ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Comparison of Serum Malondialdehyde and Paraoxonase-1 Levels in Patients with Epilepsy with and without Status Epilepticus

Status Epileptikusta Olan ve Olmayan Epilepsi Tanılı Hastalarda Serum Malondialdehit ve Paraoksonaz-1 Düzeylerinin Karşılaştırılması

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ABSTRACT

Aim: *The underlying pathophysiological mechanisms in epilepsy are still not fully known. Paraoxonase (PON)-1 activity and malondialdehyde (MDA) levels are biomarkers used in the measurement of oxidative stress. Studies show that oxidative stress has a role in the pathophysiology of epilepsy. The aim of our study is to evaluate serum PON-1 activity and MDA levels in epilepsy patients with and without status epilepticus (SE).*

Materials and Method: *The subjects included in the study were established in two groups. Group I: The patient diagnosed with status epilepticus (n=30), group II: 30 adult patients with epilepsy who were in the outpatient policlinic follow-up and were not in status were included in the study. Serum MDA levels and PON-1 activity were measured by spectrophotometric method in the biochemistry laboratory.*

Results: *Serum MDA levels were found to be 86.8±32.4 nmol/mL in patients with SE and 65.8±15.7 nmol/mL in patients without SE. Serum PON-1 activity was 180.8±28.3 U/L in patients with SE and 170.2±25.0 U/L in patients without SE. When patients with SE and patients without SE were compared, serum MDA levels were found to be higher than patients without SE and statistically significant (p<0.001). There was no significant difference between the two patient groups in terms of PON-1 activity (p>0.05).*

Conclusion: *The results of our study indicate that the oxidant/antioxidant balance in the pathogenesis of status epilepticus has deteriorated in favor of oxidative stress and the antioxidant system cannot give an adequate response. Larger research should be conducted to evaluate the use of serum MDA levels as a biomarker*

Keywords: *status epilepticus; MDA; PON-1; antioxidant/oxidant status*

ÖZET

Amaç: *Epilepside altta yatan patofizyolojik mekanizmalar halen tam olarak bilinmemektedir. Paraoksonaz (PON)-1 aktivitesi ve malondialdehit (MDA) seviyeleri oksidatif stresin ölçümünde kullanılan biyomarkerlardır. Yapılan çalışmalar oksidatif stresin epilepsi fizyopatolojisinde rolü olduğunu göstermektedir. Çalışmamızın amacı, status epileptikusta (SE) olan ve olmayan epilepsi hastalarında serum PON-1 aktivitesi ve MDA düzeylerini araştırmaktır.*

Materyal ve Metot: *Çalışmaya alınan denekler iki gruba ayrıldı. Grup I: Status epileptikus tanısı alan hasta (n=30), grup II: Poliklinik takiplerine gelen erişkin yaş grubundaki statusta olmayan 30 epilepsi hastası çalışmaya dahil edildi. Serum MDA seviyeleri ve PON-1 aktivitesi biyokimya laboratuvarında spektrofotometrik yöntemle ölçüldü.*

Bulgular: *SE'ta olan hastalarda serum MDA seviyesi 86,8±32,4 nmol/mL SE'ta olmayan hastalarda ise serum MDA düzeyleri 65,8±15,7 nmol/mL olarak bulundu. Serum PON-1 aktivitesi SE'ta olan hastalarda 180,8±28,3 U/L SE'ta olmayan hastalarda ise 170,2±25,0 U/L olarak tespit edildi. SE'ta olan hastalar ile SE'ta olmayan hastalar karşılaştırıldığında serum MDA düzeylerinin SE'ta olmayan hastalara göre daha yükseldiği ve istatistiksel olarak anlamlı olduğu bulundu (p<0,001). PON-1 aktivitesi açısından iki hasta grubu arasında anlamlı fark bulunmadı (p>0,05).*

Sonuç: *Çalışmamızın sonuçları status epileptikus patogenezinde oksidan/antioksidan dengenin oksidatif stres lehine bozulduğunu ve antioksidan sistemin yeterli cevabı veremediğini işaret etmektedir. Bir biyomarker olarak serum MDA düzeylerinin kullanımını değerlendirmek için daha geniş çaplı araştırmalar yapılmalıdır*

