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Araştırma Makalesi

An Investigation on The Correlation Between Oxidative Stress and Cognitive Functions In Patients With Euthymic Bipolar Disorder

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Abstract

To investigate the relationship between oxidative stress and cognitive functions in bipolar patients. The sample of the study consisted of 50 patients and 50 healthy volunteers who applied to the Department of Psychiatry. Global Clinical Monitoring Scale (GCMS), Hamilton Depression Scale (HAM-D), Young Mania Rating Scale (YMRS), serial step learning test (SDLT), Stroop Test Basic Sciences Research Group Form (ST-TBAG), Preliminary Evaluation Battery (ST-TBAG) FAB) was applied to healthy volunteers with a socio-demographic data form. In addition, venous blood was collected and Total Oxidant Level (TOL) and Total Antioxidant Level (TAL) were measured. TOL and OSI levels were found to be significant between the patient groups and the control group in the tests and measurements performed ($p < 0.01$). The stroop test applied to both the patient and the control group was statistically significant in terms of Frontal Assessment Battery (FAB) and number series learning test ($p < 0.05$). In addition, there was a statistically significant relationship between FAB and TOL (p: 0.012 r: -0.353) and OSI (p: 0.014 r: -0.346) applied to patients. As a result, there was a significant correlation with oxidative parameters and disorder in cognitive function tests compared to the control group.

Keywords: Bipolar disorder, cognitive functions, oxidative parameters

INTRODUCTION

Bipolar disorder (BD) is a chronic disorder characterized by (of recurrent character that is characterised with) periods of relatively elevated (good) mood called manic or hypomanic, and depressive and euthymic episodes. Previously, it was supposed (viewed) as it is a disorder in which cognitive functions are impaired in attack periods, but no cognitive impairment develops in remission episodes. Recent research has, however, led to a new perspective with the argument that it is a permanent disorder (Savitz et al., 2005).

As neuro-psychological tests mainly focus on the anatomy and functions of the brain, the classification of these tests by the areas in the brain is a widely used approach especially in clinical practice (Karakaş, 2000). Several studies have shown that the impairment in some cognitive functions in patients with BD could be as severe as that observed in patients with schizophrenia (Bora et al., 2010; Cipriani et al., 2017).

Recently, it has been shown that oxidative stress has increasingly been observed in patients with psychiatric disorders including BD (Kuloglu et al., 2002). Free radicals responsible for oxidative stress are connected with the pathologies that occur in the cell membranes in the central nervous system and play an important role in neuro-psychiatric disorders. Even though there have been several studies that have investigated the correlation between cognitive functions and BD as well as oxidative stress levels in BD, there is no research (has been found that) investigating the correlation between cognitive functions and oxidative stress. The aim of this study is to clarify the correlation between cognitive functions and oxidative stress. The study sample consisted of 50 patients who presented to Psychiatry Department of Dicle University Medical Faculty Training and Research Hospital, between 15.11.2012 and 15.05.2013. (All) The patients included who was diagnosed with Bipolar Disorder (BD) according to DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition) and that had been in euthymic episode for at least 3 months. Written consent was obtained from all the subjects prior to the study.

Criteria of Inclusion the Study

The study sample comprised of 50 patients between 18-65 years of age who were capable of giving consent and had been diagnosed as with BD according to DSM IV-TR codes and that had been in euthymic episode in the last three months, (and also agreed to participate in the study. We also used a control group consisting of healthy volunteers matched with the patient group in respect of variables such as age and gender. They were subjected to BMI scale and blood analysis for bio-chemical parameters. Patients who were pregnant and those who suffered from hypertension, diabetes, morbid obesity or another severe medical disorder such as other endocrinopathies, dementia, any disease that can potentially cause a deterioration in cognitive functions and mental deficiency were excluded from the study. Also excluded from the study were those who had drug or alcohol dependence or a history in this respect as well as the ones who had a history of severe head trauma. Patients were also excluded because of nutritional habits based on foods with higher oxidant and/or antioxidant content. Patients who took supplements affecting antioxidant capacity such as ascorbic acid, N-acethyl cysteine and omega-3 and drugs classified as psycho-stimulants or benzodiazepines were not included in the study as well.

Tools such as Global Clinical Monitoring Scale (GCMS), Hamilton Depression Scale (HAM-D), Young Mania Rating Scale (YMRS), serial digit learning test (SDLT), Stroop Test Basic Sciences Research Group Form (ST-TBAG), Frontal Assessment Battery (FAB) were administered to patients and healthy volunteers by means of socio-demographic data form.

