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Role of Neurogenesis and Oxidative Stress in Epilepsy (Study on Plasma Brain Derived Neurotrophic Factor and Malondialdehyde Level)

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Abstract

BACKGROUND: Epilepsy is a neurological disorder. Its incidence in Indonesia was 700,000–1,400,000 cases and 40–50% occurred in children. About 30–40% of cases in children had uncontrolled seizures. Biomarkers are needed to assess the prognostic value of patients with uncontrolled epilepsy. Malondialdehyde (MDA) and brain-derived neurotrophic factor (BDNF) are one of the prognostic biomarkers related to uncontrolled epilepsy to see the effect of oxidative stress and neuroplasticity.

AIM: The objective of the study was to examine cut off value of plasma BDNF and MDA level; and to compare plasma BDNF and MDA levels in uncontrolled and controlled epilepsy patients.

METHODS: The research usedanalytic observational with cross-sectional approach. Number of respondents was 30 patients of epilepsy who came to Ulin Hospital Banjarmasin. Respondents were divided into two groups (controlled and uncontrolled epilepsy). Blood plasma was examined for MDA with a spectrophotometer and BDNF with ELISA. Data were analyzed by t-test with 95% confidence level.

RESULTS: 11 children were found in the uncontrolled epilepsy group and 19 children with controlled epilepsy. The result showed that there were significant differences between type of therapy and developmental disorders/other diseases with epilepsy status. There was no significant differences of plasma BDNF in epilepsy status (controlled and uncontrolled epilepsy), and there was also no significant differences of plasma MDA in epilepsy status (controlled and uncontrolled epilepsy).

CONCLUSION: There were no significant differences of plasma BDNF and MDA in epilepsy status.

Introduction

Epilepsy according to the International League Against Epilepsy 2017 is defined as one of the following conditions: (1) At least 2 unprovoked (or reflex) seizures lasting >24 h; (2) 1 unprovoked (or reflex) seizure and a possible subsequent seizure with a general recurrence risk (at least 60%) after two unprovoked seizures, occurring more than 10 years; and (3) diagnosis of epilepsy syndrome [1]. Uncontrolled seizures were defined as seizures that persist despite taking 1 or 2 first-line anti-seizure drugs and having a frequency of more than 1 (one) seizure per month for the past 6 months [2]. Cognitive impairment is one of the effects of uncontrolled seizures [3]. Uncontrolled seizures can become a major global burden of health problems for patients, families, and communities based on the presence of disability, mortality, and high costs in epilepsy management [4], [5]. The cause of uncontrolled seizures is one of five categories, namely, poor adherence, wrong medication (misclassification), wrong dose of correct medication, diagnosis other than epilepsy, and refractory epilepsy [6].

Indonesia is a developing country with 700,000–1,400,000 cases of epilepsy, with an increase of 70,000 new cases every year and an estimated 40–50% occurring in children [7]. Monthly outpatient data at the pediatrician polyclinic of Ulin Hospital (neurologist service) was 25–30 cases of epilepsy [8]. The percentage of epilepsy having seizures that are not controlled by treatment is around 30–40% [9].

Research has shown a strong relationship between epileptogenesis and oxidative stress, inflammation and mitochondrial disorders. Reactive oxygen species (ROS) are the most studied oxidants and cause anti-epileptic drug resistance mainly through regulation of the expression and activity of the ATP-binding cassette transporter. Malondialdehyde (MDA) is a secondary lipid peroxidation product resulting from the reaction between ROS and lipid components. There is a causal relationship between oxidative stress and anti-epilepsy drug resistance. Seizures cause mitochondrial damage and increase ROS production.

Research has shown a significant increase in MDA levels in epilepsy [10].

Brain derived neurotrophic factor (BDNF) is one of the four neurotropins that belong to the class of neurotrophic factors. BDNF is a neurotrophin that is widely distributed in the central nervous system (CNS). BDNF has several functions including axonal regulation, dendritic growth, neurotransmitter release, and long-term potentiation. According to this function, BDNF has a role as a major regulator of synaptic plasticity [11], [12], [13]. Serum BDNF levels are negatively correlated with epilepsy and more seizure frequency [14]. BDNF concentrations are mainly in the hippocampus and entorhinal cortex, areas involved in the epileptogenesis of temporal lobe epilepsy (TLE) [10].

