








Relationships Between Age of Onset, Seizure Frequency, And Disease Duration with Cognitive Function in Epilepsy Patients at the Neurology Clinic of H. Adam Malik Central Hospital, Medan

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ABSTRACT

Background: Cognitive function disorders often occur in individuals with epilepsy. The decline in cognitive function in epilepsy patients can be caused by various factors, including age of onset, seizure frequency, and duration of the disease. This study aims to investigate the relationship between the age of onset, seizure frequency, and disease duration on the cognitive function of epilepsy patients at the Neurology Outpatient Clinic of Haji Adam Malik General Hospital in Medan

Method: The chosen research design is a cross-sectional analytic. The study was conducted at the neurology outpatient clinic of the Adam Malik Central General Hospital in Medan. The samples used were patients diagnosed with epilepsy at the Neurology Outpatient Clinic of Adam Malik Central General Hospital in Medan, aged 18-65 years, and without any other medical conditions aside from epilepsy. The study involved 35 subjects.

Result: The majority of the research subjects are aged 18-45 years (94.3%), with more males (51.4%) than females. Most have a high school education background (48.6%), and the largest group is unemployed (62.9%). The most common age group at onset is 0-18 years (48.6%). The majority of subjects experience seizures in the rare category (less than 1 time per month) at 62.9%. Most subjects have a disease duration of less than 15 years (65.7%). The majority of epilepsy patients at the Neurology Outpatient Clinic of H. Adam Malik Hospital (52.1%) have abnormal cognitive function based on the MoCA-Ina test results. Statistical analysis was conducted using the chi-square test and multivariate analysis with logistic regression. The chi-square test results revealed a significant relationship between age of onset and cognitive function ($p=0,008$), a significant relationship between seizure frequency and cognitive function ($p=0,004$), and a significant relationship between disease duration and cognitive function ($p=0,012$). The multivariate analysis results indicated that disease duration had a significant relationship with cognitive function, with an odds ratio of 0,081 ($p\text{-value}=0,037$, 95% CI 0,008-0,862).

Conclusion: There is a relationship between age of onset, seizure frequency, and disease duration with the cognitive function of epilepsy patients at the Neurology Outpatient Clinic of Haji Adam Malik General Hospital in Medan.

Keywords: Epilepsy, Cognitive Function, MoCA-Ina

ABSTRAK

Latar Belakang: Gangguan fungsi kognitif sering terjadi pada individu yang mengalami epilepsi. Penurunan fungsi kognitif pada pasien epilepsi dapat disebabkan oleh berbagai faktor, termasuk usia onset, frekuensi kejang, dan durasi penyakit. Penelitian ini bertujuan untuk menyelidiki hubungan antara usia onset, frekuensi kejang, dan durasi penyakit terhadap fungsi kognitif pasien epilepsi di Poliklinik Neurologi Rumah Sakit Umum Pusat Haji Adam Malik di Medan.

Metode: Mayoritas subjek penelitian berusia 18-45 tahun (94,3%), dengan jumlah laki-laki lebih banyak (51,4%) daripada perempuan. Sebagian besar memiliki latar belakang pendidikan SMA (48,6%), dan kelompok terbesar adalah yang tidak bekerja (62,9%). Kelompok usia onset terbanyak adalah 0-18 tahun (48,6%). Mayoritas subjek mengalami kejang dalam kategori jarang (kurang dari 1 kali per bulan) sebanyak 62,9%. Sebagian besar subjek memiliki durasi penyakit kurang dari 15 tahun (65,7%). Mayoritas pasien epilepsi di Poliklinik Neurologi RSUD H. Adam Malik (52,1%) memiliki fungsi kognitif abnormal berdasarkan hasil uji MoCA-Ina. Analisis statistik dilakukan menggunakan uji chi-square dan analisis multivariat dengan regresi logistik. Hasil uji chi-square menunjukkan hubungan signifikan antara usia onset dan fungsi kognitif ($p=0,008$), hubungan signifikan antara frekuensi kejang dan fungsi kognitif ($p=0,004$), dan hubungan signifikan antara durasi penyakit dan fungsi kognitif ($p=0,012$). Hasil analisis multivariat menunjukkan bahwa durasi penyakit memiliki hubungan signifikan dengan fungsi kognitif, dengan odds ratio sebesar 0,081 (nilai $p=0,037$, 95% CI 0,008-0,862).

