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Risk Factors For Recurrence In Epilepsy Patients

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ABSTRACT

Epilepsy is a chronic neurological disorder characterized by recurrent seizures resulting from abnormal electrical activity in the brain. It remains a significant global health concern, particularly in low- and middle-income countries (LMICs). The recurrence of seizures in patients with epilepsy is influenced by multiple clinical and nonclinical factors involved in epileptogenesis. This literature review aims to summarize the risk factors for recurrent seizures in patients with epilepsy based on recent scientific evidence. The literature was obtained from PubMed, Google Scholar, and manual searches and included articles published in English and Indonesian between 2010 and 2026. The study designs included meta-analyses, systematic reviews, cohort studies, case-control studies, cross-sectional studies, and case reports. The findings indicate that seizure recurrence is associated with the etiology of epilepsy (structural, genetic, infectious, metabolic, immunological, and idiopathic), as well as with lifestyle and behavioral factors such as sleep deprivation, psychological stress, alcohol consumption, smoking, and non-adherence to antiepileptic drugs. Abnormal MRI findings also increase the risk of disease recurrence. Furthermore, neuroinflammatory mechanisms, particularly microglial activation and proinflammatory cytokine release, contribute to increased neuronal excitability. In conclusion, recurrent seizures in epilepsy result from complex interactions among biological, clinical, and behavioral factors. Early identification and management of these risk factors are essential to reduce seizure recurrence and improve the quality of life of patients.

Keywords

Epilepsy, Recurrent Seizures, Risk Factors, Epileptogenesis, Seizure Triggers

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INTRODUCTION

Epilepsy is a chronic brain disorder characterized by a tendency to experience recurrent seizures that have non-contagious neurobiological, cognitive, and psychological effects and can affect people of all ages [1]. According to the Indonesian Ministry of Health in 2022, data presented by the World Health Organization (WHO) indicate that there are approximately 50 million cases of epilepsy worldwide, with around 80% of people with epilepsy living in low- or middle-income countries, and an increase of 70,000 cases per year [2].

An increase in the incidence of epilepsy has been linked to an increase in traffic accidents, congenital disabilities, infectious diseases, and improved availability and accessibility of adequate health services for the general public. (WHO 2024 — reference not available in the reference list) In Indonesia, approximately 440,000 of the 1.8 million epilepsy patients are at risk of recurrent seizures [3]. Recurrent seizures can occur due to various risk factors, which can be prevented by administering anti-epileptic drugs (AEDs) to control the frequency of seizures or epileptic episodes [4]. As recurrent seizures remain uncontrolled, understanding the current scientific evidence regarding the risk factors for recurrent seizures is crucial. The quality of life of epilepsy patients can be assessed at approximately 70–80% of being able to live like normal people if they

undergo therapy and receive appropriate treatment. It should be noted that treatment for this disease requires a long-term approach because the goal of epilepsy treatment is not to cure epilepsy itself, but to prevent seizures or recurrence of seizures [5]. Identifying these factors is necessary to support efforts to prevent recurrence and improve the quality of comprehensive health services. This literature review aims to assess and explain the risk factors for recurrent seizures in epilepsy patients to provide a clearer picture of the clinical and non-clinical determinants that play a role in the recurrence of seizures [6].

METHOD

Literature searches for the review were conducted using databases from PubMed and Google Scholar, supplemented by manual searches. The search keywords used included “epilepsy,” “incidence,” “prevalence,” “epidemiology,” “recurrent seizures,” and “risk factors for recurrent seizures.” Search filters were applied for articles in English and Indonesian, published between 2010 and 2026, with human subjects, at least an abstract available, and research article types including meta-analyses, systematic reviews, cohort studies, case-control studies, case studies, and cross-sectional studies. Textbook and clinical guideline sources were also considered.

LITERATURE REVIEW

Epilepsy

Epilepsy is clinically defined as abnormal neuronal activity in the brain that causes temporary clinical signs or symptoms and is a chronic and heterogeneous brain disorder [7]. Epilepsy is classified into two types based on its etiology: idiopathic or primary and symptomatic or secondary. Primary epilepsy, whose cause is unknown, may be due to genetic factors, whereas secondary epilepsy, whose cause can be identified, may be due to factors such as brain tumors, stroke, or severe head injuries [1]. Globally, there are 50 million people with epilepsy, and the majority of sufferers live in low- and middle-income countries, where it is estimated that more than 75% are in low-income countries and around 60% are in middle-income countries [7]. This indicates that countries with low economic levels have a higher vulnerability to epilepsy.