Neuroplasticity and oxidative stress are biomarkers that can be an alternative to assess the severity of epilepsy due to uncontrolled seizures. Based on this background, this research was conducted with the aim of examining cutoff value of plasma BDNF and MDA level, and comparing plasma BDNF and MDA levels in uncontrolled and controlled epilepsy patients.

Methods

This research used observational study with cross sectional approach. Data were taken from the history of patients who came to Ulin Hospital Banjarmasin for outpatient treatment and examination of plasma BDNF levels using the ELISA method and plasma MDA levels using a spectrophotometer.

The study population was all epilepsy patients at Ulin Hospital Banjarmasin. The research sample was taken by consecutive sampling method. The number of respondents was 30 patients (based on Gay and Diehl), divided into two groups, namely, the uncontrolled epilepsy group and the controlled epilepsy group.

Patient characteristics would be identified as descriptive analyzes. The characteristics were gender, history of therapy, age of first seizure, age group, cerebral palsy (CP), nutritional status, developmental disorders/other diseases, low birth weight at birth, birth history, and electroencephalography (EEG) results. Independent variable was epilepsy status. Dependent variables were plasma BDNF and MDA level.

The process of collecting primary data from the patient's history and secondary data from medical records. All data were presented in descriptive and inferential analyses. Inferential analysis used unpaired t-test if data distribution was normal. If data distribution was not normal, the test used Mann–Whitney U test with a 95% confidence level.

Results

Characteristics of respondents

Epilepsy patients who came to pediatrician polyclinic of Ulin Hospital (neurologist service) were 30 patients. All of those patients were get as respondents. There were 11 children who had uncontrolled epilepsy, and 19 children who had controlled epilepsy.

Table 1 shows the results of the patients characteristics. It describes gender, history of therapy, age of first seizure, age group, CP, nutritional status, developmental disorders/other diseases, low birth weight at birth, birth history, and EEG results. Epileptic waves are described in the characteristics of the research subjects in Table 1 descriptively below.

Table 1: Characteristics of respondents

Name of variable	Amount	
	Frequency	Percentage
Gender		
Male	14	46.6
Female	16	53.3
Therapy history		
1 anti-epilepsy drug	23	76.7
>1 anti-epilepsy drug	7	23.3
Age of first seizure		
<1-year-old	18	60.0
1–5-year-old	10	33.3
≥5-year-old	2	6.7
Age group		
<5-year-old	12	40
5–10-year-old	5	16.7
>10-year-old	13	43.3
Cerebral palsy		
Yes	12	40
No	18	60
Nutritional status		
Good nutrition	16	53.3
Poor nutrition	5	16.7
Malnutrition	7	23.3
Obesity	2	6.7
Developmental disorders/other diseases		
Disturbance	12	40
No disturbance	18	60
Low birth weight at birth		
Low birth weight	28	93.33
Normal birth weight	2	6.66
Delivery history		
Normal delivery	28	93.33
Premature delivery	2	6.66
EEG results show epileptic waves		
Yes	13	43.3
No	17	56.7

Based on Table 1, the basic characteristics of the research sample that describe the characteristics of the history of epilepsy patients based on their status and disease history include the sex variable where from the number of epilepsy patients as many as 30 people who came during the study period at Ulin Hospital, more women than men, with 23 people (76.7%). Epidemiological studies show no difference in the incidence of epilepsy in men and women, there is a significant difference in the impact and effect of the condition between men and women. There are studies showing that women have a slightly lower incidence of epilepsy than men [15], [16].