Hasil: Analisis statistik dilakukan dengan uji chi-square dan analisis multivariat dengan regresi logistik. Pada hasil uji chi-square didapatkan hasil adanya hubungan antara usia onset terhadap fungsi kognitif ($p=0,010$), adanya hubungan antara frekuensi kejang terhadap fungsi kognitif ($p=0,004$) dan adanya hubungan antara durasi penyakit terhadap fungsi kognitif ($p=0,012$). Hasil analisis multivariat menunjukkan durasi penyakit memiliki hubungan yang signifikan dengan fungsi kognitif dengan rasio odds 0,081 (nilai $p=0,037$, 95% CI 0,008-0,862).

Kesimpulan: Terdapat hubungan antara usia onset, frekuensi kejang, dan durasi penyakit terhadap fungsi kognitif penderita epilepsi di Poliklinik Neurologi Rumah Sakit Umum Pusat Haji Adam Malik Medan

Kata kunci: Epilepsi, Fungsi Kognitif, MoCA-Ina



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1. Introduction

Epilepsy is a clinical condition caused by increased electrical activity patterns in the brain, characterized by at least two seizures without a clear reason or reflexes occurring within more than 24 hours, one unprovoked seizure with a likelihood of subsequent seizures equivalent to a common relapse risk (at least 60%) after two unprovoked seizures within the next ten years, or a syndrome diagnosis, according to the Indonesian Association of Neurologists [1]. According to the World Health Organization (WHO), approximately 50 million people worldwide suffer from epilepsy, with nearly 80% of them residing in low- and middle-income countries, including Indonesia. In high-income countries, there are about 49 epilepsy cases per 100,000 people, while in low- and middle-income countries, such as Indonesia, this figure can reach 139 cases per 100,000 people. The higher incidence in developing countries is attributed to poor sanitation, inadequate healthcare systems, high risk of brain infections, and a lack of treatment for epilepsy patients.

In 2013, the Epilepsy Study Group of the Indonesian Neurology Specialist Association conducted a 6-month study in 18 hospitals across 15 cities. Among the 2288 epilepsy cases found, 487 were new cases, and 1801 were existing cases. The average age of existing patients was 29.2 to 16.5 years. About 77.9% of patients initially consulted with neurology specialists, 6.8% with general practitioners, while the rest consulted with traditional healers or did not seek consultation at all. A small portion of the epilepsy population in developing countries receives appropriate treatment [2]. Epileptic seizures can cause morphological and functional changes in the brain, resulting in cognitive and neuropsychological disorders. Cognitive function includes unconscious mental activities such as thinking, remembering, learning, and using language. Epilepsy patients often experience cognitive disorders in various aspects, including verbal memory, language, executive function, and attention [3]. Studies indicate that between 60% to 70% of individuals with chronic epilepsy experience cognitive disorders [4]. Total scores for verbal memory, language, executive function, and attention

are significantly lower in people with epilepsy compared to the control group. Although effective antiepileptic drugs can control seizures in 60-70% of individuals without side effects, some patients still experience seizures and their negative impact on quality of life, including cognitive function, morbidity, and the risk of death [5]. Many variables influence the decline in cognitive function in epilepsy patients, such as the etiology and type of disease, age of onset, frequency, and duration of the disease, hereditary factors, psychosocial factors, antiepileptic drugs, and other factors. This study focuses on the relationship between the age of onset, seizure frequency, and disease duration on cognitive function [2]. Although the idea that epilepsy damages the brain and progressively affects cognitive function is largely supported by cross-sectional studies, specific findings suggest that the longer the duration of epilepsy, the worse the cognitive status.

