping review seeks to identify and integrate recent findings on factors associated with refractory epilepsy, offering a consolidated perspective to guide clinical practice and reveal key gaps for future research.

Methods

Selection Criteria

This scoping review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) guidelines.[30] The research question in this review was developed using the PEO or PET framework, as outlined below:

Table 1. PEO or PET for Research Literature

P (Population)	E (Exposure)	O (Outcomes)/T (Themes)
People with epilepsy	Risk factors	Refractory epilepsy

Based on the PEO/PET framework above, the scoping review question that arises is as follows: What factors influence the incidence of refractory epilepsy? The following inclusion criteria were applied: (1) research articles investigating factors, both protective and risk factors, influencing refractory epilepsy; (2) published in English and available in full-text; (3) study designs including primary research articles such as randomized controlled trials (RCTs), observational studies (e.g., cohort, case-control, cross-sectional), and clinical trials. Review articles were also included to provide a broad synthesis of the literature, and were categorized separately; (4) articles sourced from the PubMed database; (5) studies published within the last five years. The following exclusion criteria were applied: (1) study designs including opinion papers, systematic reviews, meta-analyses, scoping reviews, narrative reviews, and case reports; (2) studies not reporting factors related to refractory epilepsy. Although no formal risk-of-bias evaluation was conducted, the quality of the included studies was assessed narratively, considering their design, sample size, and transparency of reporting.

Search Strategy

A comprehensive search was conducted in the PubMed MEDLINE database (National Library of Medicine) using the inclusion criteria and Boolean operators "AND/OR." Keywords used included: refractory epilepsy, drug-resistant epilepsy, treatment- resistant epilepsy, intractable epilepsy, factors, influences, determinants, variables, seizure, epileptic, convulsion, attack, etiology, causes, pathophysiology, risk factors, treatment, management, therapy, and intervention.

Study Selection and Data Extraction

The articles were reviewed upon eligibility assessment according to the three-phase procedure: (1) title, (2) abstract, and (3) full-text analysis (Figure 1). All three phases were performed independently by two reviewers (N and K.A.F), with a high inter-rater agreement (Cohen's kappa = 0.93). Disagreements were resolved through discussion with a predetermined third reviewer (S.D.P). The following data were extracted from each included

study: (1) first author and year; (2) study information (study design and sample size); (3) patient demographics (age); (4) type and classification of epilepsy; (5) factors influencing refractory epilepsy; (6) etiology. These extracted data were reported in Tables 2 and 3. When information was not directly stated, variables were inferred from careful examination of the manuscript.

Result

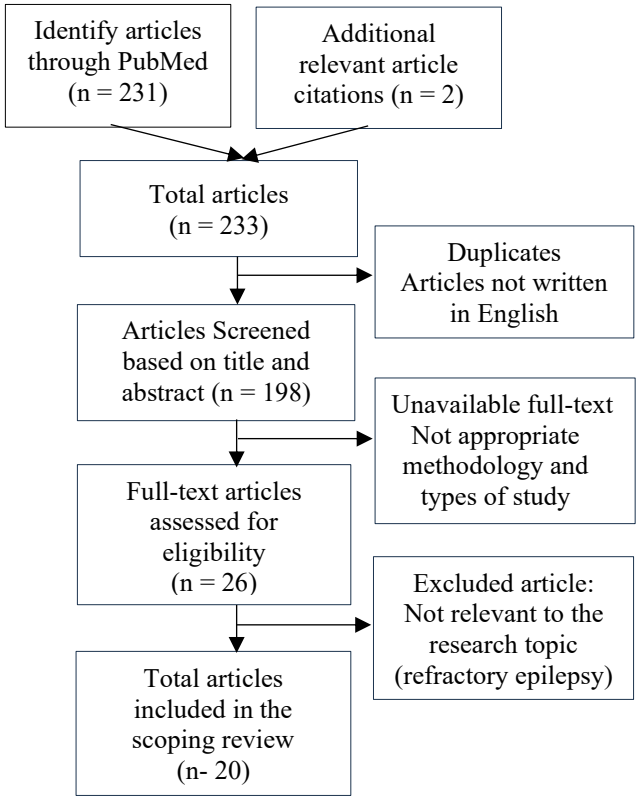

Figure 1. PRISMA-ScR Flow Diagram

This scoping review included twenty studies, of which seven were review articles discussing risk factors for refractory epilepsy in various populations (Table 2). Neuroinflammation, blood-brain barrier (BBB) dysfunction, and immune system disorders are the main causes of refractory epilepsy. Damage to the BBB can worsen epilepsy through the upregulation of P-glycoprotein (P-gp) in brain blood vessels, which then increases inflammatory mediators. This inflammatory response, triggered by cytokines and other neuromodulatory molecules, leads to neural hyperexcitability. Genetic factors, such as polymorphisms of RAGE (Receptor for Advanced Glycation End Products) and interleukin-1β (IL-1β), also contribute to the development of refractory epilepsy.[6]

