ÖZGÜN ARAŞTIRMA / ORIGINAL RESEARCH

DOI: 10.17944/mkutfd.910039
MKÜ Tıp Dergisi 2021;12(44):158-164

Investigation into Acute-phase Reactants and Oxidant-Antioxidant Parameters in Patients Diagnosed as Having Generalized Tonic-Clonic Type Epilepsy on Antiepileptic Monotherapy and Polytherapy

Suna Sarıkaya Ay[1], Sedat Yaşin[2], Mustafa Çalık[3], Tahir Kurtuluş Yoldaş[4]

[1] M.D. Spec., Antalya Ataturk State Hospital, Neurology, Antalya, Turkey.
[2] M.D. Spec., Gaziantep University Faculty of Medicine, Neurology, Turkey.
[3] Prof., Harran University Faculty of Medicine, Department of Child Health and Diseases, Şanlıurfa, Turkey.
[4] Prof., Ankara Training and Research Hospital, Neurology, Turkey.

Öz

Jeneralize Tonik Klonik Tip Epilepsi Tanısı Konulan, Monoterapi ve Politerapi Şeklinde Antiepileptik Tedavi Alan Hastalarda Akut Faz Reaktanları ve Oksidan-Antioksidan Parametrelerin Araştırılması

Amaç: Bu çalışmada akut faz reaktanları ile oksidatif stres ve epilepsi arasındaki ilişkinin araştırılması amaçlanmıştır.
Gereç ve Yöntem: Hasta grubu, Çocuk Nörolojisi polikliniğine başvuran ve ILAE sınıflamasına göre jeneralize tip epilepsi tanısı alan, 33'ü monoterapi, 34'ü ise politerapi şeklinde antiepileptik ilaç tedavisi almakta olan 67 hastadan oluşmaktaydı. Kontrol grubu, epilepsi veya bilinen herhangi bir kronik hastalığı olmayan, aynı yaş aralığında benzer sosyodemografik özelliklere sahip özelliklere sahip 30 sağlıklı gönüllü katılımcıyı içeriyordu. Toplam anti-oksidan durumu (TAS) ve toplam oksidan durumu (TOS) Erel tarafından geliştirilen yönteme göre ölçülmüş ve oksidatif stres indeksi (OSI) hesaplanmıştır. Hassas C-reaktif protein (Hs-CRP) seviyeleri ölçüldü.
Bulgular: Antiepileptik monoterapi ve politerapi alan hastaların hem TOS hem OSI düzeyleri kontrol grubuna göre istatistiksel olarak anlamlı derecede yüksek bulundu(p=0.004), antiepileptik monoterapi ve politerapi alan hastaların TOS düzeyleri sırasıyla 19.29±1.27, 19.22±1.26, kontrol grubu 14.49±1.75, antiepileptik monoterapi ve politerapi alan hastaların OSI düzeyleri sırasıyla 1.66±0.12, 1.72±0.11, kontrol grubu 1.27±0.11). Monoterapi ve politerapi alan hastaların Hs-CRP düzeyi (sırasıyla 0.59±0.06 mg/L, 1.09±0.06 mg/L), kontrol grubuna göre (0.42±0.02 mg/L) istatistiksel olarak anlamlı derecede yüksek bulundu.
Sonuç: Bu çalışmada, epileptik nöbetin oksidatif stres parametrelerini arttırdığı ve antioksidan mekanizmaların oksidatif hasarı azaltmada yetersiz kaldığı sonucuna varılmıştır. Ayrıca yüksek serum Hs-CRP seviyeleri göz önüne alındığında, dirençli epilepsinin tedavisinde inflamatuar süreci kontrol edebilen tedavi stratejilerinin geliştirilmesi son derece önemlidir.
Anahtar Kelimeler: Epilepsi, Oksidatif Stres, Sensitive C-Reactive Protein

Abstract

Investigation into Acute-phase Reactants and Oxidant-Antioxidant Parameters in Patients Diagnosed as Having Generalized Tonic-Clonic Type Epilepsy on Antiepileptic Monotherapy and Polytherapy

