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Full Length Research Paper

Myeloperoxidase enzyme levels and oxidative stress in bipolar disorders

S. Nur Aksoy[1], Eyup Ilker Saygılı[2], Ferıdun Bulbul[3], Aynur Bahar[2], Haluk Savas[4] Osman Vırıt[4], Abdurrahman Altındag[4], Aysen Bayram[5] and Mehmet Tarakçıoğlu[1]

[1]Department of Biochemistry, Gaziantep University Faculty of Medicine, Gaziantep, Turkey.
[2]Vocational School of Higher Education for Health Services, Gaziantep University Faculty of Medicine, Gaziantep, Turkey.
[3]Nizip State Hospital Psychiatry Service, Gaziantep, Turkey.
[4]Department of Psychiatry, Gaziantep University Faculty of Medicine, Gaziantep, Turkey.
[5]Department of Microbiology, Gaziantep University Faculty of Medicine, Gaziantep, Turkey.

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Oxidative stress and generalized inflammatory state are features of bipolar disorders (BD). The objective of this study was to compare the levels of products of inflammatory reaction and oxidative stress markers in patients with bipolar disorders and attention deficit/hyperactivity disorder (ADHD) and to determine the relationship between oxidative stress and inflammation in bipolar disorders. ADHD+BD (n = 30) and BD (n = 30) and healthy controls (n = 30) were enrolled. A clinical evaluation and measurements of malondialdehyde (MDA), high sensitive C reactive protein (hsCRP) and myeloperoxidase (MPO) were performed. Patients with BD+ADHD comorbidity had significantly higher mean MPO levels than BD. Patients with BD had significantly higher mean hsCRP levels than healthy controls. However, there was no significant difference in mean serum hsCRP levels between patients with BD+ADHD and healthy controls. Patients with BD and BD+ADHD had significantly higher mean MDA levels than healthy controls. Our data showed that there is an increased susceptibility to oxidative stress which is strongly related to the serum levels of MDA produced in the serum. hsCRP levels were higher in BD patients than in BD+ADHD and this is suggestive of a higher degree of inflammatory activity in BD patients. ADHD+BD comorbidity seems to augment oxidative stress which is expressed as increased MPO level in the present study. Further large scale studies are needed to extend our results.

Key words: ADHD, bipolar disorder, myeloperoxidase, CRP, MDA.

INTRODUCTION

Attention deficit/hyperactivity disorder (ADHD) consists of a persistent pattern of in attention, hyperactivity and impulsivity (APA, 2000). It is well established that ADHD is frequently comorbid with other psychiatric disorders such as oppositional defiant disorder, conduct disorder, anxiety disorders, depression, tic disorders, substance abuse and bipolar disorders (BD) (AACAP, 2007). Perhaps, the most diagnostically challenging and controversial of co-occurring disorders in ADHD is BD. There are few studies evaluating the biochemical basis of the disorder. From the syndromal aspect of view, Adult-ADHD may be involved with some other systems, such as oxidative metabolism. The oxidative status of other psychiatric disorders has already been studied and more evidences pointing out the possible etiological role of those molecules have been reported (Akyol et al., 2007). Depression may cause inflammation through altered neuroendocrine function and central adiposity. However,

*Correspondence author. E-mail: naksoy@gantep.edu.tr.

Abbreviations: BD, Bipolar disorders; **ADHD**, attention \deficit/hyperactivity disorder; **MPO**; myeloperoxidase; **MDA:** malondialdehyde; **PUFAs**, polyunsaturated fatty acids; **hsCRP**, high sensitive C-reactiveprotein; **ROS**, reactive oxygen species; **EDTA**, ethylenediaminetetraacetic acid; **AD**, Alzheimer disease.

depression may also be a consequence of inflammation, since a pathogenic role of inflammatory cytokines in the etiology of depression has been described. Myeloperoxidase (MPO) has been widely used as an inflammatory marker of both acute and chronic conditions. Moreover, MPO changes have also been associated to the severity of many diseases (Carney et al., 2002; Vaccarino et al., 2008). Oxidative stress is thought to mediate neuropathological processes of a number of neuropsychiatric disorders and recent data suggest that oxidative stress may be involved in the pathophysiology of BD. ADHD usually identified in childhood persists into adulthood in about 60% of individuals with childhood onset (Elliott, 2002). Adult-ADHD is principally a genetic disorder, but environmental and biochemical factors also play a role in its etiopathogenesis. The number of biological studies on Adult-ADHD has escalated in recent years. Neuroimaging, genetics and biochemistry are the hot points for new research. Studies have consistently reported increased lipid peroxidation and changes in the major antioxidant enzymes in individuals with BD (Ozcan et al., 2004; Ranjekar et al., 2003; Kuloglu et al., 2002) suggesting that oxidative stress may play a role in the pathophysiology of BD. The excessive generation of reactive oxygen species, such as hydroxyl radicals, can lead to lipid and protein oxidation, with consequent membrane and DNA damage (Piao et al., 2008).

