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Research Article

COMPARING OXIDANT-ANTIOXIDANT BALANCE IN CHILDREN SUFFERING CONTROLLED AND RECURRENT EPILEPSIES AND HEALTHY CHILDREN

FARAH ASHRAFZADEH[1], JAVAD AKHONDIAN[1], SHAHRZAD SEPIDBAR*[1], RAHIL HAJIALIZADEH[1], FARSHAD SEPIDBAR[2]

[1] Ghaem pediatric nursing service, Mashhad University of Medical Sciences, Mashhad, Iran.
[2] Statistician, Baft, Kerman, Iran.

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ABSTRACT

Background: Oxidant-antioxidant balance modulation may be a main determinant in assessing types and progression of seizures and also the efficacy of antioxidant medications. The present study aimed to compare the serum level of oxidant-antioxidant balance in children suffering controlled and recurrent epilepsies. Methods: This cross-sectional study was performed on children aged 2-14 years with idiopathic epilepsy (17 patients suffering controlled seizure and 14 patients with recurrent seizure) who were under treated with antiepileptic drugs. Also, 25 healthy children in the same age group and selected from the same families were considered as the healthy controls. The oxidant-antioxidant balance was measured by in-house ELISA method. Results: The mean oxidant-antioxidant balance in controlled seizure group was 155.3 ± 11.3 and in those with recurrent seizure was 155.6 ± 8.2 indicating no significant difference (p = 0.987). Compared to healthy group, the controlled seizure group had a similar mean oxidant-antioxidant balance (155.3 ± 11.3 versus 159.9 ± 15.6, p = 0.798). Similarly, there was no difference in the mean oxidant-antioxidant balance between the group with recurrent seizure and healthy group (155.6 ± 8.2 versus159.9 ± 15.6, p = 0.829). The mean oxidant-antioxidant balance was independent to gender, age, family history of seizure, the time of the first episode, the type and time of medications, mental status, economical condition, and nutritional habit. Conclusion: Our study shows no difference in oxidant-antioxidant balance between the patients suffering idiopathic epilepsy and healthy individuals. The type of seizure may not influence the situation of oxidant-antioxidant balance. Moreover, the type of antiepileptic medication may not affect the oxidant activities in epileptic patients.

Keywords: seizure; antioxidant, stress oxidative; children

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INTRODUCTION

Excessive production of free radicals in central nervous system along with neuronal hyper-excitability has been shown as potential candidates responsible for the pathogenesis of neurological defects such as epilepsy (1, 2). Molecular and biochemical studies showed hyper-activating oxidative metabolism led to releasing free radicals, low activation of antioxidant barriers and the richness in polyunsaturated fatty acids as a triad of the brain highly vulnerability in epileptic events (3,4). In other words, susceptibility of the brain to oxidants emphasizes the pathogenic basis of oxidative stress in the pathophysiology of neural defects such as seizures. Reviewing the literature can address the role of both mitochondrial dysfunction and oxidative stress in different types of seizures (5-7). The ability of antioxidants for reducing the seizure manifestations and the accompanying biochemical changes such as markers of oxidative stress further supports a role of free radicals in seizures and highlights a possible role of antioxidants as adjuncts to antiepileptic drugs for better seizure control (8, 9). In fact, pro-oxidant/antioxidant balance modulation is a main determinant in assessing types and progression of seizures and also the efficacy of antioxidant medications (10). In total, it seems that oxidant-antioxidant balance can be significantly disturbed in epileptic events. On the other hand, the response to antiepileptic drug is acceptable when the pointed balance is established. It should be noted, however, that disturbances in the above balance may play an essential role in certain types of seizures. So, Devi et al in 2008 suggested a putative role of oxidative stress in the pathophysiology of certain seizure types (11). The present study aimed to compare the serum level of oxidant-antioxidant balance in children suffering controlled and recurrent epilepsies.

