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Antioxidant Enzyme Activities and Malondialdehyde Levels in Patients with Obsessive-Compulsive Disorder

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Key Words

Obsessive-compulsive disorder · Antioxidant enzyme activities · Malondialdehyde

Abstract

To examine the importance of free radicals in the pathogenesis of obsessive-compulsive disorder (OCD), we aimed to evaluate whether malondialdehyde (MDA), a product of lipid peroxidation, and antioxidant enzyme [superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and catalase (CAT)] activity levels were associated with OCD. The patients were divided into two subgroups according to whether DSM-IV major depressive disorder (MDD) was accompanied (OCD + MDD) or not (OCD – MDD). The MDA and antioxidant enzyme levels both in patients and controls were determined. SOD activity levels were significantly higher in the OCD + MDD group compared with the control and the OCD – MDD group. Although the OCD – MDD group had slightly higher SOD activity levels as compared with the controls, the difference was not statistically significant. GSH-Px activity levels were statistically significantly higher in both groups compared with controls. Likewise, there was a significant difference in GSH-Px activity levels between the OCD + MDD and OCD – MDD group. CAT activity levels were slightly higher in the OCD + MDD group compared with the OCD – MDD and control group. MDA levels in both groups were significantly higher than in controls. In addition, the difference in MDA levels between both groups was statistically significant. In conclusion, our results suggest that OCD is associated with free radicals and that it may be a heterogeneous subtype including some biological indications of anxiety and affective disorders. More comprehensive and detailed studies are needed to decipher the exact role of free radicals in OCD.

Introduction

There is a large amount of convincing data demonstrating that reactive free radical species are involved in the initiation and development of many different forms of human pathologies. Free radicals are produced in many different ways, such as activation of phagocytes and the general immune system, lipid peroxidation, electron transport system in mitochondria, ischaemia and trauma [1]. Free radicals have a relatively short half-life and thus the determination of their levels is difficult. Therefore, they can be evaluated indirectly by measurement of some

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antioxidant enzyme levels such as superoxide dismutase (SOD), catalase (CAT) or glutathione peroxidase (GSH-Px), by products of lipid peroxidation such as malondialdehyde (MDA) or by some transition metal levels such as copper, zinc and iron [2].

There are some recent studies focused on the role(s) of free radicals in the pathogenesis of neuropsychiatric disorders and numerous studies indicating that free radical-mediated neuronal dysfunction have roles in the pathophysiology of schizophrenia [3]. Increased SOD activity levels in schizophrenia were reported [4]. Yao et al. [5] showed that in schizophrenia during the drug-free period SOD activity, but not GSH-Px and CAT activities, was significantly higher compared with normal controls. In another study [6], it was reported that the levels of plasma uric acid, a potent antioxidant, in patients with schizophrenia were significantly lower than those in healthy controls. It has also been reported that the most important source of free radicals is glial cells, and free radicals produced by these cells are related to neuropsychiatric disorders such as Sydenham's chorea and Parkinson's disease [4]. Both diseases are associated with basal ganglia with respect to aetiology. Likewise, OCD is suggested to be associated with basal ganglia because of the localization of neuropsychiatric deficits in this disease. The comorbidity of OCD and these neurologic disorders raises the chance of basal ganglia involvement in OCD [7–10]. In addition, it has recently been suggested that patients with major depression, especially melancholic ones, have elevated antioxidant enzymes levels and lipid peroxidation [11].

OCD is characterized by recurrent obsessions and/or compulsions which result in marked distress and are classified as an anxiety disorder in DSM-IV [12]. It frequently involves depressive symptoms and comorbid depressive disorder [13, 14]. On the other hand, obsessions and compulsions may accompany depressive disorder [15]. Moreover, according to most recent hypotheses, OCD may be the consequence of a developmental pathology affecting sertonergic and/or dopaminergic neuronal system which have also been suggested for the aetiopathogenesis of depression [16]. Recently, these relationships have resulted in growing researches about the biological association of OCD and affective disorders. To our knowledge, there has been no study regarding the role of free radicals in the pathogenesis of OCD. Therefore, we aimed to evaluate: (1) whether the oxidative damage (via determining of MDA), and (2) antioxidant enzyme (SOD, GSH-Px and CAT) activity levels are associated with OCD.