Malondialdehyde (MDA) is the breakdown product of the major chain reactions leading to oxidation of polyunsaturated fatty acids (PUFAs) and thus, serves as a reliable marker of oxidative stress (Sanyal et al., 2009). Recent studies have demonstrated that oxidative stress might have a role in the pathogenesis of various psychiatric disorders. Additionally, research groups have reported elevated MDA activity in various psychiatric diseases (Altuntas et al., 2000; Akyol et al., 2002; Kuloglu et al., 2002). These findings suggest that increased MDA, a destructive agent, could have an important role in the pathophysiology of psychiatric diseases.

High sensitive C-reactive protein (hsCRP) is a pentameric protein which is generated in the liver and secreted in the blood and which plays a central role in human inflammation. The measurement of CRP in the blood provides a reliable marker of chronic inflammation caused by infectious and other inflammatory agents (Lowe, 2005). Important cellular sources of oxidative stress are: (a) The formation of reactive oxygen species by incomplete reduction of oxygen in the respiratory chain of mito-chondria and (b) host defense systems, which include the reactive oxygen species (ROS) mediated by NADPH oxidase, producing superoxide radical and myeloper-oxidase, leading to the formation of hypochlorous acid (Halliwell and Gutterıdge, 2000; Graham et al., 2007; Brennan et al., 2003; Winterbourn and Kettle, 2004).

MPO is a critical component of the oxidative activity of the neutrophils as its activity functions against several microorganisms, from viruses to fungi as well as against mammalian proteins and cells (Klebanoff, 1999).

Besides leukocytes, MPO has been found in the microglia, granule containing neurons and pyuramidal neurons of hippocampus in the brain (Nagra et al., 1997; Ji et al., 2007). Unlike macrophages in other parts of the body, microglia in the brain of patients with neurodegenerative diseases are positive for MPO (Yap et al., 2007; Reynolds et al., 1999). It should be noted that normal brain microglia rarely express this enzyme (Ulvestad et al., 1994). ROS's toxicity is augmented by the presence of MPO which catalyzes the reaction between the hydrogen peroxide and the ubiquitous chloride ion resulting in formation of hypochlorous acid (HOCl) (Mander et al., 2006). Hypochlorous acid is believed to cause cell death (Haegens et al., 2008).

Even with very little data, antioxidant treatments were tried in ADHD. Therefore, evaluating the oxidative status of ADHD patients is essential for further intervention designs. Formerly, we have researched the lipid peroxidation status of ADHD and demonstrated the imbalance (Bulut et al., 2007), but a general oxidative status was not evaluated.

Another neuropsychiatric disorder in which free radicals might play a role is BD and BD+ADHD comorbidity. To the best of our knowledge, there has not yet been a study evaluating the association between free radicals and BD and BD+ADHD comorbidity. Therefore, in the present study, we hypothesized that oxidative damage and MPO enzyme levels could be implicated in BD+ADHD comorbidity.

The objective of this study was to compare the levels of products of inflammatory reaction and oxidative stress markers in patients with bipolar disorders and to determine the relationship between oxidative stress and inflammation in bipolar disorders. We aimed to investigate MPO, hsCRP and MDA levels in subjects with bipolar disease and with and without ADHD and relevance of these parameters with clinical characteristics.