The prevalence of obesity and metabolic syndrome in epilepsy patients and their responses to ASM. Results showed that obesity and metabolic syndrome are associated with refractory epilepsy across all age groups. Obesity was also commonly observed in patients on polypharmacy regimens, suggesting poorer seizure control. This may be due to metabolic disorders, such as mitochondrial dysfunction and leptin deficiency, which can impair the absorption of ASM.[25]

Another study discussed risk factors for refractory epilepsy in patients with Tuberous Sclerosis Complex (TSC). Clinically, several associated factors were highlighted, including age at first seizure, seizure type, genetics, EEG results, and Magnetic Resonance Imaging (MRI) findings. Focal seizures and infantile spasms were the strongest predictors of refractory epilepsy. The TSC2 gene variant was associated with higher MRI lesion load and predicted more severe epilepsy and increased risk for refractory epilepsy. EEG findings with interictal focal and multifocal discharges were also risk factors for refractory epilepsy.[29]

Focal Cortical Dysplasia (FCD) and its pathogenesis leading to clinical refractory epilepsy. FCD is noted as a primary cause of refractory epilepsy in children, with seizures caused by this etiology being highly difficult to control, often requiring surgical therapy as the primary option. Several risk factors for this condition were identified, including early age of seizure onset, MRI abnormalities, and poor initial response to ASM. Non-pharmacologic therapies such as ketogenic diet and molecular treatments such as mTOR inhibitors (e.g., everolimus and rapamycin) may help control seizures and improve prognosis in FCD patients.[27]

The potential of ketamine for epilepsy management and highlighted Anti-NMDA receptor encephalitis (anti-NMDAR encephalitis) as a potential etiology of refractory epilepsy. This autoimmune condition results in ultra-refractory epilepsy in nearly 50% of cases, defined as seizures that persist despite multiple interventions, including ASM, surgery, and neurostimulation. Ketamine may be a therapeutic option for such cases as it helps restore excitatory-inhibitory balance in the brain, crucial for normal neuronal function. Acting on the N-methyl-D-aspartate receptor (NMDAR) and through other mechanisms, ketamine modulates neuronal excitation, reduces excessive neural synchrony, and combats epileptic seizures, strengthening its potential as a promising treatment, especially for patients unresponsive to conventional ASM.[30]

Elevated glutamate and reduced GABA levels to contribute to tumor-related epilepsy. Molecular markers such as IDH1/2 mutations, 1p/19q codeletion, MGMT promoter methylation, and BRAF V600E mutations were associated with poor seizure outcomes post-surgery.[10,19] The potential of the ketogenic diet in treating epilepsy as it may reduce seizures by improving dysbiosis, an imbalance in the gut microbiota involved in the pathogenesis of refractory epilepsy. Rare gut flora was more prevalent in people with refractory epilepsy, suggesting that gut microbiota restoration could serve as an alternative therapy. The ketogenic diet likely has diverse anticonvulsant mechanisms depending on epilepsy type.[32] This scoping review included twenty studies, thirteen studies were identified that discuss the risk factors influencing the occurrence of refractory epilepsy from different populations (Table 3), and from these studies, the prevalence of refractory epilepsy ranged from 20% to 53% within the studied populations, reinforcing the clinical significance of this condition.

Psychiatric comorbidities and developmental delay were strongly associated with forced normalization, thus associated with refractory epilepsy.[8] This is consistent with previous findings that developmental delay is linked to the incidence of refractory epilepsy.[15] Psychiatric comorbidities such as behavioral disorders, depression, and anxiety also show a strong association with refractory epilepsy.[2] The risk factors for sudden unexpected death in epilepsy (SUDEP) during the COVID-19 pandemic have been investigated. Findings indicated that age, triple therapy, non-compliance, and anxiolytic use were associated with increased seizure frequency. Other COVID-19 lockdown-related factors contributing to uncontrolled seizures included delayed epilepsy surgery, non-compliance with medication, and psychiatric comorbidities.[21]

