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Correlation of Brain-Derived Neurotrophin Factor Levels in Epilepsy Patients Treated with Valproic Acid and Phenytoin with Cognitive Function

Kharis Madi*, Aris Catur Bintoro, M. I. Widiastuti Samekto, Endang Kustiowati, Hexanto Muhartomo, Elta Diah

Department of Neurology, FK UNDIP, Dr. Kariadi Hospital, Semarang, Indonesia

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***Correspondence:** Kharis Madi, Department of Neurology, FK UNDIP/Dr. Kariadi Hospital, Semarang, Indonesia. E-mail: madiafnan23@gmail.com
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Abstract

BACKGROUND: Epilepsy cases requiring OAE multitherapy are found in 40% of total epilepsy cases. Many epilepsy patients are referred to Dr. Kariadi Hospital Semarang because of the occurrence of intractable epilepsy. Valproic acid is one of the OAEs that are widely used in the BPJS era in Indonesia as a combination of phenytoin. Seizures increase the expression of BDNF mRNA and protein.

METHODS: This study is a cross-sectional study that took place from January to May 2022. The subjects of this study were epilepsy patients who used a combination of phenytoin-valproic acid who met the inclusion criteria. Patient data were obtained from medical records and filling out questionnaires. Patients were asked to fast for ± 8−10 h. Furthermore, blood sampling (±5 ml) of BDNF was carried out at 08.00−10.00 WIB. Cognitive function assessments were performed using MoCA-Ina and the Hamilton depression rating scale at the same time. Data were analyzed by Spearman correlation test and partial correlation test. The results are said to be meaningful if $p < 0.05$.

RESULTS: Thirty-two study subjects used a combination of phenytoin-valproic acid. The Spearman correlation test between the relationship between BDNF levels and cognitive function in epilepsy patients treated with valproic acid and phenytoin showed a significant relationship with the direction and strength of which was strongly positive ($r = 0.676$ and $p \leq 0.001$). The partial correlation test between the relationship between BDNF levels and cognitive function after controlling for age ($r = 0.692$), seizure frequency ($r = 0.641$), duration of combination therapy ($r = 0.700$), and age of seizure onset ($r = 0.693$) remained the same, while after controlling for the level of education ($r = 0.812$) and the type of seizure ($r = 0.747$) increased.

CONCLUSION: There is a strong correlation between BDNF levels and cognitive function in epilepsy patients treated with valproic acid and phenytoin. The relationship between BDNF levels and cognitive function remained the same after controlling for age, frequency of seizures, duration of combination therapy, and age of onset of epilepsy.

Introduction

Epilepsy is defined as a condition characterized by recurrent epileptic seizures lasting more than 24 h that occur without provocation [1]. Long suffering from epilepsy affects the overall quality of life of people with epilepsy. People with epilepsy tend to be difficult to heal and require long-term therapy. Quality of life is important as an indicator of the success of health care in people with epilepsy [2].

The epilepsy study group of the Indonesian neurologist association (PERDOSSI) conducted a study in 18 hospitals in 15 cities in 2013 for 6 months. There were 2288 patients consisting of 487 new cases and 1801 old cases. The average age of new cases was 25.06 ± 16.9 years, while the average age of old cases was 29.2 ± 16.5 years. A total of 77.9% of patients went to a neurologist for the 1st time, 6.8% went to a general practitioner, while the rest went to a traditional healer and did not seek treatment [3].

BDNF is found throughout the brain, especially in the cerebral cortex and hippocampus [4]. Recent evidence has implicated BDNF in the pathophysiology of epilepsy [4], [5], [6], [7]. BDNF can be regulated by limbic seizures in animal models and in humans with epilepsy. BDNF is an attractive candidate as a biomarker of epilepsy in human cerebrospinal fluid as well as in plasma or serum. Peripheral measurements of BDNF can be obtained from blood samples [5], [6], [8]. Serum BDNF levels in adults with epilepsy have not been previously described. A recent study found decreased plasma BDNF levels in people with epilepsy [5], [6]. Several factors (gender, age, and clinical variables) were evaluated for their effect on serum BDNF levels [5], [6], [8].

