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ORIGINAL ARTICLE

Nitric Oxide (NO), Xanthine Oxidase (XOD) and Malonylaldehyde (MAD) in Children with Seizures

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ABSTRACT

Background: Nitric Oxide (NO), Xanthine Oxidase (XOD), and Malonylaldehyde (MAD) are likely implicated in the initiation and progression of epilepsy. The high lipid content of the brain makes it prone to oxidative stress.

Aim of the study: Evaluate oxidative stress biomarkers in children experiencing febrile convulsions and idiopathic epilepsy.

Methods: This is a case-control study that enrolled 99 children of ages ranging from 0.5 to 6 years, conducted at Zagazig University Pediatric Hospital from April 2016 to March 2019. These children were divided into 3 groups: group I included 33 children with a history of febrile convulsions, group II included 33 children diagnosed with new idiopathic epilepsy & a control group III included 33 healthy children of similar age & gender. NO, XOD and MAD levels were measured in fasting blood serum samples of the patients and controls.

Results: There was no significant statistical difference between the studied groups as regards the demographic data. Neurological deficit and abnormal EEG pattern were observed only among group II. The levels of NO and XOD were significantly increased in the febrile and idiopathic groups compared to the control group. There was no significant statistical difference between the studied groups as regards MAD levels.

Conclusions: The neurological deficit and the abnormal EEG pattern were observed only among children with idiopathic epilepsy. Although NO and XOD levels were increased in children experiencing febrile convulsions and idiopathic epilepsy, there was no difference in MAD levels among the three groups.

Keywords: Febrile Convulsion; Idiopathic Epilepsy; NO; XOD; MAD.

INTRODUCTION

A seizure is a sudden transient paroxysmal cerebral dysrhythmia characterized by a change in motor, sensory, autonomic, and/or behavior resulting from abnormal electrical discharge in the brain. Epilepsy is diagnosed when the child has 2 or more unprovoked fits that are >24 hours apart, but a child with one unprovoked seizure has a ≥60% susceptibility to recurrent fits over the next ten years. Epilepsy is the 2nd most common chronic neurological condition seen by neurologists [1-11]. Nearly 60% of all epilepsy patients are of unknown causes. The causes of seizures are multi-factorial in any patient, for example, the reaction between genetically based convulsion threshold, hidden corresponding pathologies, or metabolic abnormalities plus acute provocation factors [2]. The tendency for febrile seizures has a serious role in the convulsions' threshold [3]. Oxidative stress occurs when oxidative factors overcome anti-oxidative factors in-vivo. This means accumulation of O2 free radicals or decline of the antioxidant pathway [4]. The reduction of O2 to H2O in the mitochondria implies the synthesis of 4 electrons that may react with O2 to produce active free radicals. Under pathological conditions, about 2% of O2 is not reduced in the mitochondria, which produces free radicals as the end reaction results [2]. Seizures' production may be due to an imbalance of O2 free radicals and antioxidants. Up till now, many experimental seizure studies have been implied to discover the role of internal antioxidants in response to excite-toxic oxidative stress. The decline of internal antioxidant factors versus oxidative stress is responsible for seizure production. The ability of antioxidants to alleviate seizures' production and the associated effects on oxidative load agree with the function of antioxidants in doing anti-seizures' action [1].

Antioxidants are natural or synthetic substances that may neutralize the free radicals once produced, so that the free radicals do not have enough time to destruct the DNA or other cyto-nuclear organelles [5]. The free radicals arising from molecular O2 originate from different sources such as mitochondria and xanthine oxidase system [6]. The brain is highly susceptible to oxidative injury due to the high use of inspired O2, the huge amount of easily oxidizable PUFA, the flooding of redox-active transition metal ions and the relative failure of antioxidant fighting mechanisms [7]. The brain is more susceptible to trauma by lipid peroxidation moieties than other organs which are a threat of neuron-axonal degeneration of membrane phospholipids. Many research about oxidative stress in convulsive children were carried out to prove the results of anticonvulsive medications on oxidative conditions [8]. Lipid peroxidation is an index of free radical metabolism and oxidative load in vivo. Malonylaldehyde (MAD, a final result of lipid peroxidation), is a moiety that can be easily measured in blood samples. Nitric oxide (NO) (a tiny diffusible gaseous mediator produced from the amino acid L-arginine by the enzyme NO synthase) has a vital action in a many of physiological and pathological processes in the brain, such as the moderation of neuron-axonal elasticity, encephalic circulation, cognitive and behavioral actions. Also, its role in neuron-axonal abnormalities like ischemia and seizures [9]. The increased total oxidant level and decreased total antioxidant level may increase the risk of experiencing febrile seizures [10]. The aim of this study was to evaluate the oxidative stress biomarkers in children experiencing febrile convulsions and idiopathic epilepsy.