[6] Epilepsy has a significant impact worldwide, with over 50 million people affected by this condition, and more than half of them residing in the Asian region. In Indonesia alone, it is estimated that around 250,000 new cases of epilepsy occur each year. [7] This is likely due to an increased risk of endemic conditions, such as malaria or neurocysticercosis, high incidence of traffic and birth-related injuries, variations in medical infrastructure, and the availability of accessible preventive health programs and care. [8] During a seizure, the first step is to obtain a detailed history from an eyewitness and conduct a thorough physical examination to rule out various possible causes. If a seizure is suspected, the initial focus is on excluding reversible causes, beginning with routine blood tests (complete/full blood count, comprehensive electrolyte profile, thyroid, kidney, and liver function). Infectious screenings, including lumbar puncture, are performed if there are symptoms or signs suggestive of central nervous system infection. [9] MoCA, commonly used in clinics, has been translated into 35 languages. It assesses various cognitive domains, including short-term memory, visuospatial skills, executive function, attention, concentration, working memory, language, and orientation. Sensitivity ranges from 67 to 100%, and specificity ranges from 50 to 95%, depending on different cutoff evaluations. [10] Historically, MMSE has been the standard for dementia screening but is limited in detecting mild cognitive deficits observed in mild cognitive impairment. Currently, the preferred test is MoCA, addressing MMSE limitations by emphasizing strong visuospatial, executive, and verbal learning functions. Understanding the relationship between factors underlying cognitive disorders in epilepsy patients, especially age of onset, seizure frequency, and disease duration, is expected to provide a foundation for interventions that can improve cognitive and neuropsychological functions, ultimately enhancing the quality of life for individuals with epilepsy, including through cognitive function screening in the neurology outpatient clinic of H. Adam Malik Medan. The research aims to investigate the relationship between age of onset, seizure frequency, and disease duration with the cognitive function of epilepsy patients in the neurology outpatient clinic of H. Adam Malik Medan.

2. Method

The chosen research design is a cross-sectional analysis at the neurology outpatient clinic of H. Adam Malik Hospital in Medan. The samples used were patients diagnosed with epilepsy at the Neurology Outpatient Clinic of Haji Adam Malik Central General Hospital in Medan, aged 18-65 years. The sampling process was carried out using a consecutive sampling technique. Exclusion criteria involved: 1) Suffering from psychiatric disorders, 2) Having congenital abnormalities, malnutrition, mental retardation before experiencing epilepsy, 3) Unable to read and write, 4) Experiencing other medical conditions besides epilepsy, such as infections in the central nervous system (CNS), non-infectious brain diseases like tumors, head injuries, or chronic diseases like tuberculosis, Human Immunodeficiency Virus (HIV), and diabetes mellitus, 5) Delayed growth and development before experiencing epilepsy, 6) Patients with incomplete medical record data. The diagnosis of epilepsy had been previously established by a neurology specialist and confirmed through the patient's medical records, including electroencephalography results. After obtaining approval from the Ethics Committee of the Faculty of Medicine, University of North Sumatra, informed consent was obtained from each subject. Based on the Slovin formula, the minimum number of subjects was 35 patients.

2.1. Data Analysis

Data analysis was performed using the SPSS 27.0 program, univariate analysis aims to describe the characteristics of each variable that is the focus of the research. The results of this analysis include the frequency distribution of age, gender, occupation, highest education level, age of onset, seizure frequency, disease duration, and cognitive function. The bivariate analysis process employs the chi-square test, while multivariate analysis utilizes multiple logistic regression. Bivariate analysis is conducted to assess the statistical relationship between each independent variable and the dependent variable. Furthermore, the multiple logistic regression test is used to identify variables that have the most significant impact on the outcome. The results of the analysis are significant if the value of p-value < 0.05.

3. Result

Table 1 presents the characteristics of the research subjects. The most prevalent age range in this study is 18-45 years (94.3%). Male subjects dominate the research population, comprising 51.4%. The highest level of education attained by the research subjects is predominantly Senior High School (48.6%). The largest group among the research subjects is the unemployed category (62.9%). The majority of epilepsy patients at the Neurology Outpatient Clinic of H. Adam Malik Hospital in Medan have abnormal cognitive function (52.1%). The most common age onset group falls within the range of 19-60 years (51.4%). Seizure frequency is most frequently found in the category of <1 per month (62.9%). The majority of patients fall within the duration of the disease range of <15 years (65.7%).