MATERIALS AND METHODS

This cross-sectional study was performed on children aged 2-14 years with idiopathic epilepsy who were under treated with antiepileptic drugs (phenobarbital, carbamazepine, and sodium valproate), who referred to the Ghaem pediatric nursing service in Mashhad and willing to participate in the study were included into the study. Also, 25 healthy children in the same age group and selected from the same families were considered as the healthy controls. Idiopathic epilepsy was defined as epilepsy with no underlying structural brain lesion or other neurologic signs or symptoms, and presumed to be genetic and subdivided as the recurrent seizure (≥2 seizures ≥ 4 weeks apart) and controlled seizure (no recurrence of seizures for at least two years, whether on antiepileptic treatment or not). Overall, the study inclusion criteria were the age ranged 2 to14 years, prophylaxis of idiopathic epilepsy based on history, physical examination and laboratory testing, use only one type of antiepileptic medication, willing of parents to do research, the blood level of the anticonvulsant medication at the therapeutic level. In this regard, the exclusion criteria were symptomatic epilepsy, progression of neurological disorders, having systemic diseases, malnutrition or mental retardation and the use of multiple therapies in treating epilepsy. Both case groups were tried to match regarding age and sex and the type of seizure. Every 6 months, the level of anticonvulsant drug in the serum of patients was measured to ensure that the patient takes the medication. If the blood level of the drug was at the therapeutic level and the type of drug was selected based on the type of seizure (epilepsy), the study primary checklist was filled out and the initial tests (including liver function and hematological tests were performed. Then, 5cc of peripheral blood

sample was collected and centrifuged with 2500 rpm for 5 minutes at room temperature. The serum was then stored at -20°C. The oxidant-antioxidant balance was finally measured by in-house ELISA method in the case and also in control healthy groups. Since the measurement of each of oxidants (hydroxyl radicals, superoxide radicals, nitric oxide and lipid peroxyl radicals) was very costly, in the In-house ELISA method, the overall balance of all antioxidants and oxidants was measured which could provide the correct attitude to the state of the body's biology. In in-house technique, oxidant-antioxidant balance is measured by tetramethylbenzidine (TMB) in two reactions, the first enzymatic reaction that chromogen is oxidized by peroxides (H2O2) to cationic TMB and then the TMB is catalyzed by an antioxidant (uric acid).

Descriptive analysis was used to describe the data, including mean ± standard deviation (SD) for quantitative variables and frequency (percentage) for categorical variables. Chi square test, t test, or Mann-Whitney U test were used for comparison of variables. For the statistical analysis, the statistical software IBM SPSS Statistics for Windows version 22.0 (IBM Corp. Released 2013, Armonk, New York) was used. P values <0.05 were considered statistically significant.

RESULTS

In this study, 17 patients suffering controlled seizure, 14 patients with recurrent seizure and 25 healthy controls were included. Regarding sex distribution, 41.5%, 39.4%, and 40.0% were male respectively with no between-group difference (p = 0.978). In addition, 29.4%, 7.1%, and 16.0% aged 2 to 6 years, 41.1%, 28.7%, and 40.0% aged 6 to 10 years and 29.5%, 64.2%, and 44.0% aged 10 to 14 years respectively with no significant difference (p = 0.097).

The mean oxidant-antioxidant balance in controlled seizure group was 155.3 ± 11.3 and in those with recurrent seizure was 155.6 ± 8.2 indicating no significant difference (p = 0.987). Compared to healthy group, the controlled seizure group had a similar mean oxidant-antioxidant balance (155.3 ± 11.3 versus 159.9 ± 15.6, p = 0.798). Similarly, there was no difference in the mean oxidant-antioxidant balance between the group with recurrent seizure and healthy group (155.6 ± 8.2 versus159.9 ± 15.6, p = 0.829). As shown in Table 1, the similarity in the mean oxidant-antioxidant balance between the two patients' groups with controlled or recurrent seizure were completely independent to baseline variables including gender, age, family history of seizure, the time of the first episode, the type and time of medications, mental status, economical condition, and nutritional habit.

DISCUSSION

The present study could not demonstrate the difference in the mean oxidant-antioxidant balance between the two patients' groups with controlled or recurrent seizure and also compared to healthy individuals in our population. In other words, in our study population, not only the oxidant-antioxidant balance condition was no different between the two types of seizures (controlled and recurrent), but also the pointed balance had similar condition between the disease and healthy status. More interestingly, oxidant-antioxidant balance was independent to underlying variables including gender, age, family history of seizure, the time of the first episode, the type and time of medications, mental status, economical condition, and prominent nutritional habit and in fact, the condition of oxidant-antioxidant balance between the patients' groups remained similar even adjusted for baseline factors. The role of oxidative stress in the pathogenesis and progression of epilepsy has been well described and in this regard, the critical role of antioxidants as adjuncts to antiepileptic drugs for better seizure control has been also revealed. Insignificant difference in oxidant-antioxidant balance in our patients group suggests that the type of seizure may not influence the status of this balance and on the other hand different types of idiopathic seizures may have similar stress oxidative pathways as the baseline pathogenesis. However, the lack of difference in oxidant-antioxidant balance between our patients and healthy groups may suggest the potential effect of other factors such as genetic variants affecting the pathogenesis of seizure. Of course, the cross-sectional planning the study and low study sample size may also affect our final conclusion.

