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Association between serum homocysteine levels and the frequency of epilepsy-related cognitive dysfunction: a cross sectional study in patients with epilepsy in Mataram, Indonesia

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ABSTRACT

Background: In patients with epilepsy (PWE), cognitive dysfunction becomes an important comorbidity. In PWE, cognitive dysfunction is thought to be linked to the processes of neurodegeneration that are triggered by the rise in homocysteine levels.
Objective: To determine whether PWE in Mataram, Indonesia, have a higher prevalence of cognitive dysfunction and higher serum homocysteine levels.
Methods: 81 PWE were recruited for this cross-sectional study from Mataram's three primary referral hospitals. The patients' serum homocysteine levels were measured by ELISA using five milliliters of fasting blood. The patients' sociodemographic (age, gender, and educational level) and clinical (etiology of epilepsy and treatment duration) characteristics were also gathered. Indonesian version of The Montreal Cognitive Assessment (MoCA-Ina) was used to evaluate the cognitive status. The association between homocysteine, clinical, and socio-demographic data, as well as the cognitive dysfunction frequency in PWE was determined with final logistic regression model.
Results: The patients' age was 33 years old on average. PWE had a cognitive dysfunction prevalence of 76.5 percent. PWE's high prevalence of cognitive dysfunction was not associated with serum homocysteine levels in the final logistic regression model ($p > 0.05$). Patients' clinical and sociodemographic characteristics were also not associated with a high prevalence of cognitive dysfunction ($p > 0.05$).
Conclusion: In Mataram, Indonesia, the high prevalence of cognitive dysfunction among PWE was not linked to serum homocysteine levels.

Keywords: epilepsy, cognitive dysfunction, homocysteine, neurodegeneration, dementia.
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BACKGROUND

One of the major comorbidities of epilepsy is cognitive dysfunction, which may occur both at the early or late onset of epilepsy.[1] The frequency of the comorbidity in patients with epilepsy (PWE) can be found up to 70%.[2] A recent study conducted in Mataram showed a higher frequency of epilepsy-associated cognitive dysfunction, up to 84%.[2] Since cognitive dysfunction in PWE has a major impact on reducing their quality of life, both early detection and intervention for cognitive dysfunction in these patients is important.[4]

The occurrence of epilepsy-associated cognitive dysfunction is determined by many factors, including epilepsy-related factors, treatment-related factors, and the reserve capacity of the patients.[5] Uncontrolled epileptic seizures as well as interictal epileptiform discharges (IEDs) in areas carrying out cognitive functions may cause neuronal cell death that lead to neurodegeneration, changes in neuronal network pattern that is important in cognitive processing, and neuroplasticity disruption in the developing brain.[6] The use of antiepileptic drugs AEDs, especially older AEDs, theoretically can cause a decrease in neuronal excitability that lead to cognitive dysfunction.[7] The use of these AEDs is also associated with an increase in serum homocysteine levels which are neurotoxic through the mechanism of oxidative stress and glutamate excitotoxicity.[8] Finally, brain reserve and cognitive reserve, a concept that explains the differences in cognitive status of the different patients with similar brain lesions, also determine the susceptibility of PWE to cognitive dysfunction.[9] Brain reserve refers to the selective vulnerability of brain of PWE to neuronal damage which is commonly genetically determined, while cognitive reserve refers to the brain's ability to compensate the impact of epilepsy-related neuronal damage to cognitive function of the patients and this is determined especially by their educational level.[10,11]

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that can be proposed is the occurrence of neuronal damage induced by glutamate excitotoxicity and oxidative stress with a very complex mechanisms.[12] Elevated homocysteine levels (≥10 µmol/l) or hyperhomocysteinemia (≥15 µmol/l), both as a result of AEDs administration and genetic predisposition is the potential mechanism for these neurodegeneration processes.[13] Elevated homocysteine levels induced by AEDs administration in PWE may be related to depletion of folic acid, B6 and B12 vitamins, the important cofactors in homocysteine metabolism.[14] In other medical conditions, elevated homocysteine levels is the risk factor for Alzheimer's disease through its action in increasing neurotoxic proteins level, beta amyloid precursor protein (β-APP) and β-amyloid, which also has ability to induce both glutamate excitotoxicity and oxidative stress-related neuronal damage.[15,16] The impact of elevated homocysteine levels on cognitive dysfunction in PWE still need to be determined.