Table 1. Subject characteristics

Characteristic	Total (n=35), n(%)
Age (year)	
18-45	33 (94.3)
46-59	1 (2.9)
>59	1 (2.9)
Gender	
Female	17 (48.6)
Male	18 (51.4)
Occupation	
Unemployed	22 (62.9)
Entrepreneur	6 (17.1)
Civil Servant	3 (8.6)
Student	4 (11.4)
Education Level	
Special needs school	2 (5.7)
Elementary School	2 (5.7)
Junior High School	3 (8.6)
High School	17 (48.6)
Diploma	2 (5.7)
Bachelor's Degree	7 (20.0)
Master's Degree	2 (5.7)
Cognitive Function	
Normal	15 (42.9)
Abnormal	20 (52.1)
Age of Onset (year)	
1-18	17 (48.6)
19-60	18 (51.4)
>60	0 (0)
Seizure Frequency	
<1 per month	22 (62.9)
≥1 per month	13 (37.1)
Duration (year)	
<15	23 (65.7)
15-30	11 (31.4)
>30	1 (2.9)

Based on Table 2, there is a significant relationship between the relationship between age of onset, seizure frequency, and disease duration on the cognitive function of epilepsy patients. There is a significant relationship between the age of onset, seizure frequency, and disease duration on the cognitive function of epilepsy patients.

Table 2. The relationship between age of onset, seizure frequency, and disease duration on the cognitive function

Variables	Cognitive Function	
	p-value	
Age of Onset	0.010	
Seizure Frequency	0.004	
Disease Duration	0.012	

Binary logistic regression analysis of age of onset, seizure frequency, and disease duration on the cognitive function of epilepsy patients.

Based on the results of multivariate analysis in Table 3, it is known that the variable most influencing cognitive function is the disease duration variable, with a p-value of 0.037, statistically significant related to the cognitive function of epilepsy patients. The Odds Ratio (OR) value is 0.081, with a 95% Confidence Interval (CI) of 0.008-0.862, indicating that patients with a disease duration of more than 15 years have a 0.862 times higher likelihood of experiencing a decrease in cognitive function compared to patients with epilepsy for less than 15 years. Meanwhile, seizure frequency and age of onset do not show a significant correlation with cognitive function impairment.

Table 3. Multivariate Analysis of Age of Onset, Seizure Frequency, and Disease Duration on Cognitive Function

Variable	B	S. E	Wald	df	Nilai p	OR	CI 95%	
							Min	Max
Disease Duration	-2.510	1.205	4.339	1	0.037	0.081	0.008	0.862
Seizure Frequency	-2.144	1.232	3.029	1	0.082	0.117	0.010	1.310
Age of Onset	-1.217	0.987	1.520	1	0.218	0.296	0.043	2.049

4. Discussion

This study consists mostly of males (51.4%) [11]. A meta-analysis indicates that the prevalence of epilepsy based on gender does not significantly differ in several countries such as Iran, Pakistan, and India. Although there are gender-based characteristic differences, the prevalence and incidence of epilepsy require further investigation through epidemiological studies. The age distribution of epilepsy patients in this study is predominantly in the 18-45 age group (94.3%) [12]. In this productive age range, factors like occupation and occupational risks can be etiological factors for epilepsy. Busy daily activities can also lead to insufficient sleep, triggering seizures. The highest education level among epilepsy patients tends to be dominated by the high school group (48.6%). This may be related to the cognitive function impairments often experienced by epilepsy patients, limiting their ability to pursue higher education. Regarding employment, the highest proportion is in the unemployed status (62.9%) [12]. This may be due to health issues leading epilepsy patients to quit or be dismissed from their jobs due to seizures, even if the seizures are controlled. Some epilepsy patients may also experience cognitive and functional disabilities. The highest onset age distribution of epilepsy is within the age range of 19-60 years (51.4%). This aligns with the literature, indicating that the incidence and prevalence of epilepsy generally occur around the age of 25.06 ± 16.9 years in new cases, while the average age in old cases is 29.2 ± 16.5 years. The research results also indicate that patients with a seizure frequency of less than once a month have the highest proportion (62.9%) [13]. Adherence to anti-epileptic medication can influence seizure frequency. Studies in adults show that non-compliance increases the risk of seizures by up to 21%. In terms of the duration of suffering, the majority falls within the category of less than 15 years (65.7%), consistent with the characteristics of epilepsy patients most commonly found in the 18-45 age group. In assessing cognitive function, the majority of epilepsy patients are found to have abnormal cognitive function (52.1%) [13]. The decline in cognitive function in epilepsy patients depends on several factors such as etiology, epilepsy type, seizure type, onset age, psychiatric disorders, and the anti-epileptic drugs consumed by the patients.