METHODS

This is a case-control study that enrolled 99 children of ages ranging from 0.5 to 6 years, conducted at Zagazig University Pediatric Hospital during April 2016 to March 2019. These children were divided into 3 groups: **Group I:** 33 children (15 boys and 18 girls) with a history of febrile convulsions. **Group II:** 33 children (16 boys and 17 girls) with newly diagnosed idiopathic epilepsy. **Group III:** 33 healthy children of similar age and gender served as a control group. **Inclusion Criteria:** Age from 0.5 to 6 years, both sexes; children with recently diagnosed simple febrile convulsions and idiopathic epilepsy; and no previous intake of antiepileptic drugs, or other related medications at the time of study. **Exclusion Criteria:** Children with 2ry epilepsy; children with complex febrile convulsions; and previous intake of antiepileptic drugs or other related medications at the time of study. **Diagnosis Criteria:** Epilepsy was diagnosed when the child had 2 or more unprovoked fits with >24 hours apart, but a child with 1 unprovoked seizure has a ≥60% susceptibility to recurrent fits over the next ten years [11]. The 1st step was to differentiate between epileptic seizures and conditions that mimic epilepsy. The 2nd step was to do an electroencephalographic (EEG). The 3rd step was to confirm if the patient with 1st unprovoked seizure has epilepsy or not [11]. Owing to the psychological and social effects of epilepsy, the diagnosis was based on strong evidence [12]. The 4th step was to identify the causes of convulsions [11]. The study was approved by the Pediatrics Department Committee, the Ethical Committee in the Faculty of Medicine, and the local Ethic Committee of Zagazig University. IRB approval was also obtained before starting the study. Written informed consent was obtained from all participants' parents. The work has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. All studied children were subjected to full history taking, clinical examination, and EEG to detect the type of seizures. Routine laboratory investigations as complete blood count and liver function test, special tests for determination of oxidative stress biomarkers including Nitric oxide [NO], Xanthine oxidase [XOD] and Malonylaldehyde [MAD]) were drawn prior to antiepileptic drug therapy and measured in fasting blood serum samples of the patients and controls after obtaining the written informed consent. ***Nitric oxide(NO) level (mmol/mL)*** was determined according to the method based on the diazotization of sulfanilic acid by NO at acid pH and subsequent coupling to N-(1-naphthyl-ethylenediamine)[13].***Xanthine oxidase (XOD) activity (IU/mL)*** was determined by measuring uric acid formation from xanthine substrate at 293 nm [14].***Malonylaldehyde (MAD) level(nmol/mL)***was measured by the thiobarbituric acid reactive substances method [13].

STATISTICAL ANALYSIS

Data analysis was performed using the Statistical Package of Social Science (SPSS), Version 22.0 (SPSS Inc., Chicago, IL). Data were expressed as mean ± standard deviation (SD). The (F)-test was used to analyze the variance among groups. Statistically significant differences obtained from ANOVA analysis were further tested by the student's (t)-test comparisons between groups. The Chi-square ($\chi 2$) test was used to compare the proportions. A repeated measures design was used to evaluate the data of each group measured at different times. P-values of <0.05 were considered statistically significant.

RESULTS

As regards the demographic data among the

studied groups, there was no significant statistical difference between the febrile group (group I) and the idiopathic group (group II) compared to the control group (group III) ($p > 0.05$) (Table 1).

As regards the seizure type, there was a significant statistical difference between groups I and II. The febrile convulsions were always generalized, but the idiopathic epilepsy was either generalized or partial ($p < 0.002$). (Table 2)The neurological deficit was observed only in group II, and the difference was significant ($p < 0.001$) (Table 3).

The abnormal EEG pattern was observed only in group II, and the difference was significant ($p < 0.001$) (Table 4).The level of NO was significantly increased in the febrile and idiopathic groups compared to the control group ($p < 0.001$), but there was no obvious difference between the febrile and idiopathic groups (Table 5).The level of XOD was significantly increased in the febrile and idiopathic groups compared to the control group ($p < 0.001$), but there was no obvious difference found between the febrile and idiopathic groups (Table 6).There was no significant statistical difference in MAD levels among all the studied groups ($p = 0.26$) (Table7).

Table 1: Demographic data among the studied groups.