Cognitive impairment reported by many journals and studies, occurs in people with epilepsy [9], [10]. Cognition is the scientific terminology of mental processes which include attention, memory, and language orientation and understanding, problem solving, and decision-making [7]. Factors that can affect

cognitive function in epilepsy, including the seizures themselves, age at onset of epilepsy, frequency and severity, damage caused by repeated or prolonged seizures, heredity, psychosocial factors, and sequelae of treatment for epilepsy, including antiepileptic drugs (OAE) and epilepsy surgery [9], [10].

BDNF has been reported to affect development, cognition, attention, and behavior. BDNF is essential for neural plasticity and facilitates long-term hippocampal and cortical potentiation, which are processes that are critical for learning and memory. BDNF plays an important role in learning and memory. The neurotrophic hypothesis of depression suggests that stress-related changes in BDNF levels occur in limbic structures [5], [6], [11], [12].

Epilepsy cases requiring multitherapy with OAE are found in 40% of total epilepsy cases worldwide, of which the percentage is higher in the developing countries [9], [13]. Various factors that influence multitherapy with OAE in epilepsy are the patient's own epilepsy, who require more than OAE monotherapy and also the level of patient compliance in taking OAE [9], [13].

Methods

This research has received permission from the Research Ethics Commission of Dr. Kariadi Hospital Semarang with the number 867/EC/KEPK-RSDK/2021 dated August 3, 2021. This research is a *cross-sectional study*, which was conducted at the Neurology Poly Hospital of Dr. Kariadi Semarang in January–May 2022.

Subjects

A total of 32 patients (18 males and 14 females) with epilepsy (aged 20–60 years) who received valproic acid-phenytoin combination treatment for more than 1 year and met the inclusion and exclusion criteria.

Measurement of serum BDNF

Serum BDNF levels were measured using Quantikine ELISA. Our patient asked to fast for ± 8±10 h. Furthermore, blood sampling (± 5 ml) of BDNF was carried out at 08.00–10.00 WIB [6], [7], [14]. Blood samples were taken in the outpatient laboratory of Dr. Kariadi Hospital Semarang. The blood sample was inverted until homogeneous, allowed to stand for 30−45 min until the blood was frozen. The blood sample taken will be examined at the Prodia Jakarta laboratory. Blood samples were immediately centrifuged at 3000 rpm for 15 min, separate the serum, and put it in 5 sample cups at 0.3 cc of serum (give identification, name, and date), stored at −20°C.

Statistical analysis

Data analysis includes descriptive analysis and statistical analysis. The stages of descriptive statistics are to determine the basic characteristics of research subjects and statistical analysis to see correlations. The normality test of the data carried out was the *Shapiro-Wilk test*, the results obtained were p = 0.05, which means that the data are not normal. To determine the relationship between BDNF levels and cognitive function, a bivariate test with Spearman correlation test was performed. The results are said to be meaningful if p<0.05. Partial correlation test was conducted to determine the effect of variables on the relationship between BDNF levels and cognitive function in epilepsy patients treated with valproic acid and phenytoin.

Results

Characteristics and demographics of research subjects demographic

Characteristics of research subjects are age, gender, and education level which are shown in Table 1. Table 2 shows the clinical characteristics of research subjects consisting of seizure frequency, duration of combination therapy, seizure onset, type of seizure, and scoring MoCA-Ina and BDNF values.

