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Malondialdehyde and superoxide dismutase levels in patients with epilepsy: a case–control study

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Abstract

Background: Oxidative stress has a significant influence in the initiation and progression of epileptic seizures. It was reported that inhibiting oxidative stress could protect against epilepsy. The aim of the current research is to estimate some biomarkers that reflect the oxidative stress in epileptics, its relation to seizure control as well as to study the impact of antiepileptic drugs (AEDs) on these biomarkers. This case–control study included 62 epileptic patients beside 62 age and gender-matched healthy controls. The epileptic patients subjected to detailed history taking with special regards to disease duration, seizure frequency, and the current AEDs. Laboratory evaluation of serum malondialdehyde (a lipid peroxidation byproduct) and superoxide dismutase (an endogenous antioxidant) were done.

Results: Malondialdehyde (MDA) was significantly higher, and superoxide dismutase (SOD) was lower in epileptic patients than in the controls ($p < 0.001$). Seizure frequency was directly correlated with MDA ($r = 0.584, p < 0.001$) while inversely correlated with SOD ($r = -0.432, p = 0.008$). High MDA and low SOD were recorded in epileptic patients receiving polytherapy as compared to monotherapy ($p < 0.001$).

Conclusions: Epileptic patients had higher oxidative stress biomarkers than healthy individuals. Frequent seizures, long disease duration, and AEDs were associated with higher MDA and lower SOD that reflects an imbalance in the oxidant–antioxidant status among these patients.

Keywords: Oxidative stress, Malondialdehyde, Superoxide dismutase, Epilepsy, Antiepileptic drugs

Introduction

Epilepsy is a neurological illness affecting over 70 million people worldwide. It is characterized by a continuous tendency for spontaneous (unprovoked) seizures that carries multiple behavioral, cognitive, and psychosocial consequences [1, 2]. The previous experimental and clinical studies had demonstrated the influence of oxidative stress on epilepsy pathogenesis. It was reported that oxidative stress can impact seizure initiation and recurrence [3–5].

Oxidative stress refers to an imbalance between generation and degradation of reactive oxygen and nitrogen species [6]. The reactive oxygen species that are generated during cellular metabolism can be neutralized by either endogenous antioxidant enzymes, for example, superoxide dismutase (SOD) [7, 8] or nonenzymatic pathway through molecules with scavenging properties, for example, vitamin E, melatonin, and glutathione [9].

Superoxide dismutase, an intracellular antioxidant enzyme, belongs to metalloenzymes. It stimulates the conversion of superoxide radical to hydrogen peroxide [4]. The SOD level is considered a biomarker that reflects the antioxidant status in various studies [10–12]

Lipid peroxidation process denotes to the damage of polyunsaturated fatty acids that caused by oxidative stress and leads to irreversible damage of cell membrane

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[13–15] and changing membrane permeability leading to hyperexcitability [16].

Malondialdehyde is considered as an important byproduct of lipid peroxidation which is formed by oxidation of polyunsaturated lipids [17]. Malondialdehyde was vastly employed as a marker of oxidative stress among many studies [12, 18, 19].

This study aimed to assess SOD and MDA levels among epileptic patients and compare them with controls. In addition, studying the impact of seizure frequency, disease duration, and AEDs on these biomarkers.

Methods

Study design and patients

A case–control study that included a total of one hundred and twenty-four subjects; 62 epileptic patients beside 62 age and gender matched healthy individuals as controls. The epileptic group consisted of patients aged 18 to 45 years old. These patients were selected from the out-patient's epilepsy clinic, Neurology Department, Zagazig University from April to December 2020. Epilepsy was diagnosed according to the International League Against Epilepsy (ILAE) 2017 classification system [20, 21].

Inclusion criteria patients aged 18 to 45 years old, on regular antiepileptic drugs either monotherapy or polytherapy. *Exclusion criteria*: smoking, pregnancy, breastfeeding, psychiatric comorbidity, acute, or chronic medical illnesses, malignancies, and metabolic disorders. Patients who take medications other than AEDs were also excluded from the study.