The chi-square test in this study found a significant relationship between the onset age of epilepsy and the cognitive function of patients ($p=0.010$) [14]. Research conducted by Cormack et al. revealed that children who experienced epilepsy in their first year of life had a significantly higher risk of intellectual dysfunction, with a percentage reaching 82.4%, compared to the general population (32.2%). [15] Another study supported

these findings, indicating that early-onset epilepsy, especially before the age of 3, could negatively impact cognitive function and increase the risk of below-average IQ [15]. Studies in humans and animals suggest that the immature brain, particularly in the hippocampus region, is vulnerable to the development of specific functional and anatomical disorders at certain ages. The onset age of epilepsy in the first year of life emerges as the most significant factor in predicting intellectual dysfunction, with a disorder rate reaching 82.4%.

The chi-square test found a significant relationship between seizure frequency and cognitive function in epilepsy patients ($p=0.004$) [16]. Epileptic seizures can disrupt memory function, especially when they occur frequently, leading to fatigue and concentration problems. Seizure frequency is also influenced by the success of therapy, where medication adherence is a key factor. Non-compliant patients tend to achieve remission for a longer duration and have poorer cognitive function [17]. A study indicates that the body's response to seizures can impact the structure and function of neurons, with high seizure frequency causing changes in neuron pathways. Children with well-controlled seizures exhibit better cognitive performance compared to those with refractory epilepsy. The chi-square test found a significant relationship between the duration of epilepsy and cognitive function in epileptic patients ($p = 0.012$). This finding is consistent with studies affirming that the length of epilepsy is a risk factor for decreased cognitive function [18]. The study categorized research subjects based on epilepsy duration, indicating that patients with over 30 years of epilepsy experience lower IQ scores compared to groups with durations of 15–30 years or less than 15 years [18]. The duration of epilepsy is also linked to the duration of OAE treatment and the number of drugs consumed. Treatment for more than 2 years increases the risk of concentration disorders nearly sixteenfold compared to treatment durations of less than 2 years. The use of epilepsy medications affects cholesterol, folate, and glucose metabolism, thereby increasing the risk of vascular diseases. Concerning memory impairment, the duration of treatment increases the risk thirteenfold [19]. Another study indicates a decline in cognitive function, particularly in memory ability, in individuals with chronic epilepsy that continues with age, especially reaching middle age.

The multivariate analysis aimed to identify dominant variables influencing the cognitive function of epilepsy patients. Utilizing multivariate logistic regression, the study found that the duration of the disease and the age of onset were independently associated with abnormal cognitive function. This implies that the longer someone suffers from the disease and the younger the age at onset, the greater the likelihood of cognitive disorders. However, after considering these factors and performing statistical adjustments, seizure frequency and age of onset are no longer significantly related to cognitive status. [20]. The research also indicates that, although cognitive reserve factors such as early IQ, education level, or job complexity partially shield against cognitive deficits, the duration of epilepsy seems to be a crucial factor in determining the development of cognitive disorders. This means that the longer someone has epilepsy, the greater the likelihood of experiencing cognitive disorders, even with a high cognitive reserve. In essence, the duration of epilepsy significantly contributes to the risk of cognitive disorders. The weaknesses in this study include the need for observational research with a longer time frame, a larger sample size, and more variables. For other researchers, it is hoped that they can examine other factors such as the duration of seizures, consciousness during seizures, and seizure types that may be related to the occurrence of cognitive dysfunction. One of the data collection tools used in this study is a questionnaire, which relies on the patient's memory, hence errors in recall may occur.

5. Conclusion

There is a significant relationship between the age of onset, seizure frequency, and duration of illness with the cognitive function of epilepsy patients. Based on the results of multivariate analysis, it is concluded that the duration of illness is a variable that significantly influences the cognitive function of epilepsy patients.

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