About 10 ml blood was taken from the antecubital veins of every study subjects, which was then centrifuged for 4 minutes at a rotor speed of 4000 r/min in a device of brand NÜVE NF 048 in biochemical tubes with EDTA. The serums thus obtained were stored in a box at -80 0C in 1.5 ml Eppendorf tubes. After thawing, serum Total Oxidant Level (TOL) and Total Antioxidant Level (TAL) values were measured with a device of brand ARCHITECT C 16000.

After the equalisation of measurement units, the Oxidative Stress Index (OSI) was calculated by dividing the Total Oxidant Level (TOL) by the Total Antioxidant Level (TAL) (Erel, 2005).

While the categorical data obtained in the study were expressed as frequency and percentage values, numerical data were defined as arithmetical mean ± standard deviation (am±sd). SPSS 14.0 (Chicago ill. USA) was used to analyse the data. The analysis of categorical data was performed with Chi-square test. To analyse quantitative data, t-test was used in dual groups. As the parametric assumptions were not met in multiple groups, Kruskal-Wallis variance analysis was used to analyse these groups. The Pearson correlation test was used to define the direction and size of the correlation between two quantitative variables. The significance level was set at measured as $p<0.05$ (in all the analyses).

Study Data

There was no statistically significant difference in respect of age, educational background, gender and civil status between the patient and healthy control group (Table 1).

Table 1. Sociodemographic data between the patient and healthy control

	Total (n:100) am±sd	Patient (n:50) am± sd	Control (n:50) am ±sd	χ^2 p
Age	32.09±9.98	32.18±11.08	32±8.86	0.90 0.929
Education Time	10.31±3.56	10.28±3.36	10.34±3.78	-0.084 0.933
	Total n(%)	Patient n(%)	Control n(%)	
Gender				0 1
Female	20 (20)	10 20	10 20	
Male	80 80	40 80	40 80	
Marital Status				
Married	46 46	21 42	25 50	0.644
Single	54 54	29 58	25 50	0.422

Table 2. Frequency of smoking in the patient and control groups on daily basis

	Total (n:100) am±sd	Patient (n:50) am±sd	Control (n:50) am±sd	χ^2	p
Tea	7.31±3.74	6.94±3.25	7.68±4.17	-0.988	0.325
Cigaret (Number)	21±11.60	24.59±13.83	17.94±8.35	2.345	**0.022**
Cigaret (Box)	1.04±0.57	1.22±0.68	0.89±0.41	2.315	**0.024**

However, patients had respectively significantly higher rates of smoking (Table 2). Comparing the patient and control groups in respect of height, weight and Body Mass Index (BMI), there was no difference (Table 3).

Table 3. Data concerning the height, weight and body mass indices of patient and control groups

	Total (n:100) ort±ss	Patient (n:50) ort±ss	Control (n:50) ort±ss	χ^2	p
Height	172.65±7.83	172.26±7.93	173.04±7.80	-0.496	0.621
Weight	73.02±9.23	73.28±9.42	72.76±9.13	0.280	0.780
BMİ	24.48±2.50	24.65±2.50	24.31±2.52	0.954	0.502

The oxidative stress values of the patient and control groups are presented in Table 4. The comparison between groups showed that TOL and OSI values of the patient group consisting of patients were significantly lower than those of the healthy control group ($p<0.01$). The study found no significant difference in the comparison of TAL values between the groups.

Table 4. Oxidative Stress Parameters of Patient and Control Groups

	Total (n:100) am±sd	Patient (n:50) am±sd	Control (n:50) am±sd	χ^2	p
TOS	9.92±13.34	4.79±10.74	15.05±13.80	-4.149	<**0.01**
TAS	1.94±0.16	1.92±0.16	1.96±0.15	-1.367	0.175
OSI	0.49±0.63	0.25±0.58	0.74±0.60	-4.123	<**0.01**

On the basis of the statistical comparisons based on cognitive function tests, the study we found a significant difference between the patient and control groups in respect of Frontal Assessment Battery (FAB); Stroop time 1, Stroop correction 1, Stroop time 2, Stroop time 3, Stroop correction 3, Stroop time 4, Stroop error 4, Stroop correction 4, Stroop time 5, Stroop error 5, Stroop correction 5 and Serial digit learning test (SDLT) parameters (Table 5).