Variables based on the age of patients with epilepsy in this study at Ulin Hospital Banjarmasin found that patients with age >10 years were 43.3% which was almost the same as the number of cases aged <5 years,

namely, 40%. While the age of 1–5 years of cases found by 16%. This illustrates that most cases of epilepsy are suffered by children aged under 1 year and the age range is >10 years. The estimated number of epilepsy in Indonesia is 1.5 million with a prevalence of 0.5–0.6% of the total population of Indonesia. The frequency of occurrence of epilepsy according to age in Indonesia is very limited, but generally in developing countries the distribution of epilepsy sufferers is greater in children and young adults compared to other age groups. The prevalence of epilepsy in infants and children to cases of epilepsy is quite high, but decreases in young and middle adults. Number of 700,000–1,400,000 cases of epilepsy with an increase of 70,000 new cases every year and it is estimated that 40–50% occur in children [7]. The peak incidence occurs in children under 15 years (50.14/100,000 new cases per year) and especially in the 1st year of life with an incidence of 92.8/100,000 new cases per year. In this regard, it should be taken into account that children with an immature CNS are more prone to seizures and at the same time refractory to the consequences of acute attacks [17].

Characteristics of epilepsy patients with a diagnosis of CP diagnosed by a pediatrician and recorded in the patient's medical record as many as 12 people (40%) who had CP while those who did not have CP were 18 (60%). CP is the most common cause associated with a complex group of disorders, including epilepsy as a comorbid, which is reported to affect approximately 40% of childhood. A retrospective study of the Pavone study, 2021 involved a group of children with CP, some of whom also had epilepsy. Epileptic seizures were found, on average, within the 2nd year of life in children with CP, whereas in the control group, the onset was around 5 years of age. CP pediatric patients with epilepsy most often undergo anti-epilepsy drug polytherapy treatment [18].

The results of this study are supported by research from Solvejg L, 2019 in his research "Suboptimal Nutrition and Low Physical Activity Are Observed Together with Reduced Plasma BDNF Concentration in Children with Severe CP." With CP neuromuscular deficits and impaired mobility have a negative impact on their level of physical activity and nutritional status [19].

Characteristics of epilepsy patients with nutritional status conditions which were divided into four groups, namely, nutritional status with obesity (BB/TB >95% according to the CDC curve and ≥3 SD according to the World Health Organization [WHO] curve) as many as 2 people (6.7%), with malnutrition (BW/TB 70–90% according to the CDC curve and −3 <SD ≤2 according to the WHO curve) as many as 7 people (23.3%), Malnutrition (BW/TB <70% according to the CDC curve and ≤3 SD according to the WHO curve) as many as 5 people (16.7%), while with good nutritional status as many as 16 (53.3%). The criteria were based on the WHO curve at age <5 years and the CDC curve at age more than 5 years. Determining nutritional status in CP patients using the CP curve.

Nutritional status in children is a condition of socioeconomic status in a family. Nutritional status can be a determining factor and trigger the occurrence of imbalances in the human body, especially in children in the period of growth and development. The WHO stipulates that the fulfillment of good nutrition begins with the time of pregnancy (1000 days of child age). It can be felt the impact that has the potential to occur stunting cases in children. It is clear that the cases in this study with problematic nutritional status have the potential for patients with severe epilepsy. This is in line with the results of Rostika's research, 2021 on "Brain Derived Neurotrophic (BDNF) serum and Intelligence Levels of Elementary School Children in Rural Areas, Seluma Regency." With the aim of the study to analyze the relationship between levels of BDNF with intelligence levels in elementary school children in rural areas. The results of the study found a significant relationship between BDNF and the intelligence level of elementary school students in rural areas. Elementary school children in rural areas with BDNF levels below the average have a 7538 times risk of having an intelligence level below the average [20].

In the study, it was found that 40% of epilepsy patients had developmental disorders and other diseases. There are 12 children with developmental disorders/diseases. There are 2 children with a diagnosis of tuberculosis. There is 1 child with a diagnosis of attention deficit hyperactivity disorder. There are four children with a diagnosis of Global development delay. There are three children with a diagnosis of laryngomalacia. There are two children with a diagnosis of mental retardation. There are three children with a diagnosis of speech delay. There is one child with a diagnosis of nephrotic syndrome. There is one child with a diagnosis of West syndrome.