Patients and Methods

Patients

The sample consisted of 34 patients (22 females, 12 males) who were first admitted to the Department of Psychiatry of the Firat University Medical Faculty and were diagnosed as having OCD according to DSM-IV. A DSM-IV diagnosis of OCD was established on the basis of independent clinical interviews by one senior psychiatrist. The patients had either no history of treatment or had been drug free at least for 1 month. The patients were divided into two subgroups according to whether DSM-IV major depressive disorder (MDD) was accompanied (OCD + MDD) or not (OCD – MDD). Thus, there were 11 patients (32.4%) in the OCD + MDD group and 23 patients (67.6%) in the OCD – MDD group.

Controls

The controls were composed of healthy subjects (n = 32) who applied to the Department of Psychiatry, College of Medicine at Firat University for driving license examination and were evaluated to be normal. In addition, their first-degree relatives had not had a history of major mood disorder, dementia, mental retardation and psychosis. The controls were matched with the patients in regard to sex and age.

All subjects gave their written informed consent which had been acceded by the local ethics committee in accordance with the Declaration of Helsinki. Physical and neurological examinations were performed in each of the patients and controls. Liver and kidney function tests were evaluated. Subjects with normal results and without any exclusion criteria were admitted to the study. Exclusion criteria were as follows: alcohol and substance abuse or dependence, tardive dyskinesia related to neuroleptics, presence of severe organic condition, users of any antioxidant agent (i.e. vitamins E and C), presence of epilepsy and severe neurologic disorder, presence of infectious disease and excessive obesity.

Blood Sampling

Venous blood samples from the left forearm vein were collected into 5-ml vacutainer tubes containing potassium EDTA between 7 and 8 a.m. after overnight fasting. Some haematological parameters were measured by using an auto-analyser (Coulter Max M, Coulter Electronics Ltd., Luton, UK).

The blood samples were centrifuged at 4,000 rpm for 10 min at 4°C to remove plasma. The buffy coat on the erythrocyte sediment was separated carefully after plasma was removed and was used in the assay of MDA levels. The erythrocyte sediment was washed three times with 10-fold isotonic NaCl solution to remove plasma remnants. After each procedure, the erythrocyte-saline mixture was centrifuged at 4,000 rpm for 10 min at 4°C. Aliquots of the samples were transferred into polyethylene tubes. Erythrocyte sediments were treated with ice-cold deionized water to obtain haemolysates.

Enzymes, Chemicals and Instruments

Xanthine oxidase, xanthine, nitroblue tetrazolium (NBT), thiobarbituric acid (TBA) and 1,1,3,3-tetramethoxypropane were purchased from Sigma Chemical Co. (St. Louis, Mo., USA). A Schimadzu UV-1201 spectrophotometer (Schimadzu Co., Japan) was used to measure GSH-px, SOD and CAT activity and MDA levels.

Determination of SOD Activity

Haemolysates of erythrocytes were used for measurement of total (Cu-Zn and Mn) SOD (ED 1.15.1.1) activity levels by the method of Sun et al. [17]. This method is based on the reduction of superoxide, which is produced by the xanthine oxidase enzyme system, with NBT. A unit of SOD was determined as the amount that decreases NBT reduction by 50%. Results were expressed as U g^{-1} Hb.

Determination of GSH-Px Activity

GSH-Px (EC 1.6.4.2) activity levels in haemolysates of erythrocytes were measured using the method of Paglia and Valentine [18] in which GSH-Px activity was coupled with the oxidation of NADPH by glutathione reductase. The oxidation of NADPH was followed spectrophotometrically at 340 nm at 37°C. The reaction mixture consisted of 50 m*M* potassium phosphate buffer (pH: 7), 1 m*M* EDTA, 1 m*M* NaN_3, 0.2 m*M* NADPH, 1 m*M* glutathione, and 1 U/ml of glutathione reductase. The absorbance at 340 nm was recorded for 5 min. The activity was the slope of the lines as micromoles of NADPH oxidized per minute. Results were expressed as U g^{-1} Hb.

