Clinical Research

# Factors associated with global cognitive impairment in epilepsy patients: a cross-sectional study in Mataram, Indonesia

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**ABSTRACT**

**BACKGROUND** Cognitive impairment is a major complication of epilepsy. This study aimed to investigate the factors associated with the prevalence of cognitive impairment in patients with epilepsy in Mataram, Indonesia.

**METHODS** This cross-sectional study involved 155 consecutive outpatients with epilepsy at Mataram General Hospital, Mutiara Sukma Mental Hospital, and Siti Hajar Hospital, Mataram, Indonesia between September 2017 and August 2020. Data on the patient's demographic characteristics, epilepsy, treatment variables, and global cognitive status were collected. The association between the determinants of epilepsy-associated cognitive impairment and the prevalence of epilepsy-associated global cognitive impairment was analyzed using logistic regression.

**RESULTS** The prevalence of epilepsy-associated global cognitive impairment was 83.9% and related to a low level of education (odds ratio [OR] = 5.24, 95% confidence interval [CI] = 1.93–14.20), early age at onset (OR = 7.85, 95% CI = 0.82–33.79), and long duration of epilepsy (OR = 8.47, 95% CI = 1.95–36.88).

**CONCLUSIONS** A high prevalence of epilepsy-associated global cognitive impairment was observed in Mataram and was associated with a low level of education, early age at onset, and long duration of epilepsy.

**KEYWORDS** cognitive dysfunction, epilepsy, neuropsychological tests, quality of life

Global cognitive impairment is an important complication of epilepsy. The prevalence of cognitive impairment in patients with epilepsy is currently estimated to be 70–80%, but this can vary by region.[1,2] The number of patients with epilepsy in developing countries tends to be higher than that of developed countries, and only a small portion of the patient population receives appropriate treatment; thus, it can be estimated that the prevalence of global cognitive impairment will be much higher in developing countries.[3,4] Our previous study in the same population who received the conventional antiepileptic drug (AED) monotherapy showed that the prevalence of cognitive impairment was 75%.[5] However, the prevalence of epilepsy-associated cognitive disorders in other parts of Indonesia is still rare. Studies conducted in Aceh and Palembang with small sample sizes showed a prevalence of 20.6–69%.[6,7] If not appropriately treated, epilepsy-associated cognitive impairment can progress to dementia, leading to decreased quality of life and increased socioeconomic and health burden on their families and the government.[2]

Global cognitive impairment in patients with epilepsy can occur at the onset of epilepsy or years after the initial diagnosis.[8,9] The susceptibility to the

impairment is largely determined by demographic (age, sex, and level of education), epilepsy (age at onset, type of seizure, epilepsy syndrome, seizure frequency, etiology, location of epileptogenic focus, and duration of disease), and treatment (type and number of AEDs and duration of treatment) variables, which could vary across regions or countries.[10] Demographic variables, particularly level of education, determine the capacity of the brain to compensate for lesions caused by seizure-induced neuronal damage; hence, the cognitive function of the patients remains intact.[11] In contrast, both epilepsy and treatment variables determine the success in seizure control and contribute to modulating the extent of seizure-induced neuronal damage and interictal epileptiform discharges (IEDs) associated with the severity of global cognitive impairment in patients with epilepsy.[12,13]

However, successful treatment can halt or even partially correct the cognitive impairment[1,9]; hence, early detection and intervention can provide satisfactory clinical outcomes for patients with epilepsy-associated global cognitive impairment. Successful treatment, either by using AEDs or cognitive rehabilitation therapy, highly depends on the ability to control the global cognitive impairment variables.[14] This study aimed to investigate the factors determining the prevalence of global cognitive impairment in patients with epilepsy in Mataram, Indonesia.