MATERIALS AND METHODS

Three groups of treatment-seeking patients were compared on demographic and clinical characteristics: ADHD patients with a comorbid bipolar disorder. Thirty patients BD from Gaziantep University Sahinbey Research Hospital, Psychiatry Clinic, diagnosed according to Turgay's Turkish version of Adult ADD/ ADHD DSM IV-Based Diagnostic Screening and Rating Scale by psychiatrist (F.B.) and thirty healthy volunteer controls were included. Case and control groups have similar distribution in age, sex and smoking status. As the researches focused on the disease entity, only attention and hyperactivity/impulsivity subscale scores were taken into consideration. The medical records of the patients were reviewed by the researcher (F.B, H.S.) and patients with a history of chronic systemic diseases such as diabetes mellitus, hypertension and severe head injury were excluded. After complete description of the study to the subjects, a written informed consent was obtained from all subjects. Ethics committee of the Gaziantep University Medical School approved the trial. Also, a semi-structured form was used to detect several sociodemographic and clinical variables of the patients. Comorbid patients were included only when the other psychiatric conditions were in remission according to their Clinical

Global Impression Scale Scores below 2 points at least 2 months; therefore, the patients were allowed to take their medications. The comorbids were having antidepressants, benzodiazepines and a typical antipsychotics. Case and control groups had similar distribution in age, sex and smoking status. The subjects strictly refrained from alcohol or food intake and physical exercise after 08:00 p.m. on the day before collection. Mentioned metabolites were measured in plasma samples of study groups. Blood samples were collected during routine laboratory evaluation at 08.00 a.m. Only one sample was collected. After immediate centrifugation (1000 x g, 10 min), serum sample were stored frozen at -70°C.

MPO enzyme levels

The assay utilizes the two-site "sandwich" technique with two selected polyclonal antibodies that bind to human MPO. Assay standards, controls and prediluted patient samples containing human MPO are added to wells of microplate that was coated with a high affine polyclonal anti-human MPO antibody. After the first incubation period, antibody immobilized on the wall of microtiter wells captures human MPO in the sample. Then a peroxidase-conjugated polyclonal anti-human MPO antibody is added to each microtiter well and a "sandwich" of capture antibody - human MPO – peroxidase conjugate is formed. Tetramethylbenzidine (TMB) is used as a substrate for peroxidase. Finally, an acidic stop solution is added to terminate the reaction. The color changes from blue to yellow. The intensity of the yellow color is directly proportional to the concentration of MPO in the sample. A dose response curve of the absorbance unit (optical density, OD at 450 nm) vs concentration is generated, using the values obtained from the standard. MPO present in the patient samples is determined directly from this curve (Harrison and Schultz, 1976).

MDA spectrophotometric determination of MDA-TBA

MDA, which is an important indicator of lipid peroxidation, was determined by spectrophotometry of the pink-colored product of the thiobarbituric acid-reactive substances complex (Jain et al., 1989). Total thiobarbituric acid-reactive substances (TBARS) were expressed as MDA. MDA was determined by the thiobarbituric acid method. Aliquots of 0.2 ml from the serum were mixed thoroughly with 0.8 ml phosphate-buffered saline (pH 7.4) and 0.025 ml butylated hydroxytoluene solution. After adding 0.5 ml 30% trichloroacetic acid, the samples were placed on ice for 2 h and then centrifuged at 2000 g at 25°C for 15 min. One ml of supernatant was mixed with 0.075 ml of 0.1 mol ethylenediaminetetraacetic acid (EDTA) and 0.25 ml of 1% thiobarbituric acid in 0.05 N sodium hydroxide and placed in boiling water for 15 min. After cooling to room temperature, the absorbance at 532 nm was determined. Total thiobarbituric acidreactive substances (TBARS) were expressed as MDA. The results were expressed as nmol/mL

hsCRP nephelomethric determination

hsCRP assay was measured with DADE BEHRING BN II. Polystyrene particles coated with monoclonal antibodies specific to human CRP are aggregated when mixed with samples containing CRP. These aggregates scatter a beam of light passed through the sample. The intensity of the scattered light is proportional to the concentration of the relevant protein in the sample. The result is evaluated by comparison with a standard of known concentration.

Statistical analysis

Analyses of data were performed using the computer software statistical package for the social sciences (SPSS) for Windows (version 13.0; SPSS Inc., Chicago, IL). The significance of differences between groups was estimated by ANOVA test. Differences were accepted as significant when $p < 0.05$. Tukey test was used for further analysis. Tukey values are represented in bold.

RESULTS

MPO levels of patient groups and control group are presented in Table 2. Patients with BD+ADHD comorbidity had significantly higher mean MPO levels than BD (190 ± 80 and 66 ± 9 ng/ml), ($p < 0.001$). However, MPO levels were not significantly different between subjects with BD and the control group ($p = 0,32$, Table 2).