The 2021 study by Gasparini et al.[12] found that SE was independently associated with age at seizure onset, female gender, and etiology. The study was conducted on 1,115 patients with seizure onset after age 18. As recurrence of SE was associated with an increased number of anti-seizure medications (ASMs) used, the study suggested that the number of ASMs taken could serve as an indirect marker of drug resistance. Although literature on the association between SE and refractory epilepsy is heterogeneous, Yuan et al.[36] found that a history of epilepsy, structural cortical abnormalities on neuroimaging, and SE duration are predictors of drug resistance after the first SE episode. These factors are also known as independent predictors of drug resistance, aside from SE. The efficacy and tolerability of Brivaracetam (BRV) as adjunct therapy in children with refractory epilepsy have been investigated. Age at seizure onset and epilepsy duration before BRV administration were found to be statistically significant independent predictors of seizure frequency in refractory epilepsy patients. Thus, regardless of BRV use, these variables were considered influential factors for refractory epilepsy.[28] This finding aligns with previous reports indicating that poor response to initial pharmacotherapy is an early risk factor for drug resistance.[4] Long disease duration increases the risk of drug resistance and polypharmacy.[3]

The factors influencing post-surgical outcomes in epilepsy and their predictors have been investigated. Outcomes were categorized as good, controlled, or poor, with poor defined as seizure recurrence and increased disease severity after surgery. Clinical factors associated with poor outcomes were assessed at two time points: immediately after surgery and at the last visit before discharge. At the first time point, developmental epileptic encephalopathy, etiology, and genetics were statistically associated with poor post-operative outcomes, with etiology being the strongest factor. At the second time point, age at first seizure, genetics, developmental epileptic encephalopathy, and etiology were also statistically significant factors.[26]

Outcomes of Radiofrequency Thermocoagulation (RFTC) as a treatment for refractory focal epilepsy have been assessed, revealing that positive MRI findings and etiology were statistically significantly correlated with patient outcomes of seizure freedom rate and response rate. In this context, a positive MRI was defined as the presence of focal lesions on brain MRI.[20] A 2015 study by Meguins et al.[23] found that the cause of refractory epilepsy in patients having undergone gross-total resection of temporal low-grade gliomas was the etiology itself: low-grade temporal glioma. Other factors associated with seizure occurrence included early intervention, total resection, a short seizure history, and seizure frequency. The researchers believed that wider tumor resection reduced epileptogenic substances secreted by the tumor, such as glutamate, thereby lowering seizure occurrences.

A total of 5,794 epilepsy patients were studied in France, with 53% categorized as refractory

providing a broad overview of the characteristics of the individual with this condition. The study found that age at first seizure onset, especially within the first year of life, was the strongest risk factor for developing refractory epilepsy. Additionally, inborn errors of metabolism and progressive myoclonic epilepsy were associated with poor seizure control outcomes. Among focal structural epilepsy etiologies, cortical developmental malformations posed a higher risk of becoming refractory, although other studies found temporal lobe epilepsy associated with hippocampal sclerosis to be the least responsive to antiepileptic drugs.[9] Evaluating prognostic tools and scoring systems for status epilepticus such as the Status Epilepticus Severity Score (STESS) and the Epidemiology-based Mortality Score in Status Epilepticus (EMSE) has been a key clinical focus. The results showed that all scoring systems examined had low accuracy in predicting refractory epilepsy.[5,13]

Risk factors for refractory epilepsy in TSC patients treated with rapamycin have been evaluated using a sample of 108 patients, where 53 had controlled seizures and 55 were categorized as refractory. Among the refractory group, statistical analysis identified cerebral parenchymal calcification as a risk factor.[36] Miszewska et al.[24] reported similar findings, noting that TSC2 gene mutations, infantile spasms, and the number of cortical calcifications were associated with a higher risk of refractory epilepsy in TSC patients. The quasi-experimental study by Gorjipour et al.[14] explored the role of chronic inflammation in causing refractory epilepsy and whether a hypoallergenic diet could help address this by reducing seizure frequency. The study included 34 patients under 16 years old, with the inclusion criteria being idiopathic refractory seizures and non-IgE-mediated food allergies. The study found a significant reduction in seizure frequency ($p < 0.001$) in this population, suggesting that chronic inflammation plays a role in the pathogenesis of refractory epilepsy in specific populations.[14] Systemic inflammation could induce neuroinflammatory responses, which impact seizure susceptibility in both the short and long term. Proinflammatory cytokines such as IL-1β, IL-6, and TNF-α are involved in this process.[7]