Determination of CAT Activity

CAT (EC 1.11.1.6) activity was determined by the method of Aebi [19]. The principle of the assay is based on the determination of the rate constant k (dimension: s^{-1}) of the hydrogen peroxide decomposition. By measuring the absorbance changes per minute, the rate constant of the enzyme was determined. Activities were expressed as k g^{-1} Hb.

Determination of Plasma MDA Levels

Levels of plasma MD were measured by the TBA method which was modified from the methods of Satoh [20] and Yagi [21]. Peroxidation was measured as the production of MDA which, in combination with TBA, forms a pink chromogen compound whose absorbance at 532 nm was measured. MDA results were expressed as $nmol^{-1}$ ml.

Instruments

Sociodemographic Information Form. All subjects were evaluated by a semi-structured questionnaire form which was arranged in accordance with clinical experience and available information sources and included gender, age, marital status, educational condition, socioeconomic status and duration of illness.

Hamilton Depression Rating Scale. Hamilton Depression Rating Scale (HDRS) [22] is used to rate the severity of depression. According to HDRS, a score over 25 is accepted as significantly severe depression, whereas 18–24 means severe, 7–17 moderate and less than 7 non-depression.

Yale-Brown Obsession Compulsion Scale. Yale-Brown Obsession Compulsion Scale (Y-BOCS) [23] is a scale that assesses the severity of OCD without focusing on the contents of obsession and compulsion. It has 10 items. Each one is assessed by a clinician giving 0–4 points.

Statistical Analysis

The obtained data were evaluated by SPSS Windows program 9.05 (SPSS, 1998). The comparisons were performed by ANOVA with Tukey HSD (for two-group and all-group comparisons). For correlation evaluations, the Pearson correlation (two-tailed) was used. The comparison of sociodemographic characteristics was performed by the Student t and χ^2 tests (Fisher's exact test). Two-tailed forms were used. The statistical significance was accepted as $p < 0.05$.

Table 1. Demographic and clinical variables of the patients and controls

Total patients	34
Sex[1]	males 12 (35.3%)
	females 22 (64.7%)
Age[2], years	25.72 ± 7.04 (range 18–48)
Duration of illness, years	5.35 ± 3.12
Subgroups	
OCD + MDD	11 (32.4%)
OCD – MDD	23 (67.6%)
Scale scores	
HDRS score	10.24 ± 8.94
Y-BOCS score	25.88 ± 7.28
According to HDRS	
Moderate depression	4 (11.8%)
Severe depression	7 (20.6%)
According to Y-BOCS	
Mild OCD	4 (11.8%)
Moderate OCD	9 (26.5%)
Severe OCD	18 (52.9%)
Significant severe OCD	3 (8.8%)
Control group	32
Sex[1]	males 13 (40.6%)
	females 19 (59.4%)
Age[2], years	29.13 ± 9.19 (range 19–51)

[1] p = 1 for Fisher's exact test.
[2] t = 1.365, p = 0.176 for the Student t test.

Results

Sociodemographic and Clinical Characteristics

A total of 34 patients (22 females and 12 males) were enrolled in this study. The control group (n = 32) had 19 (59.4%) females and 13 (40.6%) males (p = 1 for Fisher's exact test). The characteristics of the patients and controls are summarized in table 1.

Haematological Parameters

There were no statistically significant differences between haematological parameters of the patient groups and controls ($p > 0.05$).

Results of MDA and Antioxidant Enzyme Levels

SOD activity levels in the OCD + MDD, the OCD – MDD and the control group were 1,299.32 ± 254.12 U g^{-1} Hb, 1,098.34 ± 120.86 U g^{-1} Hb and 1,038.73 ±