Our aim in this research was to investigate the relationship between serum homocysteine levels and the cognitive dysfunction frequency in PWE. The subjects of this study represented a population of PWE in rural areas where conventional AEDs administration was still the main strategy for seizure control.

METHODS

Study design and participants

We conducted a cross-sectional study, which included participants that were recruited consecutively. All patients were recruited from the outpatient unit of the neurology department at 3 main referral hospitals in Mataram between September 2017 and November 2019. The inclusion criteria were PWE aged ≥14 years old, at least graduated from elementary school, fully conscious, voluntary participated, and taking AEDs either as monotherapy or in combination. Exclusion criteria were those who decided not to continue their participation in the study. Ethical approval was attained from the Ethical Committee for Medical Research of Universitas Mataram with Register Number of 213/UN18.8/ETIK/2017. All participants gave their informed consent in the written form.

Data collection

The participants' age, gender, education level, etiology, and treatment duration were all taken into consideration when compiling the socio-demographic and clinical data. Age, education level, and treatment duration were expressed in years as continuous variables. Age was divided into young adulthood (40 years) and adulthood (40 years) as categorical variables. There were two genders: male and female; The number of years of education was divided into 12 and >12 years; etiology was categorized into idiopathic and structural; length of treatment was categorized into <2 years and ≥2 years; Etiology of epilepsy was considered structural if the participants had a history of significant head trauma, infection, and stroke prior to first onset of seizure. In addition, all participants also received folic acid supplementation as adjuvant therapy.

The participants' cognitive status was assessed based on the results of cognitive function tests using the Indonesian version of Montreal Cognitive Assessment (MoCA-Ina), with score range of 0-30. This instrument has been used in previous study.[3] Based on the results of the MoCA-Ina examination, participants were categorized into participants with normal cognitive status (MoCA-Ina score ≥26) and those with cognitive dysfunction (MoCA-Ina score <26).

Serum homocysteine levels were obtained from the examination of 8-10 hours fasting blood samples of participants using ELISA technique. These examinations were conducted at Laboratorium Hepatika, Mataram, Indonesia, using the FineTest® Human HCY (Homocysteine) ELISA Kit (Catalog No. EH4011) and FineTest® Human CLU (Clusterin) ELISA Kit (Catalog No. EH0004). As a continuous variable, serum homocysteine levels were expressed in µmol/l, while as a categorical variable, the levels were categorized into elevated (≥10 µmol/l) and normal (<10 µmol/l), as described in previous study.[17]

Data analysis

The socio-demographic and clinical information, serum homocysteine levels, and mental status of the patients were shown as mean ± standard deviation (SD) if continuous variables and in percentage form if categorical variables. The simple binary logistic regression model was used to determine the correlation between serum homocysteine levels, socio-demographic, and clinical variables (as independent variables) and the prevalence of cognitive dysfunction in the participants (as dependent variable), which were shown as a crude odds ratio (OR) with a 95% CI. Furthermore, independent variables of a p-value less than 0.25 were included in the analysis of multiple logistic regression with the adjusted OR of 95% CI were reported. Results were considered significant if $p<0.05$.

RESULTS

This researched recruited 81 PWE consecutively in three main referral hospitals in Mataram, Indonesia. Table 1 shows data of the socio-demographic and clinical characteristics, serum homocysteine levels, and cognitive status of the participants. Based on socio-demographic, most of the participants were at the productive age, had a relatively low level of education, and with relatively comparable proportions between male and female participants. Clinically, most of the participants had a structural etiology and had received AEDs chronically for the treatment of their epilepsy for more than 2 years. Even though the mean serum homocysteine levels of the participants were within the normal range, 30% of the participants showed elevated serum homocysteine levels (≥10 µmol/l). There were no participants whose serum homocysteine levels showed hyperhomocysteinemia (≥15 µmol/l). Finally, there was a high frequency of cognitive dysfunction among participants, which was 76.5%.