In Syafrita's study, 2020 on "The Correlation of BDNF Serum Levels with Cognitive Disorders after Head Injury" it was found that the average serum BDNF level at the beginning was 576.85 ± 306.65 pg/mL which increased significantly 1 month later after head injury 897.46 ± 344.92 pg/mL. There was also a significant relationship between decreased serum BDNF levels at baseline and impaired cognitive function, as well as between BDNF levels at 1 month of onset, age, Glasgow coma scale scores, and length of education with impaired cognitive function after head injury [11]. The results of other studies also provide an overview related to cases of this congenital disease in people with epilepsy, namely the results of research by Sjahrir, 2018 "The Relationship of BDNF Levels in Serum with the Degree of Depression Symptoms in Patients with Psoriasis Vulgaris," from the results of this study there is a strong negative relationship between serum BDNF levels and the degree of depressive symptoms in psoriasis vulgaris patients. So the study concluded that

in patients with psoriasis vulgaris, the lower the serum BDNF level, the more severe the degree of depressive symptoms [21].

In the results of the characteristics of the EEG results of epilepsy patients with epileptic waves of 43.3% and 56.7% who did not have epileptic wave conditions. In Iwan Setiawan's 2018 study, it was related to early EEG therapy as a predictor of recurrence in epilepsy patients receiving anti-epilepsy drug therapy. The results of this study are certainly in line with the findings of this study, namely the study of BDNF and MDA. The results of this study concluded from this study that abnormal EEG images were a predictor of recurrence in epilepsy patients who received anti-epilepsy drug [22].

The table of analysis of the relationship between the characteristics of the respondents shows that only the type of therapy is related to epilepsy status and the presence of developmental disorders/other diseases. Patients who received 1 type of anti-epilepsy drug had an increased probability of controlled epilepsy status 2.74 times greater than those who received >1 anti-epilepsy drug. The use of 1 anti-epilepsy drug will minimize the risk of adverse drug reactions (ards) so that it will reduce the risk of cell damage, especially brain cells [23]. Thus, 1 type of anti-epilepsy drug will reduce the risk of seizures so that patients tend to be controlled.

Another respondent characteristic related to the status of epilepsy is the presence of developmental disorders/other illnesses suffered. If the patient has a developmental disorder/suffers from a disease other than epilepsy, it will reduce the chances of developing controlled epilepsy. Some diseases suffered by epilepsy patients will make these patients more difficult to treat, so the possibility of controlled epilepsy status is also smaller [24].

Each subject was analyzed by Chi-square test to determine the significance of the relationship between respondent characteristics and controlled or uncontrolled epilepsy status. The analysis is as in the following Table:

Table 2 above shows that there is a relationship between the type of therapy and the patient's epilepsy status with p = 0.023. Type of therapy 1 anti-epilepsy drug will cause controlled epilepsy 2.74 times >1 anti-epilepsy drug. The presence of developmental disorders/other diseases suffered related to the patient's epilepsy status. Epileptic patients who have developmental disorders or suffer from other diseases will reduce the chances of epilepsy patients being controlled.

Plasma BDNF level analysis

BDNF analysis was performed using ELISA, the average levels in epilepsy patients are presented in the following table:

Table 2: Analysis of the relationship between respondent characteristics and epilepsy status

Characteristics of respondents	Epilepsy status		Total	p-value	Prevalence risk
	Controlled	uncontrolled			
Gender					
Male	6	7	13	0.519	-
Female	11	6	17		
Type of therapy					
1 anti-epilepsy drug	14	5	19	0.023*	2.74
>1 anti-epilepsy drug	3	8	11		
Age of first seizure					
<1 year old	4	5	9	0.443	-
1–5 years old	13	8	21		
Patient age					
<5 years old	5	4	9	0.966	-
5–10 years old	6	5	11		
>10 years old	6	4	10		
Cerebral palsy					
There is Cerebral palsy	4	8	12	0.084	-
There is no Cerebral palsy	13	5	18		
Nutritional status					
Good nutrition	11	5	16	0.293	-
Poor nutrition	1	4	5		
Malnutrition	4	3	7		
Obesity	1	1	2		
Developmental disorders/other diseases					
Disturbance	3	9	12	0.013*	0.32
No disturbance	14	4	18		
Low birth weight					
Low birth weight	0	2	2	0.179	-
Normal birth weight	17	11	28		
Delivery history					
Normal delivery	16	12	28	1.000	-
Premature delivery	1	1	2		
EEG result					
Abnormalities	8	6	14	1.000	-
No abnormality	9	7	16		

*There is a relationship between respondent characteristics and epilepsy status.