Effectiveness and side effects of ketogenic diet therapy over the course of 2 years in pediatric patients, most of whom had refractory epilepsy, with the most prevalent etiologies being metabolic disorders have been identified. The results showed that etiology played an important role in refractory epilepsy. In the metabolic etiology subgroup, 90% of patients were seizure-free by the second year of treatment.[16]

Finally, the cross-sectional study by Marouf et al.[21] found that significant risk factors for refractory epilepsy included male gender (OR: 5.409; CI: 1.661–17.617; $p < 0.005$), generalized tonic-clonic seizures (GTC) (OR: 4.187; CI: 1.304–13.445; $p < 0.016$), no change in seizure frequency after ASM use (OR: 4.465; CI: 1.211–16.468; $p < 0.025$), poor response to the first ASM (OR: 9.000; CI: 2.437–33.244; $p < 0.001$), developmental delay (OR: 10.612; CI: 1.347–83.589; $p < 0.025$), presence of neurological deficits (OR: 4.227; CI: 1.145–15.601; $p < 0.030$), generalized epilepsy (OR: 3.886; CI: 1.141–13.233; $p < 0.030$), structural etiology (OR: 3.467; CI: 1.152–10.431; $p < 0.027$), abnormal EEG findings (OR: 3.467; CI: 1.152–10.431; $p < 0.027$), focal EEG activity (OR: 5.344; CI: 1.155–24.713; $p < 0.032$), and abnormal imaging findings (OR: 3.524; CI: 1.083–11.473; $p < 0.036$). For instance, an OR indicates that individuals with these risk factors are more likely to develop refractory epilepsy compared to other etiologies, underscoring its clinical significance. Multivariate logistic regression revealed that lack of change in seizure frequency after ASM use and poor response to the first ASM were independent predictors, while older age at first seizure was found to be protective. Thus, it was found that risk factors for refractory epilepsy include younger age at epilepsy onset, unchanged seizure frequency after ASM use, and poor response to the first ASM. This indicates that these factors are strongly associated with treatment failure.[21]

Table 2. Review Studies

Authors, Year (References)	Study Design	Population	Factors	Findings
Campos-Bedolla 2022[6]	Critical Review	Refractory epilepsy	Chronic Inflammatory Process	Genetic factors such as polymorphisms in the receptor for advanced glycation end products (RAGE) and interleukin-1β contribute to the occurrence of refractory epilepsy.
Nazish Saima 2023[24]	Article Review	Refractory epilepsy	Metabolic Disorders	Obesity and metabolic syndrome are associated with refractory epilepsy across all age groups.
Specchio 2023[28]	Article Review	Refractory epilepsy	Structural, Age, Genetic	Age at first seizure, seizure type, genetic factors, EEG results, and MRI findings are associated with refractory epilepsy.
Rodrigo 2024[26]	Article Review	TSC; Refractory epilepsy; FCD	Structural, Age	Early age at seizure onset, MRI abnormalities, and poor initial response to medication are risk factors for refractory epilepsy.
Tan 2024[29]	Article Review	Refractory epilepsy	Etiology (NMDAR)	Anti-NMDAR encephalitis is a primary cause of ultra-refractory epilepsy, thus requiring various interventions beyond standard AEDs.
Erturk Cetin 2017[10]	Article Review	Brain Tumor	Structural, Genetic	Tumor histology, tumor location, genetics, and the integrity of the blood–brain barrier (BBB) are associated with poor seizure outcomes.
Ulamek-Koziol 2019[31]	Article Review	Refractory epilepsy	Dysbiosis	Gut microbiota imbalance can influence the occurrence of refractory epilepsy.