The results on the simple binary logistic regression and the multiple logistic regression analysis which looked at the relationship between the frequency of cognitive dysfunction among participants and homocysteine, socio-demographic, and clinical variables are presented in Table 2. In simple binary logistic regression, serum homocysteine levels were significantly correlated with the increase of cognitive dysfunction frequency (OR:

Table 1. Characteristics of the participants.

Variables	Mean ± SD, unless otherwise stated
Age, mean ± SD	33.4 ± 14.2
Age group, n(%)	
≥40 years	27 (33.3)
<40 years	54 (66.7)
Gender, n(%)	
Male	36 (44.4)
Female	45 (55.6)
Years of education, mean ± SD	11.7 ± 3.5
Years of education, n(%)	
≤12 years	57 (70.4)
>12 years	24 (29.6)
Etiology of epilepsy, n(%)	
Idiopathic	57 (70.4)
Structural	24 (29.6)
Length of treatment, mean ± SD	4.4 ± 4.6
Length of treatment, n(%)	
<2 years	29 (35.8)
≥2 years	52 (64.2)
Homocysteine level, mean ± SD	8.7 ± 2.0
Homocysteine level, n(%)	
Elevated (≥10 µmol/l)	25 (30.9)
Normal (<10 µmol/l)	56 (69.1)
Cognitive status, n (%)	
Normal (MoCA-Ina score ≥26)	19 (23.5)
Dysfunction (MoCA-Ina score <26)	62 (76.5)

MoCA-Ina: Montreal Cognitive Assessment in Indonesia version.

5.0; 95% CI: 1.1 – 23.7). However, this correlation was not significant in the multiple logistic regression ($p > 0.05$). The multiple logistic regression also indicated that there were no significant relationship between the socio-demographic and clinical variables and the cognitive dysfunction frequency ($p > 0.05$).

DISCUSSION

At Mataram, Indonesia, PWE were studied to see if there was any correlation between blood homocysteine levels and the cognitive dysfunction frequency. To our knowledge, this is the first study to look into the relationship between PWE's cognitive impairment and serum homocysteine levels. After adjusting for age, gender, educational level, and epilepsy etiology, the study's findings showed that serum homocysteine levels were not linked to an elevated risk of cognitive dysfunction caused by epilepsy.

The insignificant correlation between serum homocysteine levels and frequency of cognitive dysfunction in PWE shown in this study appeared to be related to the protective effect of the educational

Table 2. Binary logistic regression analysis examining association between independent variables and the frequency of cognitive dysfunction among participants.

Variables	Cognitive status		Crude OR (95% CI)[a]	p-value	Adjusted OR (95% CI)[b]	p-value
	Normal (n = 19	Dysfunction (n = 62)				
Age, n (%)						
≥40 years	3 (11.1)	24 (88.9)	3.4 (0.9 – 12.8)	0.075*	2.3 (0.4 – 13.0)	0.345
<40 years	16 (29.6)	38 (70.4)	Reference		Reference	
Gender, n (%)						
Male	4 (11.1)	32 (88.9)	4.0 (1.2 – 13.4)	0.025*	2.8 (0.6 – 12.8)	0.175
Female	15 (33.3)	30 (66.7)	Reference		Reference	
Years of education, n (%)						
≤12 years	11 (19.3)	46 (80.7)	2.1 (0.7 – 6.1)	0.178*	2.2 (0.6 – 7.7)	0.200
>12 years	8 (33.3)	16 (66.7)	Reference		Reference	
Etiology, n (%)						
Idiopathic	16 (28.1)	41 (71.9)	2.7 (0.7 – 10.4)	0.142*	1.1 (0.2 – 5.7)	0.928
Structural	3 (12.5)	21 (87.5)	Reference		Reference	
Length of treatment, n (%)						
<2 years	6 (20.7)	23 (79.3)	1.3 (0.4 – 3.8)	0.661	-	-
≥2 years	13 (25.0)	39 (75.0)	Reference			
Homocysteine levels, n (%)						
Elevated (≥10 µmol/l)	2 (8.0)	23 (92.0)	5.0 (1.1 – 23.7)	0.042*	4.5 (0.9 – 22.5)	0.069
Normal (<10 µmol/l)	17 (30.4)	39 (69.6)	Reference		Reference	