Variables	Group I Febrile (n = 33)	Group II Epilepsy (n = 33)	Group III Control (n = 33)	Test of significance	P-value
Age				$F = 0.38$	**0.06**
X±SD	3.9±1.3	4.3±2.3	4.5±2.3		
Range	0.5–6	0.5-9	1-9		
Gender				$\chi^2 = 0.24$	**0.8**
Boys	15 (45.5%)	16 (48.5%)	17 (51.5%)		
Girls	18 (54.5%)	17 (51.5%)	16 (48.5%)		
Residence				$\chi^2 = 1.54$	**0.4**
Urban	17 (51.5%)	20 (60.6%)	15 (45.5%)		
Rural	16 (48.5%)	13 (39.4%)	18 (54.5%)		
Family history				$\chi^2 = 3.65$	**0.1**
-ve	23 (69.7%)	20 (60.6%)	27 (81.8%		
+ve	10 (30.3%)	13 (30.4%)	6 (18.2%)		
Consanguinity				**$\chi^2 = 4.71$**	**0.09**
-ve	**25 (75.8%)**	**23 (69.7%)**	**30 (90.9%)**		
+ ve	**8 (24.2%)**	**10 (30.3%)**	**3 (9.1%)**		

Table 2: Seizure types among febrile convulsion group I compared with idiopathic epilepsy group II.

Variables	Group I Febrile (n = 33)	Group II Epilepsy (n = 33)	χ^2	P value
Generalized seizure	33 (100%)	25 (75.8%)		
Tonic-clonic	20 (60.6%)	12 (48.0%)		
Tonic	13 (39.4%)	13 (52.0%)		
Partial seizure	0 (0.0%)	8 (24.2%)	9.1	**0.002**
Simple partial seizure	0 (0.0%)	4 (12.1%)		
Complex partial seizure	0 (0.0%)	2 (6.1%)		
Partial with 2ry generalization	0 (0.0%)	2 (6.1)		

Table 3: Neurological deficits among febrile convulsion group I compared with idiopathic epilepsy group II.

Variables	Group I Febrile (n = 33)	Group II Epilepsy (n = 33)	χ^2	P value
No neurological deficit	33 (100%)	5 (15.2%)	**48.6**	< 0.001
Neurological deficit	0 (0.0%)	28 (84.8%)		

Table 4: Electroencephalography (EEG) pattern among febrile convulsion group I compared with idiopathic epilepsy group II.

Variables	Group I Febrile (n = 33)	Group II Epilepsy (n = 33)	χ^2	P value
Normal	33 (100%)	5 (15.2%)	48.63	**<0.001**
Generalized epileptic activity	0 (0.0%)	28 (84.8%)		
Focal	0 (0.0%)	9 (27.3%)		
Focal with 2ry generalization	0 (0.0%)	3 (9.1%)		
Multifocal	0 (0.0%)	1 (3.0%)		

Table 5: Comparison of nitric oxide (NO) finding among the studied groups.

Variables	Group I Febrile (n = 33)	Group II Epilepsy (n = 33)	Group III Control (n = 33)	*F*	P value
NO (µmol/mL)					
Mean±SD	22.2±4.0	26.7±5.1	12.46±2.6	106.9	**< 0.001**
Range	14 – 35	18 - 36	8 – 16		

Table 6: Comparison of Xanthine oxidase (XOD) finding among the studied groups.

Variables	Group I Febrile (n = 33)	Group II Epilepsy (n = 33)	Group III Control (n = 33)	*F*	P value
XOD (IU/mL)					
Mean±SD	127.6±12.1	128.6±16.7	108.4±12.9	21.6	**< 0.001**
Range	100 – 155	90 - 155	80 – 130		

Table 7: Comparison of Malonylaldehyde (MAD) findings.

Variables	Group I Febrile (n = 33)	Group II Epilepsy (n = 33)	Group III Control (n = 33)	*F*	P value
MAD (nmol/mL)					
Mean±SD	2.24±0.17	2.3±0.2	2.2±0.2	1.35	0.26
Range	2 – 2.5	1.8 – 2.5	2 – 2.5		