Table 1: Demographic characteristics of research subjects

Variable	F (%)	Median (minimum–maximum)
Age (years)		34.00 (20–60)
Gender		
Male	18 (56.3)	
Female	14 (43.7)	
Level of education		
Primary school	3 (9.4)	
Junior high school	6 (18.8)	
Senior high school	17 (53.1)	
College (S1)	6 (18.8)	

Table 1 shows that the average age of the patients was 34 (20−60) years. The gender of the research subjects was male 18 subjects (56.3%) and female 14 subjects (43.7%). The education level of the research subjects obtained elementary school 3 subjects (9.4%), junior high school 6 subjects (18.8%), high school 17 subjects (53.1%), and college 6 subjects (18.8%).

Table 2 shows the average frequency of seizures 2 times (1−25) per month, the average duration of combination therapy is 10 (1−30) years, and the average age of seizure onset is 10 (1−32) years. Based on the type of seizure, there were 10 subjects (31.3%), general-onset seizures (37.4%), and 10 subjects

(31.3%). Based on the MoCA-Ina scoring, the average score was 26.50 (22−28). Based on the value of BDNF levels, an average of 39.93 (19.66−47.20) ng/mL was obtained.

Table 2: Clinical characteristics of research subjects

Variable	F (%)	Mean ± SD	Median (minimum–maximum)
Frequency of seizures (months)		3.72 ± 4.706	2.00 (1–25)
Duration of combination therapy (years)		10.88 ± 8.245	10.00 (1–30)
Age of seizure onset (years)		12.00 ± 8.977	10.00 (1–32)
Type of seizure			
Focal onset	10 (31.3)		
General onset	12 (37.4)		
Focal onset to bilateral	10 (31.3)		
MoCA-Ina scoring			26.50 (22–28)
BDNF levels		38.07 ± 6.140	39.93 (19.66–47.20)

BDNF: Brain-derived neurotrophin factor, SD: Standard deviation.

Relationship between BDNF levels and cognitive function in epileptic patients

Researchers used the Spearman correlation test to see the significance of the relationship between BDNF levels and cognitive function scores in epilepsy patients treated with valproic acid and phenytoin (Table 3).

Table 3: The relationship between brain-derived neurotrophin factor levels with cognitive function score

Variable	MoCA-Ina	
	Rho	p
BDNF level	0.676	< 0.001*

Description: p < 0.05 significant, *Spearman correlation test. BDNF: Brain-derived neurotrophin factor.

Table 3 shows that the relationship between BDNF levels and cognitive function scores has a significant relationship (p ≤ 0.001) with the direction and strength of the relationship being strong positive (r = 0.676).

Relationship of BDNF levels with cognitive function by controlling epilepsy factors

Based on Table 4, it can be seen that there was no change between BDNF levels and cognitive function before controlling for age (r = 0.676, p ≤ 0.001). After controlling for age, there was no significant change with the same strength correlation (r = 0.692, p ≤ 0.001). There was no change between BDNF levels and cognitive function before controlling for education level (r = 0.676, p ≤ 0.001). After controlling for the level of education, there was a change in the strength of the correlation which was increasing (r=0.812, p ≤ 0.001). There was no change between BDNF levels and cognitive function before controlling for seizure frequency (r = 0.676, p ≤ 0.001). After controlling for seizure frequency, there was no significant change with the correlation strength which was still the same (r = 0.641, p ≤ 0.001). There was no change between BDNF levels and cognitive function before controlling for combination therapy (r = 0.676, p ≤ 0.001). After controlling for the duration of combination therapy, there was no significant change with the correlation strength being the same (r = 0.700, p ≤ 0.001). There was no change between BDNF score and cognitive function before controlling for seizure onset (r = 0.676, p ≤ 0.001). After controlling for seizure onset, there was no significant change with the same correlation strength (r = 0.693, p ≤ 0.001). There was no change between BDNF score and cognitive function before controlling for seizure type (r = 0.676, p ≤ 0.001). After controlling for the type of seizure, there was a change in the strength of the correlation which was increasing (r = 0.747, p ≤ 0.001).