Anahtar Kelimeler: *status epileptikus; MDA; PON-1; antioksidan/oksidan statü*

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Introduction

Epilepsy is a common neurological disease that affects more than 50 million people worldwide[1]. Status epilepticus (SE), which we can define as a prolonged epileptic seizure state, is one of the neurological emergencies with high morbidity and mortality[2]. It may result in permanent changes in normal brain functions and cognitive functions[3]. Studies have shown that excessive oxidative stress is involved in the physiopathology of SE[1]. Oxidative stress occurring during SE leads to lipid peroxidation, DNA damage, and cell death[4]. The role of oxidative stress in SE is examined through lipid peroxidation levels[5].

Malondialdehyde (MDA) is the end product of nonenzymatic oxidation of lipid peroxides and is used as a biomarker of oxidative stress in many diseases[6,7]. In addition, it is a by-product of prostaglandin and thromboxane biosynthesis[8]. The increase in free radicals also increases MDA production[7]. In addition to being a biomarker, this toxic molecule is potentially mutagenic and atherogenic[9]. Highly reactive MDA reacts with proteins and DNA and causes mutations by forming crosslinks[10].

Paraoxonase (PON)-1 is an enzyme mostly produced in the liver and found in the structure of high-density lipoprotein molecules in human serum[11]. This enzyme, called paraoxonase, also hydrolyzes homocysteine, as it provides the detoxification of toxic organophosphates such as paraoxone and diazinon[12]. It is a protective enzyme against lipid peroxidation[13]. Although there are three types of paraoxonase genes, PON-1, PON-2, and PON-3, the most studied of this family is PON-1. It shows its antioxidant properties mainly in blood circulation. It is known that PON-1 is both synthesized in the brain tissue and can cross the blood-brain barrier[14,15]. It is known that it loses its activity in the oxidative phase[16].

It has been shown that antiepileptic drugs partially disrupt the antioxidant system and therefore may initiate oxygen-related tissue injury by free radicals, especially in patients treated with valproic acid and carbamazepine[17]. In addition, it has been shown that long-term use of antiepileptic drugs may increase the formation of free radicals and cause oxidative damage in neurons[18,19]. Our aim is to evaluate serum MDA level and PON-1 activity in the physiopathology of epilepsy patients with and without SE.

Material and Methods

This study was confirmed by the Ethics Committee of Dicle University (Ethics committee approval no; 22.05.2017/126). The patients with epilepsy were assessed by two expert neurologists. The seizure typing of the patients included in the study was classified according to the criteria of International League Against Epilepsy (ILAE) 2017 seizure classifications[20]. Electroencephalography (EEG) and magnetic resonance imaging (MRI) the patients were taken.

Patients with pathological EEG findings were not included in the study. Patients with psychogenic seizures were not included in the study. This study was established two groups. Group I: The patient diagnosed with status epilepticus (n=30), group II: The epilepsy patient in the adult age group who was followed up in the outpatient clinic and not in status were included in the study (n=30). Acute and chronic infection, fever, diabetes mellitus, rheumatological diseases, anemia, kidney and thyroid dysfunction, mental retardation, hypertension, use of antioxidant agents, trauma, autoimmune disease, local and systemic inflammation were determined as the exclusion criteria of the study.

All participants in the study were informed about the study. It was conducted in line with the Declaration of Helsinki. Venous blood was drawn in the first 24 hours from the onset of status for biochemical analysis. In patients who were not in status, blood samples were taken into biochemistry tubes at any time and then kept in the laboratory for 15 minutes to facilitate coagulation. The blood samples were centrifuged at 5000 rpm for 10 minutes according to the study protocol and kept in a deep freezer at -80°C until analysis.

PON-1 and MDA Measurement Method

Serum PON-1 enzyme activity was analyzed by the Eckerson method using the commercial (Rel Assay Diagnostic, Gaziantep, Türkiye) kit according to the manufacturer's instructions with the Architect C16000 brand auto analyzer and the enzyme activity was expressed as U/L[21].

Serum MDA level was read by the Ohkawa method according to the manufacturer's instructions (Northwest MDA, Abcam, USA) using a commercial kit at 532 nm and absorbance was measured by spectrophotometric method[22].