A total of 90 participants (35 males and 55 females) were recruited in the study including 30 with BD, 30 ADHD+BD and 30 healthy controls. Table 2 presents demographic and clinical data for all participants. There was no statistically significant difference between the groups in terms of mean age and gender, disease type and number of depressive episodes, disease type and number of manic attacks (Table 1). Patients with BD had significantly higher mean hsCRP level than healthy controls (3.74 ± 0.5 and 2.43 ± 0.2 mg/L, $p = 0.039$) hsCRP level was higher in patients with BD than patients with BD+ADHD however, the difference was not significant.(3.74 ± 0.5 and 2.81 ± 0.3 mg/L, $p = 0.22$) Also, there was no significant difference in serum hsCRP level between patients with BD+ADHD and healthy controls (2.81 ± 0,3 and 2.43 ± 0.2 mg/L, $p = 0.68$). Patients with BD had significantly higher mean MDA levels than healthy controls (4.31 ± 0.2 and. 3.23 ± 0.1 nmol/mL), ($p = 0.004$). Patients with BD+ADHD comorbidity had significantly higher mean MDA levels than healthy controls (4.27 ± 0.23 and 3.23 ± 0.1 nmol/mL, $p = 0.005$). However, there was no significant difference in mean serum MDA levels between patients with BD+ADHD and BD (4.27 ± 0.23 and 4.31 ± 0.2 nmol/mL, $p = 0.99$).

DISCUSSİON

A possible association between ADHD and the manic phase of bipolar disorder has attracted significant interest because the symptoms of both disorders are so similar across all age groups: talkativeness, distractibility and increased motor activity (Trantham-Davidson et al., 2008; Zepf , 2009).

MPO is a myeloid-specific enzyme produced by activated phagocytic cells, including brain microglia (Hampton et al., 1998). In contrast, inflammatory cytokines are produced by a variety of cell types, while acute-phase proteins such as CRP and fibrinogen are mostly secondary products in response to cytokine signaling. Thus, MPO is potentially a more specific marker of microglial immune activation and therefore, more relevant for major depressive disorder and other brain disorders (Faith et al., 2008).

MPO has been identified in brain areas affected by

Table 1. Distribution of demographic and clinical data.

Parameters	Control group		Bipolar group		Bipolar+ADHD group	
	Number	Percent	Number	Percent	Number	Percent
Gender*						
Female	17	56.7	18	60	20	66.7
Male	13	43.3	12	40	10	33.3
Additional type of disorder**						
There is	-	-	7	23.3	1	3.3
No	-	-	23	76.7	29	96.7
Additional psychiatric disorders**						
There is	-	-	2	6.7	-	-
No	-	-	28	93.3	30	100
Family history of psychiatric illness**						
There is	-	-	7	23.3	14	46.7
No	-	-	23	76.7	16	53.3
Number of depressive episodes**						
Did not attack	-	-	18	60	7	23.3
1 - 3 had an attack of	-	-	9	30	20	66.7
4 and on the attack had	-	-	3	10	3	10.0
Mean ± SEM	-	-	1.2 ± 0.44		1.3 ± 0.27	
Number of manic attacks**						
Did not attack	-	-	2	6.7	-	-
1 - 3 had an attack of	-	-	24	80	23	76.7
4 and on the attack had	-	-	4	13.3	7	23.3
Mean ± SEM	-		2.1± 0.37		2.8 ± 0.34	
Smoking*						
There is	5	16.7	8	26.7	6	20
No	25	83.3	22	73.3	24	80
Age						
Mean ± SEM	34.2 ± 1.88		32.8 ± 1.58		33.1 ± 1.68	
Onset age						
Mean ± SEM	-		25.4 ± 1.38		24.4 ± 1.08	
Body weight (kg)						
Mean ± SEM	70.6 ± 3.06		78.0 ± 2.89		78.0 ± 2.89	
Body height (cm)						
Mean ± SEM	168.2 ± 1.73		164.7 ± 1.3		167.8 ± 1.52	

SEM, Standart error of the mean; *Number: 90, **Number: 60.