Table 3. Research Studies

Author, Year (References)	Study Design	Population	Mean Age	Type of Epilepsy	Etiology	Findings
Carazo 2020[8]	Observational Retrospective	10 patients with psychiatric comorbidities	52 years	Focal and Generalized	HIE, LGS, MTS, Cortical Dysplasia, ME, Post-traumatic	Patients with psychiatric comorbidities and developmental disorders have a statistically significant correlation with refractory epilepsy.
Magdy 2021[20]	Cross-sectional	340 patients	30 years	Focal and Generalized	Any	Increased seizure frequency is associated with age, triple-therapy administration, and anti-anxiety medication. In relation to the COVID-19 lockdown, delayed surgery, poor medication adherence, and psychiatric comorbidities were among the causes of refractory epilepsy in the studied population.
Gasparini 2021[12]	Observational Retrospective	1115 patients with SE	52 years	Focal and Generalized	Idiopathic, Vascular, Genetic, Autoimmune, Infection, Malformation, Post-traumatic	Recurrence of SE is associated with the number of ASM taken. The study found that the number of ASM consumed is an indirect marker of drug resistance.
Russo 2022[27]	Observational Retrospective	45 refractory epilepsy patients	12.4 years	Focal and Generalized	Structural, Genetic	Age at seizure onset and epilepsy duration are independent markers of seizure frequency in people with refractory epilepsy. Therefore, with or without BRV administration, these variables are influential factors for refractory epilepsy.

Table 3. Research Studies

Author, Year (References)	Study Design	Population	Mean Age	Type of Epilepsy	Etiology	Findings
Oshino 2023[25]	Observational Retrospective	92 postoperative refractory epilepsy patients	7 years	Focal and Generalized	Malformation, Non-lesional epilepsy, Tumor, TLE, Inflammation	Factors influencing poor outcomes were assessed immediately post-surgery and at the final visit before discharge. Developmental epileptic encephalopathy, etiology, and genetics were statistically significant at the first timepoint, while age at first seizure, genetics, developmental epileptic encephalopathy, and etiology were significant at the second.
Liu 2024[1]	Observational Retrospective	82 patients	23 years	Focal and Generalized	Undefined, Malformation, HS, Tumor, Trauma, Encephalitis, HIE	Positive MRI findings and etiology were statistically correlated with seizure freedom and treatment response rate.
Meguins 2015[23]	Observational Retrospective	65 patients with temporal LGG	26 years	Focal and Generalized	Tumor	Etiology, early intervention, total resection, short seizure duration history, and seizure frequency were associated with seizure outcomes in this study.
Chipaux 2016[9]	Cross-sectional	5794 refractory epilepsy patients	18 years	Focal and Generalized	Vascular, TSC, Genetic, FCD, HS, Metabolic, Tumor	Age at first seizure onset, particularly within the first year of life, is the highest risk factor for developing refractory epilepsy. Additionally, inborn errors of metabolism and progressive myoclonic epilepsy are known to have poor seizure control prognoses.
Giovannini 2017[13]	Observational Retrospective	162 patients with SE	70 years	Focal and Generalized	Vascular, Tumor, Hypoxia/Anoxia, Others	All scoring systems explored had low accuracy in predicting refractory epilepsy.
Zhang 2018[36]	Observational Retrospective	108 patients with TSC	2 years	Focal and Generalized	TSC	Patients with brain parenchymal calcification lesions were at increased risk of developing refractory epilepsy in this study.
Gorjipour 2019[14]	Clinical trial Quasi Experimental	34 patients	3 months–16 years	Focal and Generalized	Non-IgE Mediated Food Allergy	Chronic inflammation in patients with food allergies contributes to the development of refractory epilepsy in certain populations.
Herrero 2020[16]	Observational Retrospective	26 patients	<18 years	Focal and Generalized	Metabolic, Structural, Genetic, Infection	Etiology plays a role in refractory epilepsy, with 90% of patients with metabolic etiology achieving seizure freedom when appropriately treated with the ketogenic diet.
Marouf 2023[21]	Cross-sectional	90 patients	35 years	Focal and Generalized	Structural, Metabolic, Unknown, Genetic	Risk factors for refractory epilepsy include young age at epilepsy onset, no change in seizure frequency after antisezure medication use, and poor response to the first antisezure medication.

LGG: Low Grade Glioma; SE: Status Epilepticus; HIE: Hypoxic-Ischemic Encephalopathy; LGS: Lennox-Gastaut Syndrome; MTS: Mesial Temporal Sclerosis; HS: Hippocampal Sclerosis; ME: Meningoenchepalitis; TLE: Temporal Lobe Epilepsy; TSC: Tuberous Sclerosis Complex; FCD: Focal Cortical Dysplasia; IgE: Immunoglobulin

Discussion

This scoping review aimed to identify factors contributing to refractory epilepsy. These factors largely depend on the primary etiology of the seizures, as demonstrated in various conditions such as TSC, Focal Cortical Dysplasia, brain tumors, and Anti-NMDAR encephalitis.[10,27,29,30] One modifiable aspect in the management of epilepsy pertains to obesity and metabolic syndrome. Seizure control is more easily achieved in patients with a body mass index that falls within the normal range, which underlies the rationale for using a ketogenic diet in seizure management.[6] The role of dysbiosis in the pathogenesis of refractory epilepsy has been identified, wherein obese patients are more susceptible to dysbiosis, thereby increasing the risk of developing refractory epilepsy.[32]