Objective: This study aimed to investigate the relationship between acute-phase reactants and oxidative stress and epilepsy.
Methods: The patient group consisted of 67 patients who applied to the Pediatric Neurology outpatient clinic and were diagnosed with generalized type epilepsy according to ILAE classification, 33 were receiving monotherapy and 34 were receiving antiepileptic medication in the form of polytherapy. The control group included 30 healthy volunteer participants with similar sociodemographic characteristics in the same age range, without epilepsy or any known chronic disease. Total anti-Oxidant Status (TAS) and total Oxidant Status (TOS) were measured according to the method developed by Erel, and the oxidative stress index (OSI) was calculated. Sensitive C-reactive protein (Hs-CRP) levels were measured.
Results: Both TOS and OSI levels of the patients who received antiepileptic monotherapy and polytherapy were statistically significantly higher than the control group (p = 0.004, the TOS levels of the patients who received antiepileptic monotherapy and polytherapy were 19.29 ± 1.27, 19.22 ± 1.26, respectively, control group 14.49 ± 1.75, OSI levels of patients receiving antiepileptic monotherapy and polytherapy 1.66 ± 0.12, 1.72 ± 0.11, control group 1.27 ± 0.11), respectively. The Hs-CRP level (0.59 ± 0.06 mg / L, 1.09 ± 0.06 mg / L, respectively) of the patients who received monotherapy and polytherapy was statistically significant compared to the control group (0.42 ± 0.02 mg / L) significantly higher.
Conclusion: In this study, the findings suggest that epileptic seizures increase oxidative stress parameters and antioxidant mechanisms are insufficient to reduce oxidative damage. In addition, considering the high serum Hs-CRP levels, it is extremely important to develop treatment strategies that can control the inflammatory process in treating resistant epilepsy.
Keywords: Epilepsy, Oxidative Stress, Sensitive C-Reactive Protein

Nasıl Atıf Yapmalı: Sarıkaya S, Yaşin S, Çalık M, Yoldaş TK. Investigation into Acute-phase Reactants and Oxidant-Antioxidant Parameters in Patients Diagnosed as Having Generalized Tonic-Clonic Type Epilepsy on Antiepileptic Monotherapy and Polytherapy. MKÜ Tıp Dergisi. 2021;12(44):158-164. https://doi.org/10.17944/mkutfd.910039

Sorumlu Yazar/Corresponding Author: M.D. Spec. Sedat Yaşin
Email: drsedatyasin@hotmail.com
ORCID iD: 0000-0001-8067-8388

Geliş/Received: 7 Nisan 2021
Kabul/Accepted: 17 Mayıs 2021

INTRODUCTION

Epilepsy is a chronic neurologic disorder that is fairly common. It frequently occurs at young ages and requires long-term, sometimes life-long therapy. Anti-epileptic drugs (AEDs) used in doses appropriate for types of epileptic seizures and epileptic syndromes are important in preventing seizures. Side effects of AEDs show differences. In addition to their early side effects, behavioral, endocrinologic, hematologic side effects and those in relation to memory and speech may also be seen (1). While deaths due to cardiovascular disorders may occur more frequently in epileptic patients than the general population, its exact cause is still not known (2).

Oxidative stress occurs in conditions when oxidative damage exceeds the capacity of antioxidant defense mechanisms. Although oxidative stress is known to play a key role in the pathogenesis of many acute and chronic neurologic disorders, its role in epilepsy is still not known clearly (3).

CRP, which is a member of the short pentraxins, is synthesized by hepatocytes in response to inflammatory cytokines, such as IL-1, IL-6, TNF-a or other stimulators (4). CRP is an acute-phase reactant that is synthesized in the liver and is a very sensitive marker of acute and chronic inflammation. Tests that may measure CRP in a serum sample to 0.2 mg/L sensitivity are termed high-sensitivity (Hs-CRP) assays (5). It became clear in recent years that CRP may be used in the prediction of, especially, cardiovascular risk. The low-grade chronic inflammatory process in the body was reported to play roles in both pathogenesis and prognosis of atherosclerotic heart disease (6).

In this study, we aimed to investigate the association between inflammation, oxidative stress and epilepsy by comparing acute-phase reactants and oxidative stress parameters of epileptic patients with generalized seizures under primary polytherapy or monotherapy and healthy control group in this study.

METHODS

Patient and control groups

This study group included 67 patients who were admitted at the Harran University Faculty of Medicine Hospital, outpatient clinics of Pediatric Neurology, and diagnosed as having generalized type epilepsy according to ILAE classification, 33 of whom were treated with a monotherapy anti-epileptic drug and 34 of whom were treated with polytherapy anti-epileptic drugs. Patients who had systemic, metabolic and chronic disorders in addition to epilepsy, patients having neurodegenerative disorders and those in whom the diagnosis of epilepsy was not definite were excluded from this study. Medical records of the patients were examined and age, gender, prenatal, natal, postnatal characteristics were recorded, along with a detailed family history. Physical and neurologic examinations were administered to all patients.

