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Altered Levels of Malondialdehyde and Vitamin E in Major Depressive Disorder and Generalized Anxiety Disorder

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ABSTRACT

Altered levels of malondialdehyde and vitamin E in major depressive disorder and generalized anxiety disorder

Introduction: Reactive oxygen species (ROS) may play a role in some neuropsychiatric disorders. There is some evidence that the activation of immune-inflammatory processes, an increase in monoamines catabolism and abnormalities in lipid compounds may cause overproduction of ROS and lipid peroxidation. These phenomena may be related to pathophysiology of major depressive disorder and generalized anxiety disorder. Malondialdehyde (MDA) is the end product of lipid peroxidation. Vitamin E is thought to play an important role as an antioxidant against lipid peroxidation.

This study aims to investigate the role of oxygen radicals in the etiology of major depressive disorder and generalized anxiety disorder.

Method: Plasma MDA and vitamin E levels of patients with major depressive disorder (n=42) and generalized anxiety disorder (n=37) were compared with healthy controls (n=38). To assess depressive symptoms and anxiety symptoms, Hamilton Depression Scale and Hamilton Anxiety Scale were applied.

Results: Patients with major depressive disorder and generalized anxiety disorder had higher MDA and lower vitamin E levels than those of healthy controls. Differences between the patient and the control groups according to these two parameters were found statistically significant.

Conclusion: Our results support the hypothesis that oxidative stress may affect depressive and anxiety symptoms. As a result, free radical damage and deficiency of antioxidant defence systems may have an important role in major depressive disorder and generalized anxiety disorder.

Key words: Major depressive disorder, generalized anxiety disorder, oxidative stress, antioxidant defence systems

ÖZET

Majör depresif bozukluk ve yaygın anksiyete bozukluğunda malondialdehid ve E vitamini düzeyleri

Amaç: Reaktif oksijen türleri (ROT) bazı nöropsikiyatrik rahatsızlıklarda rol oynayabilirler. İmmün-inflamatuvar aktivasyon, monoamin katabolizmasında artış ve lipid bileşenlerinde ortaya çıkan anormalliklerin aşırı ROT üretimine ve lipid peroksidasyonuna neden olduğuna dair kanıtlar bulunmaktadır. Bu fenomenler, majör depresyon ve yaygın anksiyete bozukluğunun patofizyolojisi ile ilişkili olabilir. Malondialdehid (MDA) lipid peroksidasyonunun son ürünüdür. E vitamininin lipid peroksidasyonuna karşı önemli bir antioksidan molekül olduğu ileri sürülmektedir.

Bu çalışmanın amacı, oksijen radikallerinin majör depresif bozukluk ve yaygın anksiyete bozukluğunun etiyolojisindeki rolünü belirlemektir.

Yöntem: Majör depresif bozukluk tanısı alan 42 hasta ve yaygın anksiyete bozukluğu tanısı (YAB) alan 37 hasta ile sağlıklı kontrol grubunu oluşturan 38 kişinin plazma MDA ve E vitamini düzeyleri ölçüldü. Tüm gruplara Hamilton Depresyon Ölçeği (HDÖ) ve Hamilton Anksiyete Ölçeği (HAÖ) uygulandı.

Bulgular: Majör depresif bozukluk ve yaygın anksiyete bozukluğu tanısı alan kişilerin, sağlıklı kontrol grubuna kıyasla daha yüksek MDA ve daha düşük E vitamini düzeylerine sahip oldukları saptandı. Hasta ve kontrol grupları arasındaki fark istatistiksel olarak anlamlı bulundu.

Sonuç: Bulgularımız oksidatif stresin depresyon ve anksiyete semptomlarında etkili olabileceğini desteklemektedir. Sonuç olarak, serbest radikal hasarı ve antioksidan savunma sistemindeki yetersizlik majör depresif bozukluk ve yaygın anksiyete bozukluğunun etiyolojisinde önemli rol alabilir.