Furthermore, age at first seizure was the most frequently studied factor. Early onset seizure, especially within the first year of life, is the strongest risk factor for developing refractory epilepsy.[9] Similar findings have identified a younger age at first seizure as major predictor of pharmacoresistance.[12,21,26,22,28] Early-life seizures can impair brain development. Failure of nonpruning synaptic processes may result in an excess of gap junctions; seizure-related pruning failure leads to the persistence of excessive excitatory synapses that may have pathophysiological effects analogous to the formation of aberrant connections in adult epilepsy.[18]

Structural etiology is another factor of refractory epilepsy that was found in several included studies. Patient etiology was statistically significant in the occurrence of refractory epilepsy. In the study, 53% of the intractable epilepsy group had a structural etiology, compared to 23% in the control group.[22] Focal structural epilepsy and cortical malformations are associated with higher risks of becoming refractory. [9] Similar conclusions were drawn in multiple studies where structural etiology was a significant influencing factor.[12,23,26,37] In contrast, a study of effectiveness on the ketogenic diet in people with refractory epilepsy found that populations with structural etiologies were harder to treat compared to other etiologies. In their study, only 40% of patients with structural etiology were seizure-free in the second year of therapy, while other etiologies achieved seizure-free rates of 75–90%.[16] Structural abnormalities cause permanent changes in the brain, especially affecting the electrical circuitry involved in seizures. Disruptions to normal brain electrical activity can create epileptogenic zones; areas where seizures originate and rapidly spread. These zones can evolve into more complex electrical circuits over time.[4] Antiepileptic drugs are less effective in these populations due to anatomical abnormalities, neuronal malformations, and inflammation that can interfere with medication efficacy.[19]

Genetics plays a role in the occurrence of refractory epilepsy, with specific mutations significantly influencing its incidence. For instance, mutations in the TSC2 gene have been shown to impact refractory outcomes, a view shared across various study populations.[16,26,37] Genetic factors are typically associated with diseases that cause global brain dysfunction, such as Dravet syndrome (SCN1A gene mutation), Lennox-Gastaut syndrome (LGS), and KCNQ2 encephalopathy, which reduce the effectiveness of ASM and often make surgical therapy unfeasible. Certain gene mutations may also decrease ASM effectiveness by disrupting receptors related to these medications, making targeted treatments such as Stiripentol or Everolimus necessary to manage the condition.[34]

This review highlights key clinical implications. Identifying high-risk patients at an early stage, for example, infants with early seizure onset or individuals with structural etiologies, is vital to enable comprehensive treatment, which may include dietary therapies such as the ketogenic diet or surgical assessment. Moreover, a better understanding of genetic contributions could facilitate precision medicine strategies by aligning treatment with specific pathophysiological mechanisms. Beyond these clinical and genetic considerations, evidence from studies on food allergies and metabolic disorders points to a role of inflammation, indicating that systemic and environmental factors should be incorporated into treatment planning. In addition, the association between genetic mutations and treatment resistance underscores the importance of genetic screening in patients with early-onset or refractory seizures.

Limitations of this scoping review that should be considered include how most studies utilized observational and retrospective designs, which hampers the ability to establish clear causal relationships between identified factors and refractory epilepsy. Strengthening the evidence will require more diverse and prospective approaches, particularly longitudinal cohort studies, to follow patients from diagnosis and clarify the natural history of the disease. In addition to this, several studies did not have the primary aim of identifying risk factors for refractory epilepsy, and the data provided were limited to the literature review sections. Finally, the study populations of the studies were often very general, resulting in findings that lack specificity. Several of the

aforementioned studies have identified various factors that may influence the occurrence of refractory epilepsy. Understanding these factors is important for determining subsequent management strategies and prognosis in patients. However, further research with more diverse samples is needed to identify additional risk factors related to prognosis.

Conclusion

This scoping review confirms that factors such as younger age at first seizure, structural etiology, and genetic factors are the most consistently identified determinants of refractory epilepsy. Although these factors form a solid basis for risk stratification, inconsistencies in the current evidence emphasize the need for standardized, longitudinal research. Future research should focus on genetic contributions and longitudinal cohorts to validate modifiable factors across diverse populations.

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