Table 4: Relationship of brain-derived neurotrophin factor levels with cognitive function by controlling for age, education level, frequency of seizures, duration of combination therapy, age of onset of epilepsy, and type of seizures

Variable	Relationship of BDNF levels with cognitive function	
	Rho	p
Age	0.692	< 0.001$
Education level	0.812	< 0.001$
Seizure frequency	0.641	< 0.001$
Duration of combination therapy	0.700	< 0.001$
Age of seizure onset	0.693	< 0.001$
Type of seizure	0.747	< 0.001$

Description: p < 0.05 significant, $Partial correlation test. BDNF: Brain-derived neurotrophin factor.

Discussion

Thirty-two subjects in this study obtained an average value of 39.93 BNDF levels (19.66−47.20 ng/mL). Compared to the results of other studies, Fang Chen *et al*. (2018) reported the value of serum BDNF levels in epilepsy patients 23.31 ± 8.61 ng/mL and control patients 29.52 ± 8.39 ng/mL [14], Ching Chen *et al*. (2016) reported a serum BDNF level of 26.1 ± 10.6 ng/mL [12], Jun Lee *et al*. (2015) reported a serum BDNF value of 28.9 ± 6.9 ng/mL [11], and Schmolesky *et al*. (2013) reported a BDNF 24.95 ± 7.28 ng/mL [8]. Cho *et al*. (2012) reported a serum BDNF level of 22.94 ± 2.94 ng/mL [8]. Nofuji *et al*. (2008) reported a serum BDNF level of 14.9 ± 5.0 ng/mL [8]. This shows that there is still no reference to the normal value of serum BDNF levels due to differences in the number and characteristics of research subjects in each country. In this study, with a mean BDNF level of 39.93 (19.66–47.20) ng/mL with a mean cognitive function score of 26.50 (22−28), it can be thought that the average BDNF value is normal.

Based on this study, there was a significant relationship (r = 0.676, p ≤ 0.001) between BDNF levels and cognitive function which had a strong positive correlation coefficient. The higher the BDNF level, the better cognitive function. This is supported by the study of Ching Chen *et al*. (2016) which examined 34 epileptic patients and 22 normal patients, the mean age was 39.8 ± 11.1 years, the mean seizure frequency was 3.5 ± 8.0 per month, the mean seizure onset was 26.1 ±11.6 per year, using OAE multitherapy for more than 2 years, stated that there was a significant relationship with moderate

correlation strength (r = 0.425, p = 0.001) between BDNF levels and cognitive function in epilepsy patients [7]. BDNF can relieve neurological damage caused by diseases such as Alzheimer's, Parkinson's, *Spinal Cord Injury*, stroke, and other neurological disorders, besides that BDNF is also closely related to the development of cognitive function, learning processes, memory, and depression. BDNF can regulate synaptic plasticity and *long-term potentiation* (LTP) in the hippocampus and other brain regions to influence learning and memory [15], [16], [17].

The relationship between BDNF levels in epileptic patients treated with phenytoin and valproic acid with cognitive function after controlling for age did not change (r = 0.692, p ≤ 0.001) so that age does not affect the relationship between BDNF levels and cognitive function. This is because most of the subjects in this study had a mean age of 34 (20−60) years. The study by Hong *et al*. (2014) stated that there was no significant relationship between the relationship between BDNF levels and age in epilepsy patients (p = 0.37) [5]. Age is not an important factor associated with serum BDNF levels in epilepsy patients. The results of this study are different from research by Fang Chen *et al*. (2018) which stated that there was a significant relationship (p = 0.018) decreased serum BDNF levels with age in epilepsy patients [14]. The study by LaFrance *et al*. (2010) which examined epilepsy patients, the mean age was 43.60 ± 16.57 years, stated that there was a significant relationship (p ≤ 0.001) decreased serum BDNF levels with advanced age in epilepsy patients [18].