The control group included 30 healthy volunteer participants without any chronic or acute disorders, with the same age and similar demographic characteristics. Physical and neurologic examinations of all participants were conducted.

Blood Samples

Blood samples were taken from epileptic patients in the study group and volunteer participants in the control group, and serum was separated in one hour by centrifugation at 3200 rpm for 10 minutes. Serum samples with hemolysis were not included. Blood samples were taken into tubes that did not contain any chemicals. The venous blood samples were kept at -80°C for measurements of TAS, TOS, OSI and Hs-CRP levels later at the Central Chemistry Laboratory of Harran University Medical School. All serum samples were brought to room temperature at the time of this study, and the measurements were made simultaneously.

Total Antioxidant Status (TAS)

TAS levels of the samples were measured using Rel Assay brand commercial kits. This measurement method is based on the de-colorization of colored radical as a result of reduction of the colored ABTS cationic radical by all antioxidant molecules in the sample in proportion with the total concentration of antioxidant molecules. Trolox, which is a water-soluble analog of vitamin E, is used as a calibrator. The results were expressed as mmol Trolox Equivalent/L (7). Tissue TAS results were expressed as Trolox Equivalent/L.

Total Oxidant Status (TOS)

TOS levels of the samples were measured using Rel Assay brand commercial kits. This measurement uses a colorimetric method based on cumulative oxidation of ferrous ion to ferric ion by Oxidant molecules in the sample, as reported in the label. The results were expressed as pmol H_2O_2Equivalent/L.

Oxidative Stress Index (OSI)

OSI, as a marker of oxidative stress, is expressed as the percent of TOS levels to TAS levels. In the calculation of the OSI levels of the samples, TAS levels are multiplied by 10.Thus, their units become equal to TOS levels. The results were expressed as Arbitrary Units (AU).

$$OSI = \frac{\text{TOS,}\mu\text{mol } H_2O_2 \text{ Equiv./L.}}{\text{TAS,mmol trolox Equiv./L.X10}}$$

High-Sensitivity C-reactive protein (Hs-CRP)

The Hs-CRP levels of the samples were measured using Rel Assay brand commercial kits.

Statistical Analysis

SPSS for Windows Version 11.5 (Statistical Package for the

Social Sciences) computer software was used in the statistical analysis of the data. In comparisons of the patient group with the controls, an independent samples t-test was used and in comparisons of polytherapy and monotherapy groups with controls, One-way ANOVA Tukey's Post Hoc method was used. The results were assessed in 95% confidence intervals, at $p<0.05$ significance level.

RESULTS

The patient group was aged between 1-17 years, including 43 (64.2%) males and 24 (35.8%) females (a total of 67 patients). The control group was also aged between 1-17 years, including 16 (55.2%) males and 14 (44.8%) females, to make a group of 30 volunteer participants. The mean age of the patient group was 7.99±4.91 years, and the mean age of the control group was 7.89± 5.32 years (Table 1).

Table 1. Average age in the patient and control groups

Group	Average age
Monotherapy	8.27±5.29
Polytherapy	7.72±4.53
Control	7.89±5.32

When the Body Mass Index (BMI) was compared in the patient and control groups, there was no significant difference. The BMI of the majority of the cases was below 18 (Table 2).

Table 2. BMI distribution in the patient and control groups

BMI	Patient (%)	Control (%)
Weak (18.4 or lower)	70.6	65.1
Normal (18.5-24.9)	23.4	28
Overweight (25-29.9)	3	3.4
Obese (30 or more)	3	3.4

The TOS level was 19.29±1.27 pmol H_2O_2 Equivalent/L in the anti-epileptic monotherapy group, 14.49±1.75 pmol H_2O_2Equivalent/L in the control group. TOS level was 19.22±1.26 pmol H_2O_2Equivalent/L in the anti-epileptic polytherapy group. TOS level of the anti-epileptic monotherapy group was significantly higher than the control group (p=0.001). TOS level of the anti-epileptic polytherapy group was significantly higher than the control group (p=0.001). There were no statistically significant differences between the TOS levels of polytherapy and monotherapy groups (p=0.955).