[a]Simple binary logistic regression analysis; [b]Multiple logistic regression analysis
*Eligible for final model of multiple logistic regression analysis
OR: odds ratio; CI: confidence intervals

level of the patients. Educational level, a component of cognitive reserve, is a protective factor to prevent the occurrence of neuronal damage-associated cognitive decline in the setting of various medical conditions, including epilepsy.[2] Years of education is involved in the process of establishment of more complex connectivity of neural networks in the brain. In the setting of neuronal damage, this complex connectivity of neural networks will create the compensatory mechanisms to keep the brain functioning properly through either total or partial takeover the function of those area or by activating adjacent secondary circuits.[18] A study conducted by Pai et al. showed that epilepsy patients with higher educational levels had better cognitive status compared to those with lower cognitive status.[11] However, this allegation still needs to be proven through further investigations.

As stated earlier, the molecular mechanisms underlying neuronal damage in the brain of epilepsy patients are still not well established. Homocysteine-induced oxidative stress and glutamate excitotoxicity are a mechanism that can be proposed to explain such condition, both as AEDs side effect or due to genetic predisposition. Homocysteine is an intermediate product of methionine metabolism and its normal blood levels is <10 µmol/L.[17] Once formed, homocysteine will enter re-methylation pathway to be converted to methionin which requires the the role of enzyme methylene tetrahydrofolate reductase (MTHFR) and folic acid and vitamin B12 as cofactors or enter the trans-sulfuration pathway to be converted into cysteine which requires the role of enzyme cysteine-β-synthase (CBS) and vitamin B6 as cofactors.[19] The use of AEDs is associated with a decrease in levels of folic acid and vitamin B related drugs, cofactors that are important for the process of re-methylation of homocysteine. Therefore, folic acid supplementation in all PWE participating in this study should be considered as a factor controlling their homocysteine levels resulting in both the low proportion of patients having elevated serum homocysteine levels and the insignificant relationship between serum homocysteine levels and frequency of cognitive dysfunction. However, this opinion still needs further investigation.

This study adds to giving additional proof with respect to the insignificant role of homocysteine as the risk factor for cognitive dysfunction in PWE. This study, however, has a few shortcomings. The limited sample size of the study could have had an impact on the findings, to start. This study had a small sample size since there weren't many participants who met the requirements for inclusion. Second, the cross-sectional design of this investigation prevented the establishment of a causal relationship between homocysteine and PWE cognitive impairment. Because that homocysteine's role in neurodegenerative processes is mediated by a number of chronic pathogenic processes, longitudinal investigations are necessary to prove its contribution to the emergence of cognitive dysfunction in PWE.

CONCLUSION

Serum homocysteine levels was not associated with the high frequency of cognitive dysfunction among PWE in Mataram, Indonesia. Several factors tend to influence the significance of serum homocysteine levels as a risk factor for cognitive dysfunction in epilepsy patients including age, gender, length of education, and etiology of epilepsy. However, this allegation still needs to be determined through further studies, especially with longitudinal studies using larger sample sizes.

AUTHOR CONTRIBUTION

All authors had even contributions to this article. HSH as first author was responsible for the literature search and manusript preparation. HSH, MR, YI and SBR contributed to the concepts, design of the study, literature research, clinical and experimental studies, as well as data processing. All authors also participated in manuscript finalisation.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this article.

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ETHICAL CONSIDERATION

This study was approved by Ethical Committee for Medical Research, University of Mataram (Register number: 213/UN18.8/ETIK/2017).

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