The descriptive result in Table 3 showed that the lowest BDNF level of epilepsy patients was 0.05 and the highest was 1.85. Hence, it can be assumed that the minimum level has a lower value than the cutoff value of 0.0641 pq/mL based on ROC curve in Figure 1.

Table 3: Analysis of plasma BDNF levels

No	Variable name	n	Mean	Median	Mode	SD	Max-Min
1.	BDNF	30	0.3032	0.1130	0.16[a]	0.41336	0.05–1.85

BDNF: Brain derived neurotrophic factor.

Analysis of plasma MDA levels

MDA analysis was performed using a spectrophotometer, the average levels in epilepsy patients are presented in the following Table 4:

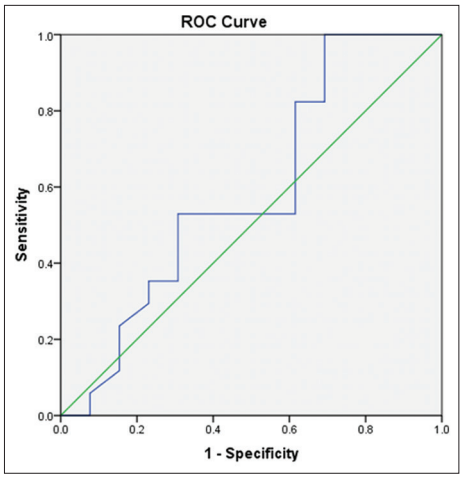

Figure 1: Graph of analysis of plasma brain derived neurotrophic factor levels

The descriptive result in Table 4 showed that the lowest MDA level of epilepsy patients was 195 and the highest was 419. Hence, it can be assumed that the minimum level has a lower value than the cutoff value of 203.5 based on ROC curve in Figure 2.

Table 4: Analysis of MDA levels in epilepsy patients

No	Name of variable	n	Mean	Median	Mode	SD	Max-min
1	MDA	30	271.20	249.00	237[a]	67.269	195–419

MDA: Malondialdehyde.

Comparison of BDNF levels in uncontrolled and controlled epilepsy

Analysis of BDNF in controlled and uncontrolled epilepsy, analysis of the mean levels of BDNF in patients with uncontrolled and controlled epilepsy is presented in the following Table 5:

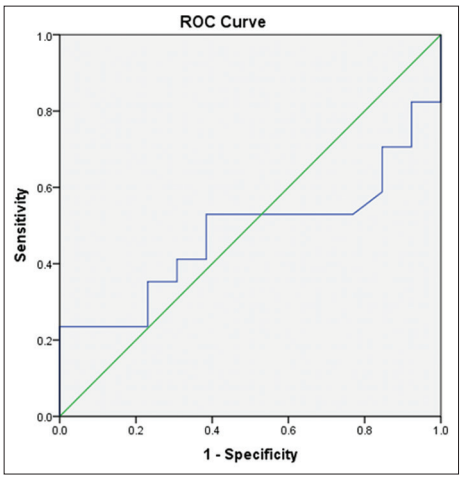

Figure 2: Graph of analysis of MDA levels in epilepsy patients

Based on Table 5 above, statistical results using SPSS obtained that BDNF data was not normally distributed so that it was continued with the Mann–Whitney test on BDNF levels, obtained $p > 0.05$ so that it could be said that there was no statistically significant difference between the two groups. From the average level of uncontrolled and controlled epilepsy BDNF, it is still above the cutoff value of 0.064.

Table 5: Comparison of BDNF levels in uncontrolled and controlled epilepsy patients

Parameter	Epilepsy group		p-value
	Uncontrolled (mean±SD)	Controlled (mean±SD)	
BDNF level (average)	0.3123±0.51978	0.2960±0.32622	0.432

The results showed that the lowest BDNF level of epilepsy patients was 0.05 and the highest was 1.85. Hence, it can be assumed that the minimum level has a lower value than the cut off value of 0.0641 pq/mL, but after the division into the uncontrolled and controlled epilepsy groups the mean value of BDNF levels did not have a significant difference between the two groups with a $p > 0.05$.