The research protocol was approved by the Ethics Committee of our institution (ZU-IRB # 6007/9-3-2020). Written consent was taken out from all included subjects.

Clinical and laboratory assessment

All patients were subjected to thorough examination and history taking including disease duration, seizure frequency, seizure control (either controlled or uncontrolled according to the response to AED treatment), and the current antiepileptic medications. Patients who were seizure free during the last year prior to the study were considered controlled while the uncontrolled patients were considered when adequate trials of two tolerated, properly selected antiepileptic drugs (whether used separately or in combination) with proper doses failed to control patient's seizure [22]. Regarding the AEDs treatment, patients who were on single AED were categorized as monotherapy and those on more than one drug were considered polytherapy recipients.

Electroencephalography (EEG) using EB Neuro machine (Italy), according to 10-20 system of electrode placement and magnetic resonance imaging (MRI) of brain by 1.5 Tesla MR imager (Achieva, Philips

Medical System) were done at the time of recruitment to all patients.

Blood sample collection

Venous blood samples were obtained from participants by venipuncture from the antecubital vein using a disposal plastic syringe and collected without using an anticoagulant. After clotting, the blood was centrifuged at 4000 rpm for 15 min. Serum was separated from the blood and stored at -20°C until chemical analysis.

Measurement of serum MDA and SOD levels were done at Medical Biochemistry and Molecular Biology Department by calorimetric method according to Ohkawa et al. [23] for MDA (nmol/ml), and to Nishikimi et al. [24] for SOD (U/ml).

Principle of MDA The methodology is based on the reaction of MDA with thiobarbituric acid in acidic medium at temperature of 95°C for 30 min to form thiobarbituric acid reactive product. The absorbance of the resulting product can be measured spectrophotometrically at 534 nm [23].

Estimation of malondialdehyde

$$\text{Serum Malondialdehyde} = (\text{A Sample} \div \text{A Standard}) \times 10 \text{ nmol/ml.}$$

Principle of SOD This test depends on the capability of SOD to inhibit the phenazine methosulphate-mediated reduction of nitro blue tetrazolium dye. The change in the absorbance over 5 min was measured at 560 nm for control (Δ_{control}) and for sample (Δ_{sample}) at 25°C . 1.5 U/assay of the purified enzyme produced 80% inhibition [24].

Calculation of SOD

$$\text{Percent inhibition} = [(\Delta_{\text{control}} - \Delta_{\text{sample}}) \div \Delta_{\text{control}}] \times 100$$

$$\text{SOD Activity (U/ml)} = \% \text{ inhibition} \times 3.75$$

Statistical analysis

Data analysis was done using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Qualitative data were expressed as number and percentage, Quantitative data were expressed as mean and standard deviation. Chi-square, Student's *t* test, and Pearson

correlation coefficient were used when appropriate. For multiple group comparisons, we used analysis of variance (ANOVA) followed by Tukey’s Post Hoc test. *p* value was set at ≤ 0.05 for significant results.

Results

Sixty-two epileptic patients (36 males and 26 females) and 62 controls (35 males and 27 females) were recruited. The mean age (\pm SD) was 27.98 ± 6.44 for epileptic patients and 26.63 ± 6.06 years for controls. In the epileptic group, 21 patients with focal and 41 patients with generalized seizures. The mean age of disease onset was 17.85 ± 4.64 years, the mean disease duration was 13.11 ± 8.19 years. 41.9% of patients were well-controlled by AEDs while 58.1% were uncontrolled. Regarding the