## METHODS

This cross-sectional study involved consecutive patients with epilepsy at Mataram General Hospital, Mutiara Sukma Mental Hospital, and Siti Hajar Hospital in Mataram, Indonesia. Mataram is the capital of West Nusa Tenggara and one of the provinces with a low human development index in Indonesia, where access to health services is relatively low.[15] This study was conducted between September 2017 and August 2020. The sample size was determined using single proportion calculation formula. As the prevalence of epilepsy was 44%, $Z\alpha = 1.96$, and margin of error (d) = 10%, the minimum sample size required was 97. However, if the number of eligible subjects exceeded the minimum sample size, all eligible subjects were included in the study. The inclusion criteria were fully conscious patients with epilepsy (aged 18–60 years) treated with oral AEDs, both as mono- and combination therapy. The patients were excluded based on the following criteria: (1) illiterate, (2) had a history of dementia, and (3) treated with antipsychotics and antidepressants at the time of global cognitive assessment. This study was approved by the Ethical Committee for Medical Research, Faculty of Medicine, Universitas Mataram (No: 213/UN18.8/ETIK/2017). All participants provided written informed consent before participating in the study.

The data collected in this study included the demographic characteristics (age, sex, and level of education), epilepsy details (age at onset, type of seizure, etiology, and duration of epilepsy), treatment variables (number of AEDs and duration of treatment), and scores of the Indonesian version of Montreal Cognitive Assessment (MoCA-Ina) test as well as the MoCA-Ina test components (visuospatial and cognitive function, naming, attention, language, abstract thinking, delayed memory, and orientation) of the patients. The MoCA-Ina test is a global cognitive function evaluation instrument validated for the Indonesian population.[16] Compared to the Mini-Mental State Examination (MMSE), the most widely used global cognitive function test, the MoCA test is more sensitive for detecting mild cognitive impairment across a wide range of medical conditions.[17,18] Moreover, MMSE is now under copyright restrictions and can no longer be freely used for research purposes.[19] The categorization of demographic, epilepsy, and treatment characteristics was conducted before data analysis. In terms of demographic characteristics, age was categorized into early (≤ median value of age) and late (> median value of age) adulthood, sex into male and female, and level of education into low (length of education ≤12 years) and high (length of education >12 years). For the epilepsy characteristics, age at onset was categorized as early-onset (≤18 years) and late-onset (>18 years), type of seizure as partial and generalized seizures, etiology as idiopathic and structural causes, and duration as ≤5 years and >5 years. Meanwhile, the AEDs treatment was categorized based on number into monotherapy (single AED) and polytherapy (≥2 AEDs) and treatment duration into <2 years and ≥2 years.[5]

Global cognitive function was assessed with the MoCA-Ina test. Originally, the total score ranged from 0 to 30, with a cut-off point of 26, which was considered normal.[17] Meanwhile, in this study, a score of ≥26 was considered normal, and <26 had global cognitive impairment. An additional score of 1 as a correction factor was assigned if the patients had a history of ≤12 years of formal education.

A simple binary logistic regression was initially performed to verify the association between demographic characteristics, epilepsy, treatment, and global cognitive function in patients with epilepsy. The results of this analysis were reported as crude odds ratios (ORs) with 95% confidence intervals. Furthermore, a multiple logistic regression analysis was conducted to determine the adjusted OR of the variables having $p<0.25$ in the previous analysis. Mann–Whitney test was used to analyze mean differences of cognitive domains listed on the MoCA-Ina test in patients with and without global cognitive impairment. Statistical significance was set at $p<0.05$.

## RESULTS

This study recruited 155 epilepsy outpatients from the main referral hospitals in Mataram, Indonesia. The percentage of global cognitive impairment was 83.9%. Male, late age at onset, partial seizure type, and epilepsy duration of >5 years were identified as the eligible associated factors for subsequent analysis ($p<0.25$) (Table 1). After adjustment, only a low level of education, early age at onset, and epilepsy duration of >5 years were associated with cognitive impairment in patients with epilepsy (Table 1). Furthermore, the cognitive function was different in all the cognitive