There is a change between the relationship between BDNF levels and cognitive function after being controlled by education level, there is a change in the strength of the correlation which is increasing (r = 0.812, p ≤ 0.001) so that the level of education affects the relationship between BDNF levels and cognitive function. This is supported by the study of Wang *et al*. (2010) showing that there is a significant difference (p ≤ 0.001) cognitive function among epilepsy patients with elementary, junior high, high school, and college education. These results indicate that a high school education level of equivalent or higher can have a protective effect on the cognitive function of people with epilepsy. A study by Pai and Tsai (2005) higher education level has better performance in cognitive function. These findings suggest that training with education can compensate for cognitive decline. A study by Yusril *et al*. (2019) examined cognitive function in 42 epilepsy patients where the higher the education level of the subject, the smaller the proportion of impaired cognitive function due to epilepsy [18].

There was no change in the relationship between BDNF levels and cognitive function after controlling for seizure frequency (r = 0.641, p ≤ 0.001) so that the frequency of seizures does not affect the relationship between BDNF levels and cognitive function. This is because in this study, the average seizure frequency was 2 times per month. The study by Hong *et al*. (2014) also said that there was no significant relationship between BDNF levels and seizure frequency (p = 0.06) [5]. This is because apart from the frequency of seizures, BDNF levels are also influenced by medication, duration of seizures, and type of seizures [5]. This is in contrast to a study by Alvim *et al*. (2017) examining 251 epilepsy patients, aged 18−70 years, who had consumed AEDs for more than 1 year, reporting that serum BDNF levels were significantly associated (p = 0.006) with seizure frequency in epilepsy patients [19]. This is supported by Alessio *et al*. who said that the frequency of seizures is one of the factors causing hippocampal atrophy and decreased levels of BDNF and cognitive function in epilepsy patients.

There was no relationship between BDNF levels and cognitive function after controlling for the duration of combination therapy with OAE (r = 0.700, p ≤ 0.001) so that the duration of combination therapy does not affect the relationship between BDNF levels and cognitive function. This is in accordance with the study by Fang Chen *et al*. (2018) which stated that the duration of OAE therapy did not have a significant relationship with serum BDNF levels (p = 0.67) [14]. Demir *et al*. (2019) showed a high level of BDNF in the duration of OAE treatment with efficient, safe, and appropriate doses and a low level of BDNF in the opposite and resistant cases mostly according to the clinical picture of the patient. This suggests a risk of neurotoxicity and reduces the neuroprotective effect of BDNF. With the minimum dose of OAE required to control seizures, duration of therapy and number of OAEs can increase BDNF levels [20]. In this study, it was found that the average duration of combination therapy was 10 (1–30) years, the mean BDNF level was 39.93 (19.66−47.20) ng/mL and the mean cognitive function was 26.50 (22−28).

There was no correlation between BDNF levels and cognitive function after controlling for age of seizure onset (r = 0.693, p ≤ 0.001) so that the age of seizure onset does not affect the relationship between BDNF levels and cognitive function. This is in accordance with the study by Fang Chen *et al*. (2018) which examined epilepsy patients with a mean age of seizure onset of 17.6 ± 10.49 years which stated that there was no significant relationship (r = −0.024, p = 0.861) between BDNF levels and age seizure onset [14].

There was a change between the relationship between BDNF levels and cognitive function after controlling for the type of seizure, a change in the strength of the correlation was increasing (r = 0.747, p ≤ 0.001). The 32 subjects in this study had focal onset seizures in 10 subjects (31.3%), general onset 12 subjects (37.4%), and focal onset to bilateral 10 subjects (31.3%) and found higher levels of BDNF in focal epilepsy patients. compared to generalized epilepsy so that the type of

seizure affects the relationship between BDNF levels and cognitive function. A study by Fang Chen *et al.* (2018) which examined 57 epilepsy patients with multitherapy OAE treatment reported that serum BDNF levels were significantly (p = 0.039) correlated with seizure type, BDNF levels were found to be higher in patients with focal epilepsy than generalized epilepsy [14]. This is in contrast to the study by Poniatowski *et al*. (2021) who reported a significant decrease in serum BDNF levels (p = 0.033) in patients with generalized tonic–clonic seizures [21]. Demir *et al*. (2019) stated regarding the effects of focal/generalized seizures, certain pharmacokinetic effects of OAE, and differences in BDNF could be attributed to the mechanism of epsilon activation of BDNF and protein kinase C (PKC) and GABA receptor-mediated responses [20].