In this study, OSI level was 1.66±0.12 AU in the monotherapy group and 1.27±0.11 AU in the control group, while the OSI of polytherapy group was 1.72±0.11 AU. OSI level of patients in the monotherapy group was statistically significantly higher than the control group (p=0.004). The OSI level of polytherapy anti-epileptic group was statistically significantly higher than the control group (p=0.001). There were no statistically significant differences in comparing OSI levels of polytherapy and monotherapy groups (p=0,670) (Chart 1).

TAS level of the monotherapy anti-epileptic group was 1,12±0,03 Trolox Equivalent/L and TAS level of the control group was 1.15±0.06 Trolox Equivalent/L. TAS level of the polytherapy group was 1.17±0.03 Trolox Equivalent/L. There were no statistically significant differences between TAS levels of monotherapy anti-epileptic group and control group. There were no statistically significant differences between TAS levels of polytherapy anti-epileptic group and the control group (p=0.719). There were no statistically significant differences between the TAS levels of polytherapy and monotherapy groups (p=0.187). (Graph 1).

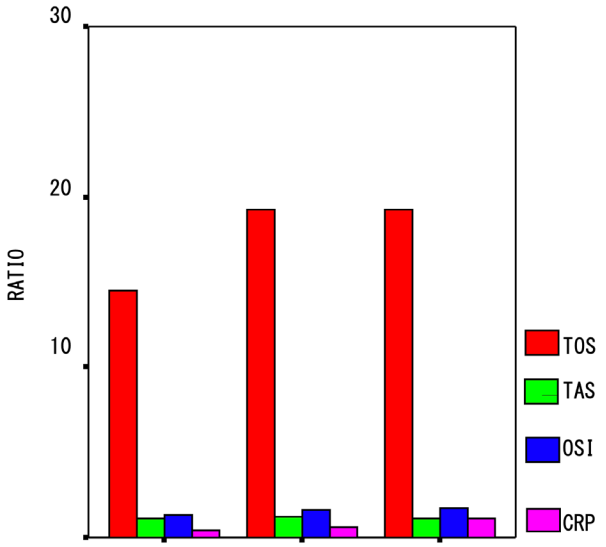

Chart 1. Control Monotherapy Polytherapy

Hs-CRP level was 0.59±0.06 mg/L in the monotherapy group, 0,42±0,02 mg/L in the control group, and 1.09±0.06 mg/L in the polytherapy group. The Hs-CRP level of monotherapy group was statistically significantly higher than the Hs-CRP level of the control group (p=0.025). The Hs-CRP level of the polytherapy group was statistically significantly higher than the control group (p=0.000). The Hs-CRP level of the polytherapy anti-epileptic group was statistically significantly higher than the monotherapy group (p=0,000).

DISCUSSION

Epilepsy is one of the important chronic neurologic disorders and it may require long-term, sometimes life-long treatment. Although large-scale, long-term investigations were conducted on epileptogenesis, the main molecular and cellular mechanisms in epileptogenesis are still not clearly known (8).

Measurement of Hs-CRP levels was recently described as a method of detecting chronic inflammation in cardiovascular

disorders, stroke, renal diseases and neuro-degenerative diseases such as Parkinson's disease and dementia (9-14).

Oxidative stress occurs in conditions when the neutralization capacity of the organism of Oxidant factors is below that of the required level. Oxidative stress may also be described as an increase of Oxidant level and/or decrease in antioxidant capacity. Detection of one of the Oxidant or antioxidant levels may provide an impression on the oxidative stress, while the determination of both may provide a more correct result. Free radicals are both causes and results of epileptic seizures, and that oxidative phosphorylation in the mitochondria produces oxygen radicals routinely in the nervous system, as in all the other parts of the body. High lipid content, oxygen consumption and oxidative metabolism of the brain make it more sensitive to oxidative stress. Oxidative stress is known to play a key role in the pathogenesis of many acute and chronic neurologic disorders, but its role in epilepsy is still unknown. Anti-epileptics and epilepsy were shown to decrease antioxidant enzyme levels and increase lipid peroxidation in multiple studies (15,16).

Hassazadeh et al. have administered sesamol as an antioxidant agent to six rats, with another six rats as the control group in their study, which have aimed to evaluate the efficacy of antioxidants on epilepsy control in rats. Generalized epileptic seizures were induced in both groups by administration of pentylenetetrazole (PTZ), and the behavior characteristics of the rats were recorded. In this study, epileptic seizures occurred later in the group which was administered sesamol, and these rats also had more preserved cognitive functions in comparison with the other group after the seizure (17).