Alzheimer disease (AD). Glial cells are in an activated state in affected brain areas of AD patients. As a result, microglia produces superoxide by the action of NADPH oxidase, which dismutates to oxygen and hydrogen peroxide (Casado et al., 2008). Thus, both substrates required by myeloperoxidase to exert its oxidative and cytolytic activity (H2O2 and chloride ions) are present in the affected brain areas. Myeloperoxidase is known to catalyze each of the aberrant oxidative reactions encountered in the affected neurons (Mahadik and Mukherjee 1996). The association between CRP levels and bipolar disorder has been the focus of only limited investigation. It was found that acutely manic patients had higher levels of CRP and other markers of inflammation as compared to healthy controls, but these studies did not examine persons with bipolar disorder who were not in an acute manic phase (Huang and Lin, 2007; Wadee et al., 2002).

Recent studies have indicated that having elevated levels of the acute phase protein, reactant CRP is a very sensitive marker of acute inflammatory reactions including patients with systemic diseases with or without depressive symptoms (Ridker, 2003; Douglas et al., 2004; Empana et al., 2005). The purpose of the current study was to investigate the association between serum levels of CRP and the severity of psychopathology within bipolar disorder.

In the present study, CRP level was found to be significantly higher in BD patient group when compared to control

Table 2. The relationship between disease type and some variables.

Parameters	Control group		BD group		BD+ADHD group		Test and p
	N	Mean ± SEM	N	Mean ± SEM	N	Mean ± SEM	
Number of depressive episodes Did not attack 1 - 3 had an attack of 4 and on the attack had			 18 9 3	1.2 ± 0.44	 7 20 3	1.3 ± 0.27	 t = 3.19 p > 0.05
Number of manic attacks Did not attack 1 - 3 had an attack of 4 and on the attack had			 2 24 4	2.1 ± 0.37	 - 23 7	2.8 ± 0.34	 t = -1.245 p > 0.05
MPO (ng / mL)	30	90.9 ± 11.3	30	66.2 ± 9.7	30	190.9 ± 80.3	F = 29.813 **p < 0.001**[ac]
hsCRP (mg /L)	30	2.43 ± 0.2	30	3.74 ± 0.5	30	2.81 ± 0.3	F = 3.204 **p = 0.039**[b]
MDA (nmol / mL)	30	3.23 ± 0.1	30	4.31± 0.2	30	4.27 ± 0.23	F = 7.155 **p < 0.005**[ab]

SEM, Standard error of the mean; the mean difference is significant at p < 0.05; BD, Bipolar disorder; ADHD, attention deficit/hyperactivity disorder; MPO, myeloperoxidase; hsCRP, high sensitive C reactive protein; MDA, malondialdehyde; [a]comparison of levels/activities between BD+ADHD and healthy control groups; [b]comparison of levels/activities between BD and healthy control groups; [c]comparison of levels/activities between BD+ADHD and BD groups.

group. MDA level was found to be higher in BD and BD+ADHD comorbidity patient groups when compared to control group. Patients with BD+ADHD comorbidity had higher mean MPO levels than BD. However, MPO levels were similar in patients with BD and the control group. This study is the first determining the MPO enzyme level in patient groups with ADHD and BD.

There is evidence that ROS play an important role in the pathogenesis of many diseases, particularly in neurological and psychiatric diseases due to the central nervous system vulnerability to oxidative stres (Sorce and Krause, 2009). Recent studies have reported alterations of antioxidant enzymes in red blood cells, lipid peroxidation and serum in BD patients (Andreazza et al., 2007; Gergerlioğlu et al., 2007). The content of plasma TBARS and erythrocyte superoxide dismutase (SOD) activity have been reported to be increased in BD patients (Kuloglu et al., 2002). On the other hand, no changes in TBARS or SOD activity were observed in another study conducted with BD patients (Ranjekar et al., 2003).

Independently, another group described a decrease in catalase activity in BD patients; this decrease was accompanied by an increase in plasma TBARS and a decrease in glutathione peroxidase (GPx) activity (Ozcan et al., 2004). More recently, Machado-Vieira observed elevated levels of TBARS and SOD activity during manic episodes in BD patients (Machado-Vieira et al., 2007). The available evidence suggests that oxidative stress may play a role in the pathophysiology of BD and ADHD (Ng et al., 2008).

Conclusion

Our data showed that there was an increased susceptibility to oxidative stress which is strongly related to the serum levels of MDA produced in the serum. hsCRP levels were higher in BD patients than in BD+ADHD and this is suggestive of a higher degree of inflammatory activity in BD patients. ADHD+BD comorbidity seems to augment oxidative stress which is expressed as increased MPO level in the present study. Further large scale studies are needed to extend our results.

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