As shown by Günes et al in 2009 (12), Erythrocyte malondialdehyde and glutathione peroxidase levels as the main oxidants were significantly higher and superoxide dismutase levels were significantly lower in the febrile seizure group indicating a possible critical role of oxidants in the pathogenesis of febrile seizure; however their study focused only on febrile seizure on younger children group. However, according to their result, febrile seizures may cause significant oxidative stress, and these changes in oxidant status may be a step along the way to cell damage subsequent to febrile seizures. Also, contrary to our observation respecting the impact of the type of medication on the oxidant-antioxidant balance, Sobaniec et al in 2006 (13) showed that the activity of superoxide dismutase, glutathione peroxidase, and glutathione reductase and the malondialdehyde concentration was different in the patients treated with carbamazepine or valproate monotherapy and thus they could demonstrated that the type of antiepileptic drugs can affect the stress oxidative situation in patients. Similarly, Varoglu et al (14) indicated that the antioxidant and oxidant enzyme activities could be influenced by the type and time of medication as monotherapy or combination therapy. Guler et al (15) also revealed the paradoxical findings. Although they could show the difference in oxidant enzyme activities in patients with epilepsy as compared to controls, there were no differences in the level of enzymes between the monotherapy and polytherapy groups. In total, it seems that the lowering level of antioxidants can be predicted in patients with different types of seizures and thus antioxidant replacement therapy may benefit those patients, however our study could not show such association might be due to our small sample size or genetic characteristics of our population. However, about the effect of antiepileptic treatment regimens on antioxidant and oxidant activities, studies have not come to an agreement and therefore it seems that polytherapy may not change the oxidant-antioxidant balance situation as compared with monotherapy.

CONCLUSION

As the final conclusion, our study could not show significant difference in oxidant-antioxidant balance between the patients suffering idiopathic epilepsy and healthy individuals. Also, the type of seizure as the controlled or recurrent could not influence the situation of oxidant-antioxidant balance. Moreover, the type of antiepileptic medication could not affect the oxidant activities in epileptic patients. The obtained results might be potentially affected by the study limitations such as cross-sectional designing and small sample size employed for the present study emphasizing further studies considering these limitations.

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Table 1: The mean oxidant-antioxidant balance between the groups with controlled and recurrent seizures according to baseline factors

Variable	Controlled seizure (n = 17)	Recurrent seizure (n = 14)	P value
Gender			0.978
Male	159.7 ± 30.7	144.3 ± 47.3	
Female	147.2 ± 41.5	164.1 ± 39.4	
Age, year			0.661
2 to 6	161.8 ± 30.0	211.7 ± 0.0	
7 to 10	158.2 ± 47.3	169.2 ± 35.8	
11 to 14	144.6 ± 29.6	143.4 ± 42.4	
Family history of seizure			0.510
Present	154.1 ± 33.0	173.6 ± 34.1	
Absent	157.6 ± 39.2	142.2 ± 45.1	
The time of the first episode			0.415
< 3 years old	165.4 ± 29.1	161.1 ± 48.6	
3 to 6 years old	146.8 ± 56.1	133.1 ± 24.3	
> 6 years old	134.8 ± 32.0	163.6 ± 43.6	
Type of medication			0.888
Valproate	153.8 ± 36.1	151.2 ± 34.1	
Carbamazepine	153.1 ± 39.1	154.4 ± 61.9	
Phenobarbital	168.7 ± 40.6	187.1 ± 40.0	
Time of drug use			0.215
< 1 years	157.4 ± 36.1	151.2 ± 51.1	
1 to 4 years	150.1 ± 39.1	182.6 ± 27.5	
> 4 years	169.7 ± 9.9	147.2 ± 44.6	
Mental status			0.834
Normal	150.2 ± 28.2	153.2 ± 43.2	
Retard	178.8 ± 56.2	187.1 ± 20.0	
Monthly income			0.823
≤500.000 tomans	162.1 ± 29.2	157.0 ± 38.3	
>500.000 tomans	153.8 ± 35.9	153.3 ± 54.0	
Prominent nutritional habit			0.786
Homemade diet	159.8 ± 35.3	155.6 ± 42.5	
Fast food diet	144.3 ± 31.8	---	