Table 2. The levels of MDA and antioxidant enzyme in all groups

Groups	SOD U g^{-1} Hb	GSH-Px U g^{-1} Hb	CAT k g^{-1} Hb	MDA $nmol^{-1}$ ml
(1) OCD – MDD (n = 27)	1,098.34 ± 120.86	29.95 ± 4.29	274.17 ± 39.20	4.15 ± 0.73
(2) OCD – MDD (n = 15)	1,299.32 ± 254.12	33.84 ± 4.86	287.19 ± 60.45	4.78 ± 0.67
(3) Control (n = 32)	1,038.73 ± 119.46	25.97 ± 3.23	270.53 ± 42.68	2.50 ± 0.41
Statistics				
1 vs. 2 vs. 3[a]	F = 12.28, p < 0.001	F = 15.15, p < 0.001	F = 0.28, p = 0.73	F = 92.76, p < 0.001
1 vs. 2[a]	p < 0.01	p < 0.05	n.s.	p < 0.05
1 vs. 3[a]	n.s.	p < 0.05	n.s.	p < 0.001
2 vs. 3[a]	p < 0.001	p < 0.001	n.s.	p < 0.001

[a] Performed by ANOVA with Tukey HSD.

119.46 U g^{-1} Hb, respectively. SOD activity levels were significantly higher in the OCD + MDD group compared with the control ($p < 0.001$) and the OCD – MDD group ($p < 0.01$). Although the OCD – MDD group had slightly higher SOD activity levels compared with the control group, the difference was not statistically significant ($p > 0.05$). In the OCD + MDD group, GSH-Px activity levels were 33.84 ± 4.86 U g^{-1} Hb compared with 29.95 ± 4.29 U g^{-1} Hb and 25.97 ± 3.23 U g^{-1} Hb in the OCD – MDD group and controls, respectively. GSH-Px activity levels were statistically significantly higher in both the OCD + MDD and the OCD – MDD group compared with the controls ($p < 0.001$ and $p < 0.05$, respectively). Likewise, there was a significant difference in GSH-Px activity levels between the OCD + MDD and the OCD – MDD group ($p < 0.05$). CAT activity levels in the OCD + MDD, the OCD – MDD and the control group were 287.19 ± 60.45 k g^{-1} Hb, 274.17 ± 39.20 k g^{-1} Hb and 270.53 ± 42.68 k g^{-1} Hb, respectively. CAT activity levels were slightly higher in the OCD + MDD group compared with the OCD – MDD and the control group. However, there were no statistically significant differences between the groups ($p > 0.05$). To evaluate the levels of lipid peroxidation, initially MDA levels were determined in controls and all patients. MDA levels in the OCD + MDD and OCD – MDD group were 4.78 ± 0.67 $nmol^{-1}$ ml and 4.15 ± 0.73 $nmol^{-1}$ ml, respectively, whereas controls had lower MDA levels (2.50 ± 0.41 $nmol^{-1}$ ml). MDA levels of the OCD + MDD and OCD – MDD group were significantly higher than of controls ($p < 0.001$). In addition, the difference in MDA levels between the OCD + MDD and OCD – MDD group was statistically significant ($p < 0.05$) (table 2).

No statistically significant correlation between enzyme activities and MDA, and HDRS, Y-BOCS, age and duration of illness was found in the OCD – MDD group. In the OCD + MDD group, a significant positive correlation with MDA, SOD, GSH-Px and HDRS was observed ($p < 0.01$, $p < 0.01$, $p < 0.01$, respectively). Additionally, there was a positive correlation between MDA and SOD ($p < 0.01$). In the OCD + MDD group, there were no correlations both between CAT and HDRS, and antioxidant enzyme levels and MDA, Y-BOCS, age and duration of illness (table 3).

Discussion

As far as we know, this is the first study regarding free radicals in OCD. Therefore, we would like to emphasize some results of the present study so as to inspire new research in this field. The major findings of our study are as follows: (1) both pure OCD and OCD with comorbid MDD were associated with elevated antioxidant enzyme and MDA levels; however, the association was significantly obvious in patients with OCD and comorbid MDD; (2) there was a link between antioxidant enzyme levels and MDA and the severity of MDD, but no association between antioxidant enzyme levels and MDA and the severity of OCD.