Anahtar kelimeler: Majör depresif bozukluk, yaygın anksiyete bozukluğu, oksidatif stres, antioksidan savunma sistemleri

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INTRODUCTION

There is equilibrium between oxidant and antioxidant systems in living organisms. Free radicals and disorders of antioxidant defense systems are among topics mentioned in the pathophysiology of some neuropsychiatric disorders (1).

The most important mechanism underlying the tissue damage caused by free oxygen radicals is peroxidation of lipids within the cellular membrane (2). Final product of lipid peroxidation is malondialdehyde (MDA). Assessment of serum MDA levels can be used as an indicator of tissue damage mediated by free oxygen radicals in vivo (2,3).

Brain tissue is particularly vulnerable to damage by free radicals due to reasons such as higher consumption of oxygen, high amount of phospholipids which can easily be peroxidized and non-regeneration of neurons. Basal ganglia which has an important role in pathophysiology of mood disorders are exposed to free radical damage (4). This is due to high amount of catecholamines in these areas and catecholamine metabolism is one of the main sources of free radical production (1,5,6).

Some recent studies indicate that depression impairs the equilibrium between oxidant and antioxidant systems (7-9). It is not clear whether increase of reactive oxygen species (ROS) is the cause or consequence of depression. Production of proinflammatory cytokines are increased and inflammatory response system is activated in depressive disorders (10,11). This process may lead to an increase in lipid peroxidation. In conclusion, lipid peroxidation may increase in conditions with psychological stress such as depression.

Lower vitamin E levels can be detected during activation of inflammatory response system (12). Vitamin E stops peroxidation chain reaction of polyunsaturated fatty acids in cellular membrane. Alterations in the structure of phospholipids and cholesterol which are basic structural components of cellular membrane in brain may change flexibility of membrane and consequent alterations in various neurotransmitter systems which are thought to have roles in pathophysiology of depression (13,14).

There are few studies investigating the relationship between generalized anxiety disorder (GAD) and oxidative stress in the literature. In the study of Mathew and colleagues which compared patients with GAD and "chronic fatigue disorder" and healthy control group, no significant difference was found for ventricular lactate concentrations. This study did not support the increased oxidative stress hypothesis in GAD. This study had limited number of cases and did not assess antioxidant status (15).

There are studies indicating that oxidative stress is increased in anxiety disorders such as obsessive compulsive disorder, panic disorder and social phobia. Serum MDA levels in patient groups of these studies were found to be higher than healthy controls (16-18).

Epidemiological studies showed that depressive disorders and anxiety disorders emerge highly synchronously (19,20). These disorders with interrelated symptoms were proposed to share a similar underlying genetic basis (21). In this study we aimed to determine the role of oxygen radicals in major depressive disorder (MDD) and GAD which have similar characteristics of prevalent comorbidity, clinical features and treatment and were proposed to share a common etiopathogenesis.

METHODS

Selection of Study Group and Evaluation

Forty-two patients (37 women, 5 men) diagnosed with major depressive disorder and 37 patients (32 women, 5 men) with generalized anxiety disorder according to DSM-IV diagnostic criteria who were admitted to psychiatry outpatient clinic of Mersin University Medical School were recruited to the study. None of the patients were taking psychotropic medications. Thirty-eight healthy people (32 women, 6 men) without any systemic disorder were recruited as control group.

Cases that had an infectious or inflammatory disease or allergic reaction in the previous two weeks, cases with any medical disorder including endocrine

and metabolic diseases, cases under antioxidant treatment, having history of any drug or substance abuse and cases with severe malnutrition were not included in the study. Patients with first and second axis diagnoses were excluded and both Hamilton Depression Scale (HDS) and Hamilton Anxiety Scale (HAS) were administered to both groups (22,23). Patients with comorbid MDD and GAD diagnoses were not included in the study. Severity of depression for patients diagnosed as major depressive disorder was determined as follows: mild=14-27, moderate=28-41 and severe=42-53.