Ben-Menachem et al have compared blood antioxidant enzyme levels of epileptic patients with progressive myoclonic epilepsy, which is hard to treat and which has a high potential for developing resistance, with healthy controls. Antioxidant levels of patients were significantly low. Afterwards, the patients were treated with high doses of N-Acetylcysteine. Patients and controls were compared before and after treatment. After treatment, oxidative stress parameters of red blood cells decreased, along with a decrease in seizure scores. It was concluded that it might be effective in decreasing neuronal death caused by oxidative stress and controlling seizures (18).

The effects of oxidative stress on epileptic seizures were investigated in a study conducted by Shin et al. Oxidative stress, which occurs due to the increased free radical release, was associated with the underlying pathogenesis in initiating and continuing epileptic seizures. It was concluded in this study that antioxidant treatment may be used in the treatment of epilepsy in order to decrease oxidative stress and may exert a neuro-protective effect (19).

The effects of anti-epileptic drugs on oxidative stress parameters are still controversial. The effects of AEDs used in epilepsy on oxidative stress have started to attract attention recently. While anti-epileptic drugs are believed to decrease oxidative stress by some authors of studies on this issue, polytherapy was concluded to increase oxidative stress in the study by Martinc et al (8). In an investigation by Yürekli et al. topiramate and lamotrigine were concluded to exert a protective effect on the antioxidant redox system of patients with epilepsy (20). In many studies, especially older antiepileptic drugs were concluded to increase oxidative stress (21,22).

In a study by Menon et al, oxidative stress levels of 75 patients taking AEDs and 25 patients who were not taking any AEDs were evaluated. Oxidative stress parameters of 25 epileptic patients not taking AEDs were compared with patients on anti-epileptic treatment and the control group. No differences were found between the patients taking or not taking AEDs in terms of oxidative levels. On the other hand, there were no differences in oxidative stress levels of polytherapy or monotherapy patients in the treated group. Oxidative stress increased in both patients on AEDs and patients not taking any AEDs, but it was concluded that AEDs did not exert any effects on oxidative stress (23).

In a study conducted by Varoğlu et al. effects of valproate (VPA), carbamazepine (CBZ), levetiracetam (LEV) on antioxidant and Oxidant enzyme activities, and their clinical significance were investigated. A total of 32 patients taking VPA, 17 patients taking CBZ, eight patients taking LEV, and 11 patients on polytherapy and age and gender-matched 30 healthy volunteers as controls were included in this study. Oxidative stress was observed to increase at the end of the 2nd month with all three anti-epileptic drugs (24).

In a study conducted by Shahar et al. oxidative stress parameters were investigated in the saliva of resistant (n=11) and non-resistant (n=22) epileptic children. Level of oxidative stress was higher in resistant and non-resistant epileptic patients than control group. On the other hand, there were no significant differences between resistant and non-resistant epileptic groups (25).

TOS level of epileptic patients on monotherapy was statistically significantly higher than the control group (p=0.001). TOS level of patients on polytherapy was also statistically significantly higher than the control group (p=0.001). Also, a significant difference was not found between epileptic patients on monotherapy or polytherapy (p=0.955).

When the monotherapy anti-epileptic group was compared with the control group concerning TAS levels, a significant difference was not found (p=0.829). There were no significant differences between the polytherapy anti-epileptic drug group and the control group (p=0.719). There were no

statistically significant differences between the polytherapy and monotherapy anti-epileptic drug groups (p=0.187). The absence of a significant difference between patient groups and the control groups concerning TAS suggests that anti-epileptic treatment may have a negative effect on the Oxidant system rather than the antioxidant system.

OSI levels of patients on anti-epileptic monotherapy were statistically significantly higher than the control group (p=0.004). OSI level of patients on anti-epileptic polytherapy was statistically significantly higher than the control group (p=0.001). When the groups on polytherapy and monotherapy were compared, no statistically significant differences were observed (p=0,670).