Epileptogenesis

Epileptogenesis is the process of forming neural networks capable of generating spontaneous seizures, leading to the development of epilepsy or disease progression [8]. This process is associated with neuronal damage, gliosis, and microglial activation, which create neuroinflammatory conditions in the brain, either due to intrinsic disorders of the central nervous system or damage to the blood–brain barrier [9]. The development of epilepsy is characterized by structural and molecular changes that increase neuronal hyperexcitability and the tendency for recurrent seizures. Microglial activation after seizures causes the release of proinflammatory cytokines such as IL-1β, IL-6, and TNF-α, which affect synaptic plasticity, neurotransmitter transmission, and neuronal excitability through modulation of glutamate receptors and the GABAergic system [10].

The imbalance between excitation and inhibition is the primary mechanism in epileptogenesis and ictogenesis. Increased extracellular glutamate levels and/or decreased GABA activity can cause excitotoxicity, seizures, and neuronal cell death. Glutamate regulation involves neurons and astrocytes through the transporter system and glutamate–glutamine cycle; therefore, disruption of this mechanism contributes to neuronal hyperexcitability [11]. Disregulation of the glutamatergic system, whether due to neuron–astrocyte dysfunction or genetic factors such as NMDA and AMPA receptor mutations, can cause excessive glutamate receptor activation [12]. This condition promotes excitotoxicity and neural tissue changes that underlie the development of epilepsy and the occurrence of recurrent seizures [13].

Recurrent Seizures

Epilepsy is a condition characterized by recurrent seizures occurring more than 24 h apart, which can occur without triggers. Recurrent seizures are a clinical manifestation of excessive and abnormal electrical activity in the brain, which can lead to various disorders such as epilepsy. Several factors can trigger an increase in seizure frequency in people with epilepsy; these are known as triggers. By recognizing these triggers, it is

hoped that people with epilepsy can avoid them anytime and anywhere in the future. Some seizure triggers include behavioral factors (compliance with medication, lack of sleep, psychological stress, alcohol consumption, and smoking), and abnormal MRI findings.

Noncompliance with medication is a risk factor for recurrent seizures in patients with epilepsy. Hovinga et al. reported that noncompliance with treatment contributed to 29% of recurrent seizures [14]. In Suzuki et al.'s study, patients who had forgotten to take their anti-seizure medication were associated with factors causing the onset of seizures in patients with epilepsy. This is because antiepileptic drugs work by stabilizing neuronal activity in the epileptogenic focus, thereby preventing seizures [15]. When patients forget to take their medications, the concentration of the drug in the plasma decreases, and the stabilizing effect on the epileptogenic focus is reduced. In addition to medication adherence, recurrent seizures are influenced by other factors. According to Raru et al., various factors influence recurrent seizures in patients with epilepsy, including smoking, lack of sleep, depression, and fatigue [16]. Approximately 40–50% of epilepsy patients report that fatigue, lack of sleep, and skipping meals can trigger more frequent seizures. Research by Dansen found that poor sleep quality increases the risk of more than one seizure in epilepsy patients at Dr. Moewardi General Hospital in Surakarta by 10 times, based on an observational study of 44 patients (p=0.003) [17]. Lack of sleep generally lowers the seizure threshold through disruption of brain electrical activity during NREM sleep. Research by Saeed et al. shows that irregular eating patterns, such as the habit of skipping meals, are known to play a role as a trigger for seizures in epilepsy patients [18] Irregular food intake can cause hypoglycemia, dehydration, and metabolic imbalance, which contribute to increased neuronal excitability and a decrease in seizure threshold. This condition indicates that nutritional factors not only play a role in the general health status of epilepsy patients, but also have a direct influence on seizure control, making regular meal patterns an important part of comprehensive epilepsy management.