The brain is especially vulnerable to free radical damage because it is a highly oxygenated organ that needs one fifth of the body's oxygen use [24]. In addition, the brain contains large amounts of iron and polyunsaturated fatty acids, and it is relatively poor with respect to antioxidants such as CAT [25, 26]. Catecholamines including dopa-

Table 3. Correlation analyses between parameters studied in the patients and controls

	OCD – MDD				OCD + MDD				Control			
	M	S	C	G	M	S	C	G	M	S	C	G
S	n.c.	–	n.c.	n.c	0.60*	–	n.c.	n.c.	n.c.	–	n.c.	n.c.
C	n.c.	n.c.	–	n.c.	n.c.	n.c.	–	n.c.	n.c.	n.c.	–	n.c.
G	n.c.	n.c.	n.c.	–	n.c.	n.c.	n.c.	–	n.c.	n.c.	n.c.	–
Age	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.
HDRS	n.c.	n.c.	n.c.	n.c.	0.65**	0.78**	n.c.	0.70**	–	–	–	–
Y-BOCS	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.	–	–	–	–
Duration of illness	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.	–	–	–	–

M = MDA; S = SOD; C = CAT; G = GSH-Px; n.c. = no correlation.
* $p < 0.05$; ** $p < 0.01$.

mine and norepinephrine are probably associated with the production of free radicals, and conditions causing increased catecholamine metabolism may increase the radical burden [27, 28].

In previous studies, controversial results were observed in patients with psychiatric disorder. Abdalla et al. [29] reported that schizophrenic patients had higher erythrocyte SOD activity levels than healthy controls. In two studies by Cohen et al. [30, 31], schizophrenic patients were compared with healthy controls with respect to SOD activity and toxic oxygen metabolites and there was not found any significant difference. GSH-Px activity levels were reported to be decreased in another study [29]. GSH-Px provides an effective protection mechanism against cytosolic injury because it eliminates H_2O_2 and lipid peroxides. Hence, it is regarded to be critical for maintaining low levels of cellular H_2O_2 and lipid peroxides. GSH-Px levels are high in brain areas prone to oxidative injury [32]. In a study reported by Buckman et al. [33], low peripheral GSH-Px activity was found to be associated with both cortical sulcal prominence on CT and prominent negative symptoms. Herken et al. [34], who investigated the importance of free radicals in schizophrenia subtypes, reported that oxidative stress might have a pathophysiological role in all the subtypes of schizophrenia. Altuntas et al. [35] demonstrated that antioxidative defence mechanisms might be impaired in schizophrenic patients. In our previous study [36], significant differences between a lipid peroxidation product (MDA) and antioxidant enzymes (SOD and GSH-Px) activity levels in schizophrenia and bipolar disorder patients compared with controls led us to believe that these differences are related with the heterogeneities in the aetiology of these disorders. Recently, Bilici et al. [11] have suggested that the patients with major depression, especially melancholic ones, are associated with elevated antioxidant enzyme levels and lipid peroxidation. Controlled studies demonstrate increasing monoamine oxidase activity in major depression [37]. The fact that MDD responds to monoamine oxidase inhibitors may be explained by this condition. It has been suggested that there may be a relation between excessive production of free radicals and increased monoamine oxidation [1].

The comorbidity of OCD and depressive disorder is a finding that is frequently observed. While the patients with OCD have an approximately 80% rate of secondary depression, 30% of the patients with depressive disorder have obsessive-compulsive symptoms [38]. Likewise, in this study, 15 (38.6%) of the patients (moderate in 6 patients, severe in 9 patients) had depression. Under these circumstances, an important question for us was whether antioxidant enzyme levels and MDA were associated with both pure OCD and the comorbidity of OCD and MDD. In the present study, the comorbidity of OCD and MDD is more associated with free radicals. However, the patients with pure OCD seem to be related to the antioxidant enzyme system. We suggest that OCD may be linked with the antioxidant system and the products of lipid peroxidation. Depressed patients have been reported to have increased T helper cells and increased interleukin-2 in serum [39]. This condition suggests that immune cells are activated in major depression. The activation of the immune system probably causes overproduction of free radicals. In OCD, some observations result in possible alterations in the immune function. For example, an increased rate of OCD is observed in patients with

Sydenham's chorea and a triggered autoimmune subtype has been observed in OCD. However, some studies demonstrated that OCD was not associated with changes in some immunological markers [40, 41].

In conclusion, our results suggest that OCD is related to free radicals and that it may be a heterogeneous subtype including some biological indications of anxiety and affective disorders. More comprehensive and detailed studies are needed to decipher the exact role of free radicals in OCD.

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