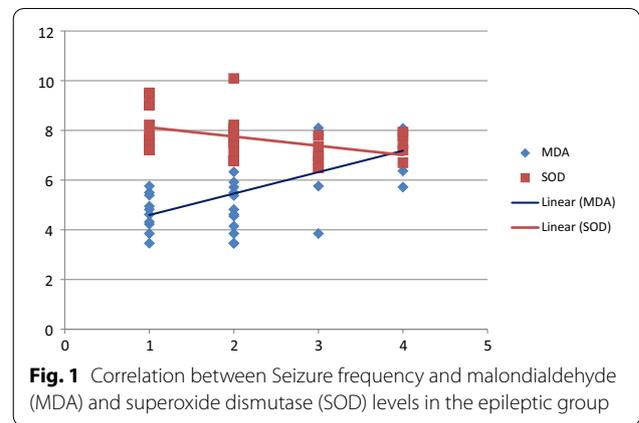


Fig. 1 Correlation between Seizure frequency and malondialdehyde (MDA) and superoxide dismutase (SOD) levels in the epileptic group

Table 1 Demographic, clinical and laboratory data of the studied subjects

	Epileptic group (n = 62)		Controls group (n = 62)		test	<i>p</i>
Age (years)						
Mean \pm SD	27.98 \pm 6.44		26.63 \pm 6.06		t = 1.207	0.230
Range	18.0–43.0		19.0–39.0			
Sex	No	%	No	%		
Male	36	58.1	35	56.5	$\chi^2 = 0.033$	0.856
Female	26	41.9	27	43.5		
Age of onset						
Mean \pm SD	17.85 \pm 4.64		–			
Disease duration (years)						
Mean \pm SD	13.11 \pm 8.19		–			
Seizure type	No	%				
Focal	21	33.9	–			
Generalized	41	66.1	–			
Seizure control	No	%				
Controlled	26	41.9	–			
Uncontrolled	36	58.1	–			
Seizure frequency of uncontrolled patients	No	%				
More than once /month	10	27.8	–			
Once/ 1–2 months	14	38.9	–			
Once/ 3–4 months	7	19.4	–			
Once/ 5–6 months	5	13.9	–			
Type of therapy	No	%				
Monotherapy	27	43.5	–			
Polytherapy	35	56.5	–			
MDA (nmol/ml)						
Mean \pm SD	5.83 \pm 1.46		4.80 \pm 0.62		5.075	< 0.001*
SOD (U/ml)						
Mean \pm SD	7.59 \pm 0.85		11.98 \pm 1.39		21.228	< 0.001*

t Student t test, χ^2 Chi square test, *p* *p* value for comparing between the studied groups, MDA malondialdehyde, SOD superoxide dismutase, * significant

AEDs, there were 27 (43.5%) patients on monotherapy and 35 patients (56.5%) on polytherapy (Table 1).

Malondialdehyde was significantly higher ($p < 0.001$) among the epileptic group (5.83 ± 1.46 nmol/ml) than controls (4.80 ± 0.62 nmol/ml). Superoxide dismutase (SOD) was significantly lower (7.59 ± 0.85 U/ml) among epileptics than controls (11.98 ± 1.39 U/ml) ($p < 0.001$) (Table 1).

There was a direct correlation between seizure frequency and MDA ($p < 0.001$), and an inverse correlation between seizure frequency and SOD ($p = 0.008$) (Fig. 1). Regarding the relation of disease duration with laboratory parameters, low SOD and high MDA concentrations were observed among patients with disease duration > 5 years than those ≤ 5 years. No significant difference in levels of MDA or SOD was observed between patients with focal and generalized seizures (Table 2).

Regarding AEDs, lower SOD and higher MDA were demonstrated in patients receiving polytherapy than

those on monotherapy and healthy controls (Table 3). Nonsignificant difference was detected between individual AEDs as regard MDA or SOD levels (Table 4).

Discussion

Oxidative stress attracts great interest in the pathogenesis of epilepsy [25]. It could aid in recognizing individuals at risk of developing epilepsy. Hence, it might facilitate the clinical trials concerned with antiepileptogenesis [26].