Statistical Analysis

IBM Statistical Package for Social Sciences (SPSS) program version v. 17 statistical package program was conducted for calculations. The descriptive statistics were submitted as standard deviation, means, minimum and maximum values, while presented as numbers and percentages for categorical variables. The conformity of the data to the normal distribution was checked with Kolmogrov-Smirnov and Shapiro-Wilk tests. The categorical data using the Chi-Square test were compared. The 2-group Student-T test was used for parameters that were normally distributed, and the Mann-Whitney-U test was used to compare pairwise groups for parameters that were not normally distributed. The statistical significance level was taken as p-values less than 0.05.

The sample size was calculated by using the mean and standard deviation values of the pilot study with 10 patients (G*Power v3.1.9.4). For the MDA variable, 1.33 effect size was obtained, yielding 80% power, and it was seen that the minimum number of patients to be included in each group was 10. However, since PON-1 variable values have very high standard deviation, it was seen that it had a very small effect size value (0.01) and required a very high sample size. According to the central limit theorem[23], it is appropriate to include 30 patients in samples with non-parametric distribution (especially considering the budget). Therefore, it was decided to include 30 patients in each group.

Results

Sixty patients were enrolled in our study. The mean age of the patients who were not in SE was 24.5±6.7 (14 males and 16 females). It was observed that the mean age of patients with SE (17 females and 13 males) was 26.4±7.2. No statistically significant difference was found in the comparison of age and gender of patients with and without SE (p>0.05) Table 1.

The mean serum MDA levels of the patients without SE were 65.8±15.7 nmol/mL, and the serum MDA levels of the patients with SE were 86.8±32.4 nmol/mL. It was observed that the serum MDA level of the patients with SE was higher than the patients without SE and it was statistically significant (p<0.001). The mean serum PON-1 activity of patients without SE was found to be 180.8±28.3 U/L nmol/mL in patients with a mean serum PON-1 activity of 170.2±25.0 U/L. It was observed that serum PON-1 activity was increased in patients with SE compared to patients without SE, but it was not statistically significant (p>0.05) Table 2.

Discussion

Brain tissue is more sensitive to oxidation than other tissues due to its high content of oxidation-sensitive unsaturated fats and metals, high oxygen consumption, high metabolic rate, and fewer antioxidant mechanisms[24]. While the balance between the oxidant and antioxidant system was investigated in various

Table 1. *Demographic data of patient groups*

		Patients without status epilepticus (n=30)	Patients with status epilepticus (n=30)	p value
Gender [a]	Female	16 (53%)	17 (57%)	0.795
	Male	14 (47%)	13 (43%)	
Age (Years) [b]		24.5±6.7	26.4±7.2	0.095
High (cm) [c]		171.0 (160–181)	173.0 (164–184)	0.084
Weight (kg) [c]		66 (63–71)	67 (64–72)	0.940
BMI (Kg/m^2) [c]		26.0 (24,8–27,8)	26.5 (24,0–28,1)	0.210

Data are median (min-max) or mean ± SD (standard deviation). Statistical method: [a] Chi-Square Tests; [b] Student-T test; [c] Mann Whitney-U test. Gender: patients without status epilepticus female: 16(53%); male 14(47%); patients with status epilepticus female: 17(57%); male: 13(43%).

Table 2. *Serum MDA levels and PON-1 activities of patients with and without status epilepticus*

Parameters	Patients without status epilepticus	Patients with status epilepticus	p value
MDA (nmol/mL) [b]	65.8±15.7	86.8±32.4**	0.0002
PON-1 (U/L) [b]	180.8±28.3	170.2±25.0	0.779

Statistical method: [b] Student-T test. MDA data are shown as mean ± SD (standard deviation) and PON-1 data as mean ± SE (standard error). ** p<0.001. Significance between serum MDA levels of patients with and without status epilepticus. MDA: Malondialdehyde; PON-1: Paraoxonase-1.

neurological diseases in the 1990 s, these studies have also been carried out in epilepsy since the 2000 s[25].