As we know BDNF is a neurotrophic factor that plays an important role in plasticity and the learning process. BDNF is a hormone that belongs to the neurotrophin family, which has a trophic effect on peripheral and central neurons. BNDF is significantly involved in the molecular mechanisms of synaptic plasticity of neuronal growth and cell survival [25].

For the results of this study, the severe damage that causes BDNF to become abnormal is like the characteristic variable as the triggering factors, namely, the age variable that the prevalence of epilepsy in infants and children to epilepsy cases is quite high. This illustrates that the findings of epilepsy cases in hospitals. Ulin Banjarmasin mostly affects children under 5 years old and the age at first having a seizure is <1 year. Likewise with epilepsy patients who have CP conditions, that children with CP have low levels of BDNF in plasma. This is considering the potential for severe CP conditions in children with epilepsy so that there is a significant decrease in BDNF concentrations. In this study, patients who did not experience CP by 60% so that it could affect the BDNF value did not decrease significantly.

There are several factors that affect BDNF levels, including age, gender, weight, iron deficiency anemia, and depression. BDNF is inversely related to age and body weight. The older the age and the heavier a person is, the lower his BDNF will be. Research proves that respondents aged 20–33 years have higher BDNF than respondents aged 34 years and over. Women also tend to have lower BDNF than men. Pregnant women with depression also have low BDNF concentrations. The level of BDNF in the umbilical cord is also influenced by maternal ferritin where the levels tend to be lower in mothers with iron deficiency anemia (<12 ng/mL) than mothers with normal ferritin levels (≥12 ng/mL). The brain that produces BDNF is the place where iron concentrations are highest. Iron is one of the important micronutrients needed for the development and function of brain cells. When iron deficiency occurs, there is a further reduction in BDNF expression in the brain which results in behavioral and cognitive changes that are usually observed in patients with depression [26].

BDNF levels in children with good nutritional status were higher than those with lower nutritional status (1.047 ± 1.735 ng/ml vs. 0.458 ± 1.055 ng/ml) [27]. In this study, 53.3% good nutritional status could affect the results so that the value did not decrease in BDNF levels.

The pattern of BDNF expression in the brain, high levels of this molecule were detected in the hippocampus, amygdala, cerebellum, and cerebral cortex, the highest was found in hippocampal neurons. Lower levels of BDNF have been detected in organs like liver, heart, lungs. The regulation of each transcript is controlled and/or modulated by factors such as neural activity, antidepressant exercise, stress, and the hormone estrogen [20]. In healthy people, the mean plasma BDNF level was found to be ~92.5 pg/mL (8.0–927.0 pg/mL). It is higher in women, and decreases with advancing age [27].

In epilepsy, peripheral BDNF levels may increase in serum after seizures associated with increased glutamate signaling, whereas BDNF levels in the brain may increase mRNA expression of BDNF exons in the hippocampus and cortex of TLE patients, and increase BDNF protein expression in the temporal lobe hippocampus of epilepsy patients. Overexpression of BDNF leads to an inflammatory response mediated by NF-B, which leads to astrocyte activation, increased production of cytokines and neurotoxic reactive oxygen and local recruitment of activated microglia. Activated pro-inflammatory microglia are known to elicit an apoptotic response after chronic stimulation, leading to toxicity and further neuronal death [28].

BDNF secreted by neurons is an important component of synaptic plasticity. The level of BDNF is thus easily detectable in human serum and has been widely associated as an indicator of brain function [29]. BDNF levels in the study were not significantly different in the controlled and uncontrolled epilepsy status groups, which could be due to the nature of BDNF itself. BDNF is a protein in the brain and peripheral nerves. So that the presence of BDNF that appears in the blood cannot be identified only from the CNS or brain. In addition, the synthesis of BDNF is also influenced by the intake of nutrients and drugs consumed by the patient [30].

Comparison of MDA levels in uncontrolled and controlled epilepsy

Analysis of MDA in controlled and uncontrolled epilepsy, analysis of the mean levels of MDA in patients with uncontrolled and controlled epilepsy is presented in Table 6.