In the current study, the oxidant status was studied through assessment of MDA as a byproduct of lipid peroxidation, while the antioxidant status was assessed by measuring SOD as an endogenous antioxidant. There was a significant increase in mean values of MDA in epileptic group than controls. This is in consistence with many previous human [11, 12, 18, 19, 27–30] and experimental studies [25, 31]. A significant ($p < 0.001$) reduction in mean values of SOD was demonstrated among epileptic group than controls as observed in the previous studies

Table 2 Differences in laboratory findings as regard disease duration and seizure type

	MDA (nmol/ml)			SOD (U/ml)		
	Mean \pm SD	t	p	Mean \pm SD	t	p
≤ 5 years (n = 15)	5.16 \pm 1.38	2.085	0.041*	8.11 \pm 1.02	2.875	0.006*
> 5 years (n = 47)	6.04 \pm 1.44			7.43 \pm 0.72		
Focal (n = 21)	6.17 \pm 1.51	1.345	0.184	7.78 \pm 0.84	1.256	0.214
Generalized (n = 41)	5.65 \pm 1.43			7.50 \pm 0.85		

MDA malondialdehyde, SOD superoxide dismutase, t student t test, SD standard deviation, * significant

Table 3 SOD and MDA comparison between healthy controls, monotherapy and poly-therapy groups

	Monotherapy patients (n = 27)	Polytherapy patients (n = 35)	Healthy controls group (n = 62)	ANOVA (F value)	p
MDA (nmol/ml)					
Mean \pm SD	5.39 \pm 1.38 [¥]	6.16 \pm 1.46 ^{¥, §}	4.8 \pm 0.62	17.299	$< 0.001^*$
SOD (U/ml)					
Mean \pm SD	7.86 \pm 1.01 [¥]	7.39 \pm 0.64 ^{¥, §}	11.98 \pm 1.39	229.121	$< 0.001^*$

MDA malondialdehyde, SOD superoxide dismutase, SD standard deviation, * significant

[¥] Significantly (higher MDA and lower SOD) than healthy controls (Tukey Post Hoc Test)

[§] Significantly (higher MDA and lower SOD) than monotherapy group (Tukey Post Hoc Test)

Table 4 Comparison between individual AEDs as monotherapy regarding laboratory findings

	CBZ (N = 2)	VPA (N = 11)	LMG (N = 3)	LEV (N = 3)	OXC (N = 8)	F	p
MDA (nmol/ml)							
Mean \pm SD	3.85 \pm 1.63	6.62 \pm 1.32	6.81 \pm 0.69	5.77 \pm 1.34	6.02 \pm 1.14	2.437	0.077
SOD (U/ml)							
Mean \pm SD	7.72 \pm 0.92	7.92 \pm 0.88	6.87 \pm 0.42	7.36 \pm 0.26	7.18 \pm 0.73	1.756	0.174

CBZ carbamazepine, VPA valproate, LMG lamotrigine, LEV levetiracetam, OXC oxcarbazepine, F ANOVA test, SD standard deviation

[10–12, 29, 32] in which the SOD level among epileptic patients was significantly less than controls.

In contrary, other studies had demonstrated no significant alteration in SOD values between the epileptics and controls [30, 33–35]. Moreover, Ercegovic et al. [36] observed a significant elevation of SOD among patients with first seizure. They explained this rise in SOD level as an adaptive mechanism to face the increased free radical generation during seizure.

From the above data, we observed that epileptic patients had an imbalance in the oxidant–antioxidant status. It could be explained as recurrent epileptic seizures can cause oxidative stress and free radicals formation leading to macromolecular damage, neuroinflammation and neurotoxicity [37]. The seizure, as a brain insult, produces free radicals that disturb the mitochondrial function and energy metabolism and lead to enhancement of lipid peroxidation, gliosis and abnormal rearrangements of neural circuits that promote the formation of hyperexcitable networks [38, 39].

On studying the relation between biomarkers of oxidative stress and seizure profile, we found a direct correlation between seizure frequency and MDA. However, an indirect correlation was observed between SOD and seizure frequency. Similarly, Maes et al. [40] found that highly frequent seizures were associated with high levels of oxidative stress markers as MDA.