While TOS, which is a general marker of oxidant molecules and OSI, was a marker of oxidative stress, increased in patient groups with generalized type tonic-clonic seizures under monotherapy or polytherapy in this study, the difference between the control group was statistically significant. However there were no statistically significant differences between polytherapy and monotherapy anti-epileptic groups. Oxidative stress may develop due to epileptic seizures or AED use in patients with epilepsy. Reactive oxygen products are known to be effective in epileptic seizures. Development of oxidative stress in the central nervous system and a return to basal values in the inter-ictal periods were shown in epilepsy models in experimental animals (26). Oxidative stress was higher in epileptic patients who were newly diagnosed and who had not used AEDs before than epileptic patients using AEDs in human studies (21). This suggests that epilepsy alone may increase oxidative stress in epileptic patients taking anti-epileptic medications, without the effects of AEDs. Thus, the frequency of seizures should also be considered when the effects of AEDs on oxidative stress are evaluated in epileptic patients.

While our study supports the study conducted by Menon et al. it does not support the study by Martinic et al. which has shown that polytherapy with anti-epileptic drugs increased oxidative stress. A statistically significant difference was not found in our study between the groups who were under monotherapy or polytherapy, concerning oxidative stress levels. Differences in results on this issue suggest a need for more clinical investigations.

In a study by Ishikawa et al. (27), the Hs-CRP level of patients with daily generalized type motor seizures was significantly higher than other epileptic patients and control groups and it was concluded that frequent motor seizures could cause chronic inflammation. Epileptic seizures were concluded to initiate brain inflammation in glial cells and caused damage in the blood-brain barrier independent of leukocytes and inflammatory molecules of blood-origin in a study by Librizzi et al. (28). Also, brain inflammation was claimed to cause recurrent and continuing seizures.

Long-term use of anti-epileptic drugs may cause low-grade systemic inflammation and increase oxidative stress (29,30). A study by Yuen et al. has shown the absence of an association between the number of anti-epileptic drugs used and CRP levels (31). Atherosclerosis risk values of 195 patients taking anti-epileptic medications were evaluated in another study by Tan et al and CRP levels were higher than the control group (32).

Hs-CRP levels of patients on anti-epileptic monotherapy were statistically significantly higher than the control group (p=0.025). Hs-CRP levels of patients on antiepileptic polytherapy were statistically significantly higher than the control group (p=0,000). Hs-CRP levels of patients on polytherapy was statistically significantly higher than patients on monotherapy with anti-epileptics (p=0,000). This result may show the presence of increased systemic inflammation in pediatric patients with generalized type motor seizures.

CONCLUSION

An increase in TOS and OSI levels of epileptic patients with generalized tonic-clonic type epilepsy reflects an increase in oxidative stress. These findings support the role played by oxidative stress in the pathogenesis of generalized type epilepsy. We observed an increase in parameters of oxidative stress due to the seizure itself, as well as a contribution of anti-epileptic treatment by increasing the oxidative stress. Conflicting results of previous studies on the effects of anti-epileptic drugs on oxidative stress and antioxidant system create a requirement for further clinical investigations. Also, the finding of increased serum Hs-CRP levels in this study, suggests that various anti-inflammatory treatment strategies that could control the inflammatory process may be beneficial for treating resistant epileptic patients.

ACKNOWLEDGEMENT

Some part of this study was presented as poster presentation at “WFNS15-0519 The World Federation of Neurosurgical Societies in Istanbul, entitled as “Acute phase reactants in generalized tonic-clonic epileptic patients.

Peer-Review

Externally/Internally Peer Reviewed

Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article..

Financial Support

The Authors report no financial support regarding content of this article.

Ethical Declaration

Ethical approval was obtained from the Harran University Ethics Committee with date 23rd of May 2014, and number 6 and Helsinki Declaration rules were followed to conduct this study.

Support Resources

This investigation was supported by Scientific Research Coordination Committee of Harran University on the 13th of March 2013 (protocol number 13014) with the project number 2014/14.06.13