Table 6: Comparison of MDA levels in uncontrolled and controlled epilepsy patients

MDA level	Epilepsy group		p-value
	Uncontrolled (mean±SD)	Controlled (mean±SD)	
MDA level (Average)	263.3077±45.79371	277.2353±80.86758	0.837

MDA: Malondialdehyde.

Based on Table 6 above, statistical results using SPSS obtained that MDA data were not normally distributed so that it was continued with the Mann–Whitney test on MDA levels obtained $p > 0.05$ so that it could be said that there was no statistically significant difference between the two groups. The mean value of uncontrolled epilepsy MDA levels is above the cut off value of 203.5 or has increased.

The results showed that the patient's lowest MDA level was 195 and the highest was 419. Hence, it can be assumed that the highest level of these results increased from the cutoff value obtained at 203.5 M. However, after the division into the uncontrolled and controlled epilepsy groups the mean MDA level did not have a significant difference between the two groups with a $p > 0.05$.

Oxidative stress is a consequence of an increased oxidant load affecting endogenous antioxidants and the repair capacity or consequence of a reduced endogenous antioxidant. Glutamate acts as a CNS stimulating neurotransmitter and its excitation potential, especially at higher concentrations, is believed to be one of the key factors involved in the generation of oxidative stress. Increased ROS generation results in increased intracellular Ca concentration, which is seen in changes in neuroplasticity, as well as seizure-induced neuronal death via necrosis or apoptosis. The increase in intracellular Ca2+, which persists even through the chronic phase of epilepsy and is therefore critical for the recurrence of seizures, may affect GABA receptor recycling and thus alter neural excitability. In addition, increased intracellular Ca2+ can alter gene transcription, protein expression and turnover, neurogenesis, nerve growth, and other cellular physiological functions. One of the most studied reactive aldehydes is MDA. In addition, peroxidation products, known as peroxyl radicals, are less reactive than ROS and therefore have a longer action time. As a result, they are able to spread further, even though cells, where they can react with other cellular constituents and cause diffuse cellular damage. Due to their greater stability, peroxidation end products are valuable laboratory markers. From several studies that epilepsy with partial complex seizures and drug resistance will cause a significant effect of increasing the number of MDA.

MDA is a secondary lipid peroxidation product, resulting from the reaction between ROS and lipid components in cells, especially polyunsaturated fatty acids. Several studies have found that MDA levels in epilepsy patients are significantly increased. A study by Menon *et al*., involving 100 epilepsy patients, showed that MDA levels in epilepsy patients were significantly ($p < 0.001$) higher (6.80 ± 2.84 mmol/mL) than in the control group (1.64 ± 0.82 mmol/mL). In the study, 75 out of 100 epilepsy patients received treatment for 5 ± 4 years and showed that MDA levels were very high [10].

In this study, all patients received anti-epilepsy drug therapy, most patients experienced the first seizure at the age of <1 year (60%) and at the time of this study the age of patients who came to the polyclinic was mostly over 10 years (43.3%), so that it can describe duration of treatment but for adherence to medication only based on statements from parents.

Peroxidation of membrane lipids in the CNS can cause many effects including decreased activity of membrane-bound enzymes, increased membrane rigidity, impaired membrane receptor activity, and altered permeability. MDA as a secondary product of lipid peroxidation can cause irreversible modifications of proteins, DNA, and phospholipids that lead to impaired function and cell death. Therefore, the evaluation of MDA levels can be used as an important indicator of lipid peroxidation for children with epilepsy [33]. The role of oxidative stress and inflammation that has been shown to cause resistance AOA and drug-resistant epilepsy of 23.3% this number illustrates the effect of

increasing MDA on anti-epilepsy drug resistance, but still does not describe a significant difference between the two groups.

The MDA levels that were not significantly different could also be caused by other oxidation processes in the body, so it could not be distinguished whether it was from seizures and cell damage due to epilepsy or other causes. MDA is a product/product of the lipid peroxidation process, so all cell damage that triggers lipid peroxidation will increase MDA levels.

Limitation of this research was only had few respondents because the time of research was done in pandemic time. It made the number of patients who came to Ulin Hospital to have routine control of epilepsy getting less.

Conclusion

This research was that there were no significant differences of plasma BDNF and MDA in epilepsy status.

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