On stratifying our epileptic patients based on disease duration (>5 years and ≤ 5 years duration), there was significantly high values of MDA and lower values of SOD in patients with disease duration >5 years. In contrast, Turkdogan et al. [41] found no relation between antioxidant enzymes or MDA levels and disease duration.

Regarding seizure type of our patients, no significant difference in MDA or SOD values could be observed between patients with focal and generalized seizures. Similarly, Yis et al. [42] found no difference in oxidant and antioxidant biomarkers between patients with generalized and focal epilepsy. This denotes that epilepsy type does not disturb oxidant/antioxidant status in different ways.

In this study, we compared patients on single drug (monotherapy) with those on multiple drugs (polytherapy) to study the effect of antiepileptic drugs, if any, on MDA and SOD. we observed higher MDA and lower SOD levels in polytherapy than monotherapy patients and healthy controls. This finding suggests that currently used antiepileptic drugs did not improve the antioxidant status in those patients and an additional oxidative stress could be induced by AEDs.

Similarly, Iwuozu et al. [43] demonstrated that patients on AED polytherapy had significantly higher MDA and lower SOD levels than AED naïve patients

as well as patients on monotherapy. Also, Ethemoglu et al. [37] found higher oxidant and lower antioxidant biomarkers in polytherapy in comparison to monotherapy groups. They believed that the patients on monotherapy consisted of patients with controlled seizures, while patients receiving polytherapy had higher seizure frequency and being uncontrolled. While Menon et al. [18, 44] and Guler et al. [11] recorded no significant alterations in the biomarkers of oxidant–antioxidant status between patients receiving monotherapy and polytherapy.

The oxidative stress induced by AEDs was explained as many conventional AEDs are metabolized to active metabolites able to combine with vital molecules such as lipids and proteins and resulting in impairment of cellular function and structure rather than having a neuroprotective effect [45].

Accumulating evidence suggests that new generations of AEDs are superior on the conventional AEDs in terms of neuroprotection and antioxidant effects by scavenging-free radicals [3, 46]. To address this point, 27 epileptic patients on monotherapy were tested in the current study for MDA and SOD. We found no significant changes between individual AED groups as regard MDA and SOD concentrations. This could be attributed to small number of patients in each individual AED group. Therefore, the superiority of an individual AED on antioxidant status could not be inferred from the results of this study and future studies with large sample size recruiting patients receiving different AEDs including the newer and old AEDs might reveal this issue.

Conclusions

In this study, we observed that epileptic patients had an imbalance in the oxidant–antioxidant status as we found higher MDA and lower SOD levels in patients than healthy individuals. Types of epilepsy did not affect oxidative status and antioxidant enzyme activities. Poor seizure control impaired the oxidant–antioxidant regulatory system. AEDs did not improve the antioxidant status in epileptic patients and an additional oxidative stress could be induced by AEDs. Future research should focus on novel drug treatments that can modify the development and progression of epilepsy through having antioxidant effect.

Abbreviations

AEDs: Antiepileptic drugs; SOD: Superoxide dismutase; MDA: Malondialdehyde; ILAE: International league against epilepsy; EEG: Electroencephalography; MRI: Magnetic resonance imaging; CBZ: Carbamazepine; VPA: Valproate; LMG: Lamotrigine; LEV: Levitracetam; OXC: Oxcarbazepine.

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Author contributions

All authors were involved in crafting the study topic and design. All authors read and approved the final manuscript. NS analyzed and interpreted the data, wrote, and prepared the final manuscript. AEK supervised clinical/laboratory work, interpreted results, and participated in manuscript drafting. ES recruited the patients, carried out clinical/laboratory investigation, collected data and submitted manuscript. MHE supervised clinical/laboratory work, and participated in manuscript drafting. All authors read and approved the final manuscript.

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Availability of data and materials

The data results generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the ethics committee of the faculty of Medicine, Zagazig University. The reference number is (ZU-IRB # 6007/9-3-2020). The purpose of the study was explained, and an informed written consent was taken before taking any data or doing any investigations. The participants were informed that their participation was voluntary and that they could withdraw from the study at any time without consequences.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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