REFERENCES

1. Menkes JH, Sarnat HB. Paroxysmal disorders. In: Menkes JH, Sarnat HB. Child Neurology (6th Ed). Philadelphia. Lippincott Williams&Wilkins. 2000; 919-1026.
2. Dasheiff RM. Sudden unexpected death in epilepsy: a series from an epilepsy surgery program and speculation on the relationship to sudden cardiac death . J Clin Neurophysiol. 1991; 8: 216-22. https://doi.org/10.1097/00004691-199104000-00010
3. Conway JM, Kriel RL, Birnbaum AK. Antiepileptic Drug Therapy in Children: An Overview. In: Swaiman KF, Ashwal S, Pediatric Neurology Principles &Practise (3th ed). Philadelphia. Mosby Elsevier. 2006; 1105-30.
4. Gershov D, Kim S, Brot N, et al. C-reactive protein binds to apoptotic cells, protects the cells from assembly of the terminal complement components, and sustains an antiinflammatory innate immune response: Implications for systemic autoimmunity. J Exp Med 2000; 192:1353-64. https://doi.org/10.1084/jem.192.9.1353
5. Doumatey AP, Zhou J, Adeyemo A, Rotimi C. High sensitivity C-reactive protein (Hs-CRP) remains highly stable in long-term archived human serum. Clin Biochem.2014 Mar;47(4-5):315-8. https://doi.org/10.1016/j.clinbiochem.2013.12.014
6. Rafieian-Kopaei M, Setorki M, Doudi M, Baradaran A, Nasri H. Atherosclerosis: process, indicators, risk factors and new hopes. Int J Prev Med. 2014 Aug;5(8):927-46.
7. Erel 0. A new automated colorimetric method for measuring total oxidant status. Clin Biochem. 2005; 38 (12): 1103-11. https://doi.org/10.1016/j.clinbiochem.2005.08.008
8. Bostjan Martinc, Iztok Grabnar, and Tomaz Vovk. The Role of Reactive Speciesin Epileptogenesis and Influence of Antiepileptic Drug Therapy on Oxidative Stress. Curr Neuropharmacol. 2012; 10(4): 328-43. https://doi.org/10.2174/157015912804499447
9. Gomez-Marcos MA, Recio-Rodriguez JI, Patino-Alonso MC, Agudo-Conde C, Gomez-Sanchez L, Rodriguez-Sanchez E, et al. Relationships between high sensitive C-reactive protein and markers of arterial stiffness in hypertensive patients. Differences by sex. BMC Cardiovasc Disord 2012; 12: 37-8. https://doi.org/10.1186/1471-2261-12-37
10. Assadpour Piranfar M. The correlation between high-sensitivity C-reactive protein (HSCRP) serum levels and severity of coronary atherosclerosis. Int Cardiovasc Res J 2014; 8: 6-8.
11. Wasilewska A, Tenderenda E, Taranta-Janusz K, Zoch-Zwierz W. High-sensitivity C-reactive protein and mean platelet volume in paediatric hypertension. Pediatr Nephrol 2010; 25:1519-27. https://doi.org/10.1007/s00467-010-1513-2
12. VanGilder RL, Davidov DM, Stinehart KR, Huber JD, Turner RC, Wilson KS, et al. C- reactive protein and long-term ischemic stroke prognosis. J Clin Neurosci 2014; 21: 547-53. https://doi.org/10.1016/j.jocn.2013.06.015
13. Almroth G, Lonn J, Uhlin F, Nayeri F, Brudin L, Andersson B, et al. Fibroblast growth factor 23, hepatocyte growth factor, interleukin-6, high-sensitivity Creactive protein and soluble urokinase plasminogen activator receptor. Inflammation markers in chronic haemodialysis patients? Scand J Immunol 2013; 78:285-90 . https://doi.org/10.1111/sji.12082
14. Engelhart MJ, Geerlings Ml, Meijer J, Kiliaan A, Ruitenberg A, van Swieten JC, et al. Inflammatory proteins in plasma and the risk of dementia: the Rotterdam study. Arch Neurol 2004; 61: 668-72 https://doi.org/10.1001/archneur.61.5.668
15. Calik M, Oğuz E, Sarikaya S, Kocaturk O, Koca B, Gungor HE, Aksoy N, Yoldaş TK, Iscan A. An evaluation of serum paraoxonase together with arylesterase activities and oxidative stress in children with intractable epilepsy: across-sectional study. Epilepsy Res. 2014 Nov; 108(9): 1591 -6. https://doi.org/10.1016/j.eplepsyres.2014.08.007
16. Ethemoglu O, Ay H, Koyuncu I, Gönel A. Comparison of cytokines and prooxidants/antioxidants markers among adults with refractory versus well- controlled epilepsy: A cross-sectional study. Seizure. 2018 Aug;60:105-109. https://doi.org/10.1016/j.seizure.2018.06.009
17. Hassanzadeh P, Arbabi E, Rostami F. The ameliorative effects of sesamol against seizures, cognitive impairment and oxidative stressin the experimental model of epilepsy. Iran J Basic Med Sci. 2014 Feb; 17(2): 100-7.
18. Ben-Menachem E., Kyllerman M., Marklund S. Superoxide dismutase and glutathione peroxidase function in progressive myoclonus epilepsies Epilepsy Res. 2000; 40: 33-9. https://doi.org/10.1016/S0920-1211(00)00096-6
19. Shin EJ, Jeong JH, Chung YH, Kim WK, Ko KH, Bach JH, Hong JS, Yoneda Y,Kim HC. Role of oxidative stres in epileptic seizures. Neurochem Int. 2011; 59(2): 122-37. https://doi.org/10.1016/j.neuint.2011.03.025
20. Yürekli VA, Nazıroğlu M. Selenium and topiramate attenuates blood oxidative toxicity in patients with epilepsy. Biol Trace Elem Res. 2013 May; 152(2): 180-6. : https://doi.org/10.1007/s12011-013-9616-9