Biochemical Analyses

Ten ml. of venous blood samples were taken into standard biochemistry tubes from both patient and control groups. These samples were centrifuged immediately in laboratory environment at 3500 rpm for 5 minutes and their serums were separated.

Vitamin E levels were assessed by Isocratic HPLC (high pressure liquid chromatography) device which uses UV detector (HP 1100) and Chromosystems Vitamin E kit (Chromosystems, GmbH Germany). All solutions used to assess vitamin E were HPLC grade and HPLC conditions to assess vitamin E were as follows: Injection volume: 50 µl, speed of flow: 1.5 ml/min, room temperature: 25°C, wave length: 295 nm (24).

Assessment of MDA levels was based on spectrophotometric measurement of 553 nm pink color produced by reaction of MDA with thiobutiric acid (25).

Statistical Analyses

Data were evaluated by chi-square and Kolmogorov Smirnov tests, one way analysis of variance (ANOVA) and Kruskal-Wallis test. Numeric variables were presented as mean ± standard deviation. Statistical significance level was taken as $p<0.05$.

RESULTS

There was no statistically significant difference between age and gender distributions of MDD, GAD and control groups (Table 1).

Mean MDA levels were found significantly higher in patients with MDD (3.6±3.5 µmol/l) and GAD (4.9±5.2 µmol/l) compared to healthy controls (1.3±0.4 µmol/l) ($p<0.001$) (Table 2).

Mean vitamin E levels were found significantly lower in MDD and GAD groups (23.7±9.71 mg/dl and 24.7±9.7 mg/dl, consecutively) than control group (41±5.5 mg/dl) ($p<0.001$) (Table 2).

When correlation between age and vitamin E and MDA levels for all three groups were tested, same way

Table 1: Comparison of age and gender characteristics between groups

	MDD (n: 42)	GAD (n: 37)	Control (n: 38)	F	p
Age, Mean±SD	44.1±12.3	46.4±13.6	44.0±9.3	0.495	>0.05
				χ^2	p
Men, n (%)	5 (11.2%)	5 (13.5%)	6 (18.8%)	0.256	>0.05
Women, n (%)	37 (88.8%)	32 (86.5%)	32 (81.2%)		

MDD: Major Depressive Disorder, GAD: Generalized Anxiety Disorder, F: One-way analysis of variance, χ^2: Chi-square test, SD: Standard deviation

Table 2: Comparison of MDA and vitamin E levels between groups

	MDD (n: 42)	GAD (n: 37)	Control (n: 38)	F	p
MDA (µmol/l)	3.6±3.5	4.9±5.2	1.3±0.4	9.631	<0.001
Vit. E (mg/dl)	23.7±9.71	24.7±9.7	41±5.5	49.624	<0.001

MDA: Malonyldialdehyde, MDD: Major Depressive Disorder, GAD: Generalized Anxiety Disorder, F: One-way analysis of variance

Table 3: Correlation of scale scores and vitamin E and MDA levels for both patients groups

		Vitamin E	MDA
MDD (n=42)	HDS	r=0.117	r=0.01
		p=0.459	p=0.949
	HAS	r=0.244	r=0.126
		p=0.119	p=0.426
GAD (n=37)	HDS	r=-0.261	r=-0.019
		p=0.119	p=0.912
	HAS	r=-0.133	r=-0.203
		p=0.43	p=0.228

MDA: Malonyldialdehyde, MDD: Major Depressive Disorder, GAD: Generalized Anxiety Disorder, HDS: Hamilton Depression Scale, HAS: Hamilton Anxiety Scale

correlation was found only between age and MDA parameter ($p<0.05$, r:0.543). When presence of correlation between vitamin E and MDA parameters regardless of group difference was examined, reverse correlation was found between these two parameters ($p<0.05$, r:-0.297). No correlation was found between HDS and HAS scores and MDA and vitamin E levels at both patient groups (Table 3).