DISCUSSION

Oxidative stress resulting from excessive free-radical release is likely implicated in the initiation and progression of epilepsy. Therefore, antioxidant therapies aimed at reducing oxidative stress have received considerable attention in epilepsy treatment. However, much evidence suggests that oxidative stress does not always have the same pattern in all seizures' models [15].NO synthesis seems to be defective when there is endothelial damage. Endothelial damage is accepted as the hallmark in the etiology of various diseases. The role of NO in epilepsy has been examined in a number of in-vivo and in-vitro studies, however, the obtained results are still contradictory, reporting both pro- and anti-convulsion properties of NO [9]. Moreover, O2 radicals interfere with many cellular elements, leading to the damage of cellular structure and functions, and the endpoint could be cellular death. Lipids are known to be the most sensitive biomolecules to free radical generated damage. MAD is the end product of lipid peroxidation and can have hazardous effects on nearby and remote tissues [6]. Therefore, the current study aimed to evaluate the oxidative stress biomarkers in children experiencing febrile convulsions or idiopathic epilepsy. Most of the studies that evaluated the levels of NO, lipid peroxidation markers (MAD) and antioxidant status were performed on children receiving antiepileptic treatment. Clinical studies evaluating oxidant status in children with epilepsy before drug treatment are rare. In contrast to the current study, one of these studies found increased lipid peroxidation (MAD). Other studies agree with the current study, showing no change in lipid peroxidation markers (MAD) in newly diagnosed epileptic patients [16,17].A total of 66 children aged 0.5 to 6 years enrolled in the present study were divided into 2 groups according to the presence of newly diagnosed idiopathic epilepsy and a history of febrile convulsion: group I:

included 33 children aged 0.5-6 years, with a history of febrile convulsion. They were 15 boys and 18 girls a mean age of (3.9±1.3 years). Group II: included 33 children of similar age group with a newly diagnosed idiopathic epilepsy. They were 16 boys and 17 girls. In contrast, a total of 33 healthy children of similar age and gender served as the control group (Group III). According to the demographic data, the present study shows a non-significant statistical difference between the studied groups, which is contrary to the results of other research that has found that there are elements of hereditability in epilepsy [6,18].Our study matches with the study of Arhan et al. [6] who reported a non-significant difference of socioeconomic status (including age, sex, residence and family history) between the febrile convulsions group and epilepsy group in their study. Ashour et al. [18] stated that the number of their patients with a positive family history of seizure and neurological disease in the febrile and epilepsy groups was insignificantly different (P >0.05) when compared with the corresponding value in the control group. While the number of patients with a positive family history of seizures and neurological diseases in the epilepsy group was 16 (64%) patients, which was significantly higher (P <0.001) when compared with the corresponding values in the control group. In addition, the number of patients with a positive family history of seizures and neurological diseases in the epilepsy group was 18 (72%) patients, which was significantly higher (P <0.001) when compared with the corresponding values in the control group. The current study showed that 75.8% of epileptic children and all of the febrile convulsion group had generalized seizures. On the other hand, 24.2% of epileptic children had simple partial seizures. Statistically, there was a significant difference between the febrile seizures and epilepsy groups as regards seizure types. Neubauer et al. [19] agree with the current study, as about 70% of all febrile seizures was simple, usually generalized tonic-clonic seizures lasting about three minutes. The present study found that the neurological deficit was observed only in the idiopathic convulsion group (group II), and the difference was significant. This finding was consistent with the findings of a previous study [20].EEG recording is not usually indicated for the evaluation of seizures, either in hospitalized or outpatient settings. EEGs are most helpful if there is any doubt about whether febrile seizures have really occurred, because EEGs done on the day of seizures are abnormal in as many as 88% of patients [21]. In the current study, the abnormal EEG pattern was observed only among the idiopathic convulsion group (group II), and this difference was significant. In contrast, the results of a study done by Owolabi et al. [22] showed that the seizure frequency was significantly associated with the presence of abnormal EEG (P ≤0.0001). In contrast to the current study, Rasool et al. [23] demonstrated that an abnormal EEG was found in 56.2% of their epilepsy patients.In a study done by Joshi et al. [24], the results showed that children with complex febrile seizures are approximately 3.5 times more likely to show an abnormal EEG in the 2-day post-ictal period compared to children with complex febrile seizures, when the EEG was done beyond the 7-day post-ictal period [24].In contrast to the current study, abnormal EEG findings in the study of Rosenow et al. [25] and the nonspecific abnormal discharges were determined in all patients with simple febrile seizures. The epileptiform discharges were detected in patients with the complicated febrile seizure and epilepsy groups. This might indicate that complicated febrile seizure patients are very risky in terms of the inclusion of epileptic discharges [28]. It is reported also in a study conducted by Yücel et al. [26] that the EEG disorder might be in the important part of these patients and this condition might be together with the epilepsy. Therefore, Rasool et al. [23] concluded that, most of the patients with generalized and partial seizures had EEG abnormalities, while EEG abnormalities were uncommon in patients with complex febrile seizures, and this agrees with the current study.