21. Ashrafi MR, Azizi Malamiri R, Shams S, Rashidi Ranjbar N, Ebrahimi Nasrabadi S, Haghi Ashtiani M, Saladjegheh N, Vakili Zarch V. Serum Total Antioxidant Capacity of Epileptic Children before and after Monotherapy with Sodium Valproate, Carbamazepine, and Phenobarbital. Iran J Child Neurol. 2018 Summer;12(3):24-31.Aycicek A, Iscan A. The effects of carbamazepine, valproic acid and phenobarbital on the oxidative and antioxidative balance in epileptic children. Eur Neurol. 2007;57(2):65-9. Epub 2006 Dec 15. https://doi.org/10.1159/000098053

22. Menon B, Ramalingam K, Kumar RV. Oxidative stress in patients with epilepsy is independent of antiepileptic drugs. Seizure 2012; 21 (10): 780-4. https://doi.org/10.1016/j.seizure.2012.09.003

23. Varoglu, A.O., Yildirim, A., Aygul, R., Gundogdu, O.L., Sahin, Y.N., Effects of valproate, carbamazepine, and levetiracetamon the antioxidant and oxidant systems in epileptic patients andtheir clinical importance. Clin Neuropharmacol 2010; 33:155-7. https://doi.org/10.1097/WNF.0b013e3181d1e133

24. Shahar E, Attias U, Savulescu D, Genizin J, Gavish M, Nagler R. Oxidative stress, metalloproteinase and LDH in children with intractable and non-intractable epilepsy as reflected in salivary analysis. Epilepsy Res. 2014 Jan; 108(1): 117-24. https://doi.org/10.1016/j.eplepsyres.2013.10.003

25. Rubio C, Rubio-Osornio M, Retana-Marquez S, Veronica Custodio ML, Paz C. In vivo experimental models of epilepsy. Cent Nerv Syst Agents Med Chem. 2010 Dec 1;10(4):298-309. https://doi.org/10.2174/187152410793429746

26. Ishikawa N, Kobayashi Y, Fujii Y, Kobayashi M. Increased interleukin-6 and high- sensitivity C-reactive protein levels in pediatric epilepsy patients with frequent, refractory generalized motor seizures. Seizure. 2015 Feb; 25:136-40. https://doi.org/10.1016/j.seizure.2014.10.007

27. Librizzi L, Noe F, Vezzani A, de Curtis M, Ravizza T. Seizure-induced brain-borne inflammation sustains seizure recurrence and blood-brain barrier damage. Ann Neurol 2012; 72: 82-90. https://doi.org/10.1002/ana.23567

28. Rojas A, Jiang J, Ganesh T, Yang MS, Lelutiu N, Gueorguieva P, et al. Cyclooxygenase-2 in epilepsy. Epilepsia 2014; 55:17-25. https://doi.org/10.1111/epi.12461

29. Kwon YS, Pineda E, Auvin S, Shin D, Mazarati A, Sankar R. Neuroprotective and antiepileptogenic effects of combination of anti-inflammatory drugs in the immature brain. J Neuroinflamm 2013; 10: 30-1. https://doi.org/10.1186/1742-2094-10-30

30. Yuen AW, Bell GS, Peacock JL, Koepp MM, Patsalos PN, Sander JW. Effects of AEDs on biomarkers in people with epilepsy: CRP, HbA1c and eGFR. Epilepsy Res 2010; 91:187-92. https://doi.org/10.1016/j.eplepsyres.2010.07.011

31. Tan TY, Lu CH, Chuang HY, Lin TK, Liou CW, Chang WN, et al. Long-term antiepileptic drug therapy contributes to the acceleration of atherosclerosis. Epilepsia 2009; 50:1579-86. https://doi.org/10.1111/j.1528-1167.2009.02024.x