**Table 1.** Association between the eligible determinants and cognitive impairment in epilepsy patients

| Variables | Cognitive function | | Crude OR (95% CI) | $p$* | Adjusted OR (95% CI) | $p^{\dagger}$ |
|---|---|---|---|---|---|---|
| | Declined, n (%) (N = 130) | Normal, n (%) (N = 25) | | | | |
| Age | | | | 0.361 | | - |
| ≤18 years | 65 (81.2) | 15 (18.8) | 1.50 (0.63–3.58) | | - | |
| >18 years | 65 (86.7) | 10 (13.3) | 1.00 | | - | |
| Sex | | | | **0.051** | | 0.058 |
| Female | 55 (77.5) | 16 (22.5) | 2.42 (1.00–5.89) | | 2.71 (0.97–7.58) | |
| Male | 75 (89.3) | 9 (10.7) | 1.00 | | 1.00 | |
| Level of education | | | | **0.001** | | **0.001** |
| Low | 104 (89.7) | 12 (10.3) | 4.33 (1.77–10.60) | | 5.24 (1.93–14.20) | |
| High | 26 (66.7) | 13 (33.3) | 1.00 | | 1.00 | |
| Age at onset | | | | **0.093** | | **0.006** |
| ≤18 years | 54 (78.3) | 15 (21.7) | 2.11 (0.88–5.04) | | 7.85 (0.82–33.79) | |
| >18 years | 76 (88.4) | 10 (11.6) | 1.00 | | 1.00 | |
| Type of seizure | | | | **0.153** | | 0.148 |
| Partial | 62 (88.6) | 8 (11.4) | 1.94 (0.78–4.80) | | 2.11 (0.77–5.78) | |
| Generalized | 68 (80.0) | 17 (20.0) | 1.00 | | 1.00 | |
| Etiology | | | | 0.672 | | - |
| Idiopathic | 88 (83.0) | 18 (17.0) | 1.23 (0.48–3.16) | | - | |
| Structural | 42 (85.7) | 7 (14.3) | 1.00 | | - | |
| Duration of epilepsy | | | | **0.185** | | **0.004** |
| >5 years | 81 (87.1) | 12 (12.9) | 1.79 (0.76–4.24) | | 8.47 (1.95–36.88) | |
| ≤5 years | 49 (79.0) | 13 (21.0) | 1.00 | | 1.00 | |
| Number of AEDs | | | | 0.638 | | - |
| Polytherapy | 21 (80.8) | 5 (19.2) | 1.30 (0.44–3.84) | | - | |
| Monotherapy | 109 (84.5) | 20 (15.5) | 1.00 | | - | |
| Duration of treatment | | | | 0.459 | | - |
| <2 years | 47 (81.0) | 11 (19.0) | 1.39 (0.58–3.30) | | - | |
| ≥2 years | 83 (85.6) | 14 (14.4) | 1.00 | | - | |

AEDs=antiepileptic drugs; CI=confidence interval; OR=odds ratio
Variables with $p<0.25$ in the first analysis was included to multiple logistic regression analysis. *Simple binary logistic regression analysis; †multiple logistic regression analysis, significant if $p<0.05$

**Table 2.** Mean scores of cognitive domains listed in the MoCA-Ina between subjects with normal cognitive status and those with cognitive impairment

| Variables | Cognitive function, median (min–max)* | | $p^{\dagger}$ |
|---|---|---|---|
| | Decline (N = 130) | Normal (N = 25) | |
| Visuospatial/ executive function | 3 (0–5) | 5 (3–5) | **<0.001** |
| Naming | 2 (0–3) | 3 (2–3) | **<0.001** |
| Attention | 4 (0–6) | 6 (4–6) | **<0.001** |
| Language | 2 (0–3) | 3 (2–3) | **<0.001** |
| Abstract thinking | 1 (0–2) | 2 (0–3) | **<0.001** |
| Delayed memory | 1 (0–5) | 4 (0–5) | **<0.001** |
| Orientation | 5 (0–6) | 6 (4–6) | **<0.001** |

MoCA-Ina=Indonesian version of Montreal Cognitive Assessment
*Mann–Whitney test; †significant difference ($p$<0.05)

domains of the MoCA-Ina instrument (visuospatial and executive function, naming, attention, language, abstract thinking, delayed memory, and orientation) (Table 2).