Limitation of this study is that this study is a *cross-sectional*, data on the duration of combination therapy, age of onset of epilepsy, frequency of seizures, and types of seizures using medical records and questionnaires so that it relies on information from patients which can lead to memory bias. Dosage and drug levels of phenytoin and valproic acid were not taken into account, examination of BDNF levels, Hamilton depression scale, and MoCA-Ina which were not carried out simultaneously by considering the time of the study and did not evaluate compliance factors patients on epilepsy treatment.

Conclusion

There is a strong correlation between levels of *Brain-Derived Neurotrophin Factor* (BNDF) and cognitive function in epilepsy patients treated with valproic acid and phenytoin.

The relationship between *Brain-Derived Neurotrophin Factor (BDNF)* and cognitive function was still strong after controlling for age, frequency of seizures, duration of combination therapy, and age of seizure onset, in epilepsy patients treated with valproic acid and phenytoin.

The relationship between levels of *Brain-Derived Neurotrophin Factor* (BDNF) and improved cognitive function after controlling for education level and type of seizure in epilepsy patients treated with valproic acid and phenytoin.

References

1. Fisher RS, Cross JH, D'Souza C, French JA, Haut SR, Higurashi N, *et al*. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia. 2017;58(4):531-42. https://doi.org/10.1111/epi.13671
   PMid:28276064
2. Kurita T, Sakurai K, Takeda Y, Horinouchi T, Kusumi I. Very long-term outcome of non-surgically treated patients with temporal lobe epilepsy with hippocampal sclerosis : A retrospective study. PLoS One. 2016;11(7):e0159464. https://doi.org/10.1371/journal.pone.0159464
   PMid:27415827
3. Kelompok Studi Epilepsi Perhimpunan Dokter Spesialis Saraf Indonesia (PERDOSSI). In: Kusumastuti K, Gunadharma SK, editor. Pedoman Tatalaksana Epilepsi. PERDOSSI; Jakarta: 2014. p. 1-96.
4. Lähteinen S. Brain-Derived Neurotrophic Factor in the Development of Epilepsy (Aivoperäisen Hermokasvutekijän Vaikutus Epilepsian Kehittymiseen). Kuopion: Kuopion Yliopisto; 2004.
5. Hong Z, Li W, Qu B, Zou X, Chen J, Sander JW, *et al*. Serum brain-derived neurotrophic factor levels in epilepsy. Eur J Neurol. 2014;21(1):57-64. https://doi.org/10.1111/ene.12232
   PMid:23879572
6. Chen NC, Chen HH, Chuang YC, Huang CW, Chang YT, Hsu SW, *et al*. Serum brain-derived neurotrophic factor level and depressive severity in patients with chronic temporal lobe epilepsy : A case-control study. Neuropsychiatry. 2017;7(3):238-45. https://doi.org/10.4172/Neuropsychiatry.1000205
7. Guimarães DF. The Role of Brain Derived Neurotrophic Factor (BDNF) on Epilepsy, PhD Thesis. Portugal: University of Lisbon Faculty of Medicine; 2016. p. 1-44.
8. Goda A, Ohgi S, Kinpara K, Shigemori K, Fukuda K, Schneider EB. Changes in serum BDNF levels associated with moderate-intensity exercise in healthy young Japanese men. Springerplus. 2013;2:678. https://doi.org/10.1186/2193-1801-2-678
   PMid:24386624
9. Natriana T. Perbedaan Pengaruh Pengobatan Monoterapi Fenitoin dan Karbamazepin terhadap Memori Penderita Epilepsi Grand Mal. Masters Tesis. Indonesia: Bagian/KSM Neurologi UNDIP; 2001.
10. Taylor J, Baker GA. Newly diagnosed epilepsy : Cognitive outcome at 5 years. Epilepsy Behav. 2010;18(4):397-403. https://doi.org/10.1016/j.yebeh.2010.05.007
    PMid:20558112
11. Lee SJ, Baek JH, Kim YH. Brain-derived neurotrophic factor is associated with cognitive impairment in elderly Korean individuals. Clin Psychopharmacol Neurosci. 2015;13(3):283-7. https://doi.org/10.9758/cpn.2015.13.3.283
    PMid:26598587
12. Chen NC, Chuang YC, Huang CW, Lui CC, Lee CC, Hsu SW, *et al*. Interictal serum brain-derived neurotrophic factor level reflects white matter integrity, epilepsy severity, and cognitive dysfunction in chronic temporal lobe epilepsy. Epilepsy Behav. 2016;59:147-54. https://doi.org/10.1016/j.yebeh.2016.02.029
    PMid:27152461
13. Ladino LD, Moien F, Téllez-Zenteno JF. A comprehensive review of temporal lobe epilepsy. In: Epilepsia. 2011. p. 442-66.
14. Chen SF, Jou SB, Chen NC, Chuang HY, Huang CR, Tsai MH, *et al*. Serum levels of brain-derived neurotrophic factor and insulin-like growth factor 1 are associated with autonomic dysfunction and impaired cerebral autoregulation in patients with Epilepsy. Front Neurol. 2018;9:969. https://doi.org/10.3389/fneur.2018.00969
    PMid:30524358
15. Müller P, Duderstadt Y, Lessmann V, Müller NG. Lactate and BDNF : Key mediators of exercise induced neuroplasticity ? J Clin Med. 2020;9(4):1136. https://doi.org/10.3390/jcm9041136
    PMid:32326586