In the baseline measurement, we evaluated the role of epilepsy on NO, XOD, and MAD levels. The present study demonstrated that the mean of NO levels in the febrile children group was (22.2±4.0 µmol/ml) ranged from 14-35 µmol/ml, the mean NO in the idiopathic epilepsy children group was (26.7±5.1 µmol/ml) ranged from 18-36 µmol/ml, and the mean NO in the control group was (12.46±2.6 µmol/ml) ranged from 8-16 µmol/ml. The level of NO was significantly increased in the febrile and idiopathic groups compared to the control group. These results also confirmed the previous studies' results conducted by Arhan et al. [6] and Ashour et al. [18].In contrast to the current study, Arhan et al. [6] found that the levels of serum NO were found to be significantly higher in epileptic children pre-treatment (p <0.005). Although the role of NO in the pathophysiology of epilepsy remains unclear and debatable, this observation may suggest that NO induces neuronal loss and reactive glial proliferation, thus it could be potentially involved in the pathogenesis of epilepsy [6]. However, there are also studies claiming the opposite, that is, endogenous NO may play a neuron-protective role [27]. These contradicting findings indicate that the relationship between NO and epilepsy is complex [28]. Consequently, more

research will be needed before a final conclusion about the possible contribution of NO to the pathophysiology of epilepsy seizures can be known. According to the effect of XOD levels on epilepsy seizures, the present study demonstrated that, the mean of XOD levels in the febrile children group was (127.6±12.1 IU/ml) ranged from 100-155 IU/ml, the mean of XOD levels in idiopathic epilepsy children group was (128.6±16.7 IU/ml) ranged from 90-155 IU/ml and the mean of XOD levels in the control group was (108.4±12.9 IU/ml) ranged from 80 – 130 IU/ml. Statistically, the level of XOD was significantly increased in the febrile convulsion and idiopathic epilepsy groups compared to the control group ($p < 0.001$), but there was no obvious difference in XOD in the idiopathic group when compared to the febrile convulsion group. This agrees with Lorigados pedre et al. [29] who found the levels of serum XOD significantly increased in febrile and epileptic groups when compared with control group ($p < 0.005$).The present study demonstrated that the mean of MAD level in the febrile children group was (2.24±0.17 nmol/ml) ranged from 2-2.5 nmol/ml, that the mean of MAD level in the idiopathic epilepsy children group was (2.3±0.2 nmol/ml) ranged from 1.8-2.5 nmol/ml and that the mean of MAD level in the control group was (2.2±0.2 nmol/ml) ranged from 2-2.5 nmol/ml. Statistically, there was no significant difference in MAD found between the studied groups ($p = 0.26$). The current study findings agree with other studies which concluded that there is oxidative stress in febrile seizure and epileptic patients [30, 31].However, in the study of Ashour et al. [18], the mean value of serum MAD level was significantly increased in the febrile group when compared with the epilepsy group.In contrast, Lorigados padre et al. [29] found significantly higher levels of MAD in children with febrile convulsion group (39.78 ± 3.23 µm/l) when compared to the epilepsy group (18.23 ± 0.81 µm/l) ($p \leq 0.00001$). These results were in agreement with previous studies, in which it has been reported that a higher level of MAD is associated with febrile seizures [32,33]. Finally, the current study results were in agreement with Menon et al. [34]. This study determined the MAD and NO levels in 100 patients with febrile seizures and patients without febrile seizures and compared to the control group in an equal number of age and sex matched healthy subjects. The authors of these studies demonstrated that the NO levels were significantly higher in patients with febrile seizures than in epilepsy children and control groups ($P<0.0001$). But there was no significant difference in the MAD levels of these patients and those of control group. This confirms the current study results about MAD. However, Arhan et al. [7] found XOD and MAD levels in the pretreatment and control groups were found to be similar and serum NO levels was found to be increased in the febrile group compared to the epilepsy group.

Limitations: A hospital-based study does not represent the community because most children with febrile convulsions can be managed in out-of-hospital clinics, and the majority of cases are discharged from the emergency room. Kits and laboratory measurements are too expensive.

CONCLUSION

At screening 66 children of both sexes, aged 0.5-6 years, with recently diagnosed simple febrile convulsions and idiopathic epilepsy, at Zagazig university, the neurological deficit and abnormal EEG pattern were observed only among children with idiopathic epilepsy although NO & XOD were increased in both children experiencing febrile convulsions and idiopathic epilepsy, with no change in MAD level.

RECOMMENDATIONS

Oxidant levels should be measured in febrile convulsions and epilepsy. Usage of antioxidants may be beneficial in the management of febrile convulsions and epilepsy. Further research should be done in multi-centers and on a large scale to support the current study's observations and evaluate the value of using antioxidants in the treatment of febrile convulsions and epilepsy.

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