## DISCUSSION

A high prevalence (83.9%) of cognitive impairment was found in patients with epilepsy in Mataram, Indonesia, with decreased functioning in all cognitive domains. This result is in line with a previous study conducted in another country that used MMSE and Brief Cognitive Battery-Edu.[20] However, this study had a higher prevalence than studies conducted in other regions of Indonesia with smaller sample sizes and different patient characteristics[6] as well as the research method used which was MMSE.[7]

This study demonstrated that a low level of education, early age at onset, and long duration of epilepsy were the major determinants of cognitive impairment in patients with epilepsy living in Mataram; whereas age, sex, type of seizure, etiology, number of AEDs, and duration of treatment were not related to cognitive impairment. A previous study conducted in another country also showed the level of education and age at onset as the main determinants of epilepsy-associated cognitive impairment.[20] However, another study in another region in Indonesia found that the number of AEDs was the major determinant.[7] These findings emphasize the importance of identifying factors related to cognitive dysfunction in patients with epilepsy as the important components in developing strategies for managing executive dysfunction. Since cognitive impairment is correlated with decreased functional capacity, loss of productivity, and high dependency (on caregivers), it is important to conduct an early implementation of cognitive rehabilitation (including internal compensatory strategies, external memory assistance, psychoeducation, and exercises for attention) and executive function that can improve cognitive function and functional capacity.[21]

Education is one of the determinants of brain capacity to compensate for the impact of epilepsy-related brain lesions on cognitive function; thus, they may still have intact cognitive function.[11] Since cognitive rehabilitation therapy requires the patient's understanding of the instructions provided during therapy sessions, an adequate level of education will support the success of the therapy. Therefore, developing a management strategy for epilepsy-associated cognitive impairment is challenging in areas with a low development index, where a low level of education was associated with cognitive impairment in epilepsy.[22] The success of cognitive management strategy in these patients will be largely influenced by the active participation and care of caregivers who understand the therapy sufficiently.[23] Thus, it is important to empower the families by providing adequate knowledge on the impact and management of epilepsy-related cognitive impairment to lessen socioeconomic and health burdens.

This study also showed that the early onset and duration of epilepsy determined cognitive impairment. These are relevant, considering seizures that occur at an early age are closely related to the inhibition of the brain maturation process and chronic recurrent epileptic seizures, and IEDs cause neuronal damage that negatively affects cognitive function.[12,24] Thus, adequate seizure control with AEDs was the main treatment for epilepsy patients. Therefore, the availability of AEDs at affordable prices and easy access to these drugs should be guaranteed. Since most AEDs, including those with a good safety profile on cognitive function, are covered by national health insurance, increasing the coverage of epilepsy patients and their families in the insurance is critical.

This study had several limitations. First, despite careful and thorough interviews with epilepsy patients and their families during data collection,

recall bias that could affect the results of data analysis could not be ruled out. This possibility increased when data were collected from patients and families with a low level of education. Second, data on the characteristics of epilepsy, such as the frequency of seizures, epilepsy syndromes, and factors that can trigger seizures which are usually retrieved from the family of patients with a high level of education and a good understanding of epilepsy, could not be obtained in this study. By the results of this study, the local health authorities are suggested to conduct continuing education programs about the routine examination of cognitive function in managing epilepsy. In addition, it is necessary to ensure the availability of well-trained healthcare personnel for cognitive screening and to refer epilepsy patients with cognitive impairment to higher healthcare facilities. In conclusion, this study demonstrated a high prevalence of cognitive impairment in patients with epilepsy in Mataram. Low level of education, earlier age onset, and longer duration of epilepsy were the determinants of global cognitive impairment in these patients.

**Conflict of Interest**

The authors affirm no conflict of interest in this study.

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