16. Lenck-Santini PP, Scott RC. Mechanisms responsible for cognitive impairment in epilepsy. Cold Spring Harb Perspect Med. 2015;5(10):a022772. https://doi.org/10.1101/cshperspect.a022772

PMid:26337111

17. Silakarma D, Sudewi AA. The role of brain-derived neurotrophic factor (BDNF) in cognitive functions. Bali Med J. 2019;8(2):427-34. https://doi.org/10.15562/bmj.v8i2.1460

18. LaFrance WC Jr., Leaver K, Stopa EG, Papandonatos GD, Blum AS. Decreased serum BDNF levels in patients with epileptic and psychogenic nonepileptic seizures. Neurology. 2010;75(14):1285-91. https://doi.org/10.1212/WNL.0b013e3181f612bb

PMid:20921514

19. Alvim MK, Yasuda CL, Morita ME, Coan AC, Barbosa R, Vieira EL, *et al*. The relationship between blood serum BDNF and seizure frequency in temporal lobe epilepsy patients. J Neurol Sci. 2017;381:334. https://doi.org/10.1016/j.jns.2017.08.948

20. Demir M, Akarsu EO, Dede HO, Bebek N, Yıldız SO, Baykan B, *et al*. Investigation of the roles of new antiepileptic drugs and serum BDNF levels in efficacy and safety monitoring and quality of life: A clinical research. Curr Clin Pharmacol. 2020;15(1):49-63. https://doi.org/10.2174/1574884714666190312145409

PMid:30864528

21. Poniatowski ŁA, Cudna A, Kurczych K, Bronisz E, Kurkowska-Jastrzębska I. Kinetics of serum brain-derived neurotrophic factor (BDNF) concentration levels in epileptic patients after generalized tonic-clonic seizures. Epilepsy Res. 2021;173:106612. https://doi.org/10.1016/j.eplepsyres.2021.106612

PMid:33774427