Severe stress is thought to trigger seizures in some people with epilepsy through psychological and physiological mechanisms. Stress is the most commonly reported trigger for seizures in people with epilepsy. In one study, 86.9% of patients were aware of the early symptoms and triggers of seizures [19]. This study is in line with the research by Sugandi et al., who showed that the higher the stress, the higher the frequency of seizures [20]. The physiological response to stress is mediated by the neuroendocrine system, which initiates the process of activation and subsequent recovery of bodily functions to adapt to stressors. This process involves various areas of the brain, including the amygdala, cingulate and prefrontal cortex, septohippocampal region, hypothalamus, and brainstem structures. There are two main components in this stress response, namely the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic–adrenomedullary (SAM) system, which play a role in seizure generation [21]. Alcohol consumption is one of the factors that trigger seizures in epilepsy patients. Alcohol consumption can reduce epileptiform activity and EEG in the central nervous system, as alcohol suppresses central nervous system stimulation by activating the GABA system, which inhibits brain activity. However, when the effects of alcohol in the blood begin to wear off, there is an increase in epileptiform activity on the EEG, which is associated with a higher risk of seizures [22].

Smoking may be associated with an increased risk of seizures in patients with epilepsy, particularly in individuals with high smoking frequency and duration. Nicotine, the primary addictive substance in cigarettes, has proconvulsant effects through the activation of nicotinic acetylcholine receptors (nAChR) in the brain; therefore, in individuals with slower receptor desensitization, sensitivity to seizures due to nicotine exposure is higher. Several studies have indicated that smoking is quite common among individuals with epilepsy and may influence the risk of seizures or epilepsy [23]. Picard et al. reported a prevalence of smoking among people with epilepsy of 32.1%, which is higher than the general population in Switzerland (19.0%), although another study in Western China found a lower prevalence of smoking among men with epilepsy compared to the general population [24]. The relationship between smoking and epilepsy remains complex and controversial, as some prospective studies have shown that smoking is associated with an increased risk of seizures, including single seizures or provocative seizures unrelated to stroke, as well as an increased risk of seizures in the past year and refractory epilepsy in smokers. According to research by Lusiana et al., out of 79 patients, 47 (59.5%) had abnormal MRI results. This finding is consistent with epidemiology, where structural

brain abnormalities are the most common cause of focal seizures [25]. According to Adamczyk-Sowa et al., structural brain abnormalities detected through MRI examination, such as hippocampal sclerosis and cortical lesions, can act as epileptogenic foci that trigger seizures in patients with epilepsy [26].

In 2019, the Indonesian Neurological Society categorized the etiology of epilepsy into six categories: structural, genetic, infectious, metabolic, immunological, and unknown (idiopathic) [1]. Structural causes include anatomical abnormalities of the brain, such as stroke, head injury, infection, or cerebral cortex malformation, which can increase the risk of recurrent seizures by 50–70% owing to permanent lesions that interfere with neuronal inhibition mechanisms. Genetic factors are related to gene mutations, in which seizures are the main manifestation, such as in childhood absence epilepsy and juvenile myoclonic epilepsy, which tend to cause refractory seizures. Infectious etiologies include epilepsy due to intracranial or post-infectious infections, including neurocysticercosis, tuberculosis, HIV, and congenital infections. Metabolic causes are associated with specific metabolic disorders that require specialized management, whereas immunological etiology is caused by autoimmune processes that induce inflammation in the central nervous system. In the unknown (idiopathic) category, the cause of epilepsy cannot be definitively determined; thus, the diagnosis is based on clinical characteristics and electroencephalography (EEG) findings [7].

CONCLUSION

Recurrent seizures in epilepsy are shaped by etiological, epileptogenic, and behavioral factors. Structural etiologies, such as stroke, head injury, intracranial infection, and cortical malformations, raise the risk of recurrence by disrupting neuronal inhibition. Genetic factors contribute to refractory syndromes. Epileptogenesis involves microglial activation, cytokine release, and excitatory-inhibitory imbalance, promoting hyperexcitability. Modifiable triggers, including medication non-compliance, sleep deprivation, stress, alcohol consumption, and smoking, lower the seizure threshold. Abnormal MRI findings indicate the risk of recurrence; controlling risks improves life.

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AUTHORS' CONTRIBUTIONS

All authors have reviewed and approved the final version of the manuscript, and they all agree to be accountable for all aspects of the work.

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