In experimental epilepsy models, it has been shown that excessive free oxygen radical formation, an increase in lipid peroxidation and reduced glutathione levels during SE[24]. Free oxygen radicals, which are formed in small amounts during normal cell metabolism, are produced in large quantities during prolonged seizure activity and oxidative stress occurs when these formed free oxygen radicals exceed the antioxidant capacity. These formed free oxygen radicals interact with biological materials such as proteins, lipids, carbohydrates and nucleic acids in the cell. By interacting with lipids, it disrupts the physical properties of the cell membrane and indirectly the structural connection between cells, and causes damage and even neuron death by interacting with DNA[10,26]. Experimental epilepsy studies and some clinical studies have shown that the presence of neuronal damage and excessive oxidative stress plays a vital role in the pathophysiology of SE[2,27]. In different studies, it has been found that the oxidant-antioxidant system balance is impaired and PON-1 activity levels decrease in case of increased oxidative stress[28]. Serum PON-1 levels were evaluated in some neuropsychiatric diseases. In particular, PON-1 activity decreases in the pathophysiology of of dementia, stroke, Alzheimer's and Parkinson's[13,29]. Studies have shown that there is a decrease in the functions of antioxidant systems during SE. This decrease results in an increase in lipid peroxidation and the level of free oxygen radicals[19]. In the study conducted by Dönmezdil et al.[30] no significant difference was found between PON-1 levels between newly diagnosed epilepsy patients and the control group. PON-1 level was found to be lower in epilepsy patients, but it was not statistically significant. In another study, serum PON-1 level measured in the interictal period in epilepsy patients was found to be low[31]. In our study, it was found that PON-1 activity in patients with SE was lower than in patients without SE, but it was not found statistically significant.

It has been reported that MDA, the end product of lipid peroxidation, which is a biomarker of oxidative stress, may be an indicator of the production of free oxygen radicals[32]. Related studies have been conducted on MDA levels in many different neurological diseases. It has been shown that MDA plays an important role in the pathophysiology of diseases such as migraine, multiple sclerosis, and stroke[33–35]. Different results were obtained in different studies on epilepsy patients and serum MDA levels[30,31]. Verotti et al.[36] showed that MDA level was high in pediatric epilepsy patients who received valproic acid treatment for one year. Tong et al.[37] reported that the MDA concentration was significantly higher on the 14th day of rats given valproic acid. Hamed et al.[38] reported that serum MDA concentration was higher in epilepsy patients treated with phenytoin. Das et al.[39] demonstrated that MDA level was higher in epilepsy patients compared to the control group.

Menon et al.[40] demonstrated that oxidative stress was not different in treated and untreated epilepsy patients. Pandey et al.[41] reported that MDA concentration was higher in epilepsy patients receiving carbamazepine treatment. However, they reported a decrease in oxidative stress in those receiving antiepileptic therapy for one year. They have shown that this situation can be achieved with adequate antiepileptic therapy. It has been reported that oxidative stress is reduced due to the fact that antiepileptic drugs such as carbamazepine can have antioxidant effects[42].

This study has several limitations. One of the limitations of our study is that the control group was not included in the study. Another limitation of our study is that epilepsy type, duration of disease, medications used and seizure frequency were not followed up in epilepsy patients.

In our study, although there was a significant increase in MDA level, which is a biomarker of oxidative stress, between epilepsy patients with and without SE, no significant increase was found in PON-1 activity, which is a part of the antioxidant system responsible for preventing lipid peroxidation. This result makes us think that the oxidant/antioxidant balance has deteriorated in favor of oxidative stress in the pathogenesis of SE and the antioxidant system cannot give an adequate response.

Conclusion

It was observed that serum MDA level was increased and statistically significant in SE patients receiving antiepileptic therapy, and there was no significant difference in PON-1 activity. The results of our study indicate that while conventional treatments used in the treatment of SE are effective in stopping seizure activity, they may cause neuronal damage by increasing oxidative damage.

It shows that neuronal loss can be minimized by adding antioxidant treatments to these treatments. Therefore, studies on oxidant damage and antioxidant activity in SE will contribute to the development of new drugs that will have a positive effect on morbidity and mortality by minimizing oxidant damage.

Conflict of Interest

The authors report no declarations of interest.

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