DISCUSSION

MDA levels were found higher in MDD and GAD groups than control group.

There are several studies which found elevated serum MDA levels in MDD (7,19,27,28). Özcan and colleagues (8) found elevated MDA levels at both pre- and post-treatment periods in their studies which compared patients with mood disorders and control group.

Galecki and colleagues (28) found that total plasma antioxidant levels were decreased in depressive patients and did not improve after three months of fluoxetine treatment. In a more recent study they found that when fluoxetine and acetyl salicylic acid were co-administered for three months, reduction of MDA levels and free radicals and increase in non-enzymatic antioxidative defense system (9). Sarandol and colleagues (7) found that MDA levels are increased in patients with depression compared to controls. Our study supports the literature in this context.

MDA oxidizes polyunsaturated fatty acids found in the brain in vast amounts. It is the end-product of lipid peroxidation and an indicator of free radical damage. Excess production of ROS may cause destruction of phospholipids and may decrease cellular membrane flexibility. These changes may affect the density and function of serotonin, dopamine and catecholamine receptors such as noradrenaline which have important roles in pathophysiology of depression and GAD at different levels (29, 30). MDA may exert an inhibitor action on serotonin binding sites of receptors directly and thus may have a role on etiology of these psychiatric disorders (31, 32).

We found increased plasma MDA levels and decreased vitamin E levels in patients with GAD. No study was found investigating MDA and vitamin E levels in generalized anxiety disorder in the literature. However, in an experimental study, impairment of plasma antioxidant system was shown in rats exposed to stress (33).

In patients with social phobia which is an anxiety disorder, plasma MDA levels were found elevated and returned to normal with citalopram treatment (34). Moreover, in studies done with patients with OCD and panic disorder which are among anxiety disorders, elevated oxidative stress was detected (16,17). Plasma MDA levels were found higher than healthy control group in both studies. These studies support the effect of oxidative metabolism on regulation of anxiety.

Our study provides evidence about decrease in plasma antioxidant system in GAD. However, further studies having higher number of cases are needed to clarify this issue.

Several studies were done in MDD patients investigating plasma vitamin E levels. Shibata et al. (35) found low vitamin E levels in male depressive patients. Teiemer and colleagues (36) reported normal vitamin E levels in MDD patients but Sarandol and colleagues (7) found higher serum vitamin E levels in this patient group.

Results of studies about this issue seem to be contradictory in the literature. In our study, we found low vitamin E levels at both MDD and GAD group.

Reasons of low vitamin E levels are unknown. Diet is suggested not to have a clear impact on vitamin E

levels (37).

Vitamin E is a member of plasma antioxidant system. Vitamin E which is a fat-soluble antioxidant stops polyunsaturated fatty acid peroxidation chain reaction. Low vitamin E levels occur during activation of inflammatory response system (38). It can be proposed that low vitamin E levels lead to increase in lipid peroxidation and consequently weaken antioxidant defense systems in these patients and these patients are sensitive to lipid peroxidation.

Our findings suggest that oxidative stress is increased in both major depressive disorder and generalized anxiety disorder. It is already known that oxidative stress may affect development of depression by various means. Structural and proportional deficits of polyunsaturated fatty acids, excessive cytokine production, decrease in amount of catecholamines, impairment of densities and functions of serotonergic and catecholaminergic receptors and decrease in catecholamine binding sites of receptor may all be suggested to have roles in development of depression (14,39).

In conclusion, impairment of balance between ROS-producing systems and antioxidant defense mechanisms seems to play a role in pathophysiology of psychiatric disorders such as MDD and GAD.

Not having studied other biochemical parameters and antioxidant enzymes indicating oxidative stress and not having evaluated total antioxidant status of patients were limitations of our study.

In order to better understand the pathophysiology of these two disorders which are among the most prevalent psychiatric disorders in adults, further studies with wider samples are needed. We also suggest that examining the post-treatment changes will enrich our knowledge about this topic.

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