Table 5. The results of the cognitive function tests administered to patient and control groups

	Total (n:100) am±sd	Patient (n:50) am±sd	Control (n:50) am±sd	χ^2	p
FAB	15.99±2.24	14.76±2.88	17.22±1.29	-5.502	<**0.01**
Stroop Time1	9.38±3.09	10.48±3.28	8.28±2.45	3.792	<**0.01**
Stroop Mistake1	0.01±0.10	0.0±0.0	0.02±0.141	-1.00	0.322
Stroop Correcting 1	0.04±0.197	0.08±0.27	0.0±0.0	2.064	**0.044**
Stroop Time 2	10.01±3.54	10.66±3.42	9.36±3.57	1.857	**0.066**
Stroop Mistake 2	0.07±0.29	0.06±0.24	0.08±0.34	-0.340	0.735
Stroop Correcting 2	0.15±0.41	0.14±0.40	0.16±0.42	-0.242	0.809
Stroop Time 3	14.19±5.1	15.88±5.33	12.50±4.27	3.496	**0.001**
Stroop Mistake 3	0.11±0.49	0.16±0.61	0.06±0.31	1.020	0.310
Stroop Correcting 3	0.41±0.71	0.64±0.87	0.18±0.38	3.398	**0.001**
Stroop Time 4	19.59±7.69	22.62±8.24	16.56±5.74	4.266	<**0.01**
Stroop Mistake 4	0.24±0.69	0.38±0.92	0.10±0.30	2.037	**0.044**
Stroop Correcting 4	0.69±1.24	1.06±1.57	0.32±0.62	3.099	**0.003**
Stroop Time 5	28.54±12.35	33.52±14.35	23.45±7.01	4.421	<**0.01**
Stroop Mistake 5	0.92±1.25	1.16±1.50	0.67±0.89	1.950	**0.054**
Stroop Correcting 5	1.62±1.60	2.14±1.88	1.08±1.02	3.426	**0.001**
SDLT	13.25±7.30	9.58±8.52	16.92±2.74	-5.795	<**0.01**

The usage rates of anti-depressive drugs (ADs), mood stabiliser drugs (MSDs) and antipsychotic drugs (APs) in remission episode period broken down by patients was 88% (n=44), 94% (n=47) and 20% (n=10) respectively. While 4.5% (n=2) used 1st generation APs, 84.1% (n=37) used 2nd generation APs. On the other hand, 11.4% (n=5) of the patients used a combination of 1st and 2nd generation APs. Table 6 shows the scores of CGMS, Hamilton Depression Scale and Young Mania Scale administered to the patients.

Table 6. Scores of the scales administered to the patients

	Patient (n:50) am±sd
CGI 1	1.36±0.598
CGI 2	1.38±0.567
CGI 3	1.22±0.582
HAM-D	4.80±4.286
YMRS	1.96±2.010

DISCUSSION

There is a large number of studies that investigated the oxidative stress level in bipolar disorder, with the results indicating an impairment in oxidative balance (Lohr, 1991; Andreazza et al., 2013). These studies have provided evidence that oxidative stress increases

in BD (Kuloglu et al., 2002). Furthermore, (Besides), several other studies have reported that oxidative stress level which increases related to (in connection with) the disease can decrease with (medications to be administered for) the treatment (Xu et., 2008; Kropp et al., 2015).

Haiyun Xu et al. (2008), argued that quetiapine has antioxidant effect against the oxidative stress involved in the pathophysiology of diseases such as schizophrenia and Alzheimer. Another study on cell culture has shown that lithium (used to improve mood balance) reduces oxidative stress by increasing the gluthatione-s transferase activity in cerebral cortical cells (Shao et al., 2008).

In an (their studies designed in experimental) animal study (in which they) investigating the neuron protecting effect of valproic acid used in (many disorders such as) bipolar disorder and epilepsy, Suda et al. (2013), reported that it generates this effect by reducing the oxidative stress in the damaged area, (in other words by behaving like an antioxidant).

A study performed by Kropp et al. (2005), to compare the effects of antipsychotics of 1st and 2nd generation on oxidative stress found that MDA level, which is a significant indicator for oxidative stress, was significantly low in patients using 2nd generation APs.

The results of our study are similar to (those observed in) the studies indicated above. While 84.1% (n=37) of our patients used 2nd generation Aps, 11.4% used 1st and 2nd generation AP (in a combined form) combination. This might have contributed to the lower result of TOL and OSI levels in our patients using 2nd generation APs (drugs in greater numbers were found to be significantly lower than those observed in the control group). A study conducted by Cumurcu et al. (2009), compared the serum TOL and OSI (values) levels (measured) in patients diagnosed with MD prior to treatment with TOL and OSI levels after a 3-month's AD treatment and reported that oxidative stress parameters significantly decreased after the treatment.

The AD usage rate was found to be 20% (n=10) in our study; in this sense, we believe that, besides the high usage of 2nd generation APs, AD usage may have also contributed to lower TOL and OSI levels.

Previous research has shown that impairment of cognitive functions occurs at a higher rate in patients with BD than healthy individuals (in control groups) (Sparding et al., 2017; Lima, 2018). Similarly, our study demonstrated that patients with bipolar disorder showed a significantly lower performance than the healthy control group in (numerical sequence) serial digit learning test (Table 5).

Another study that examined the verbal memory and learning functions in BD has (provided evidence that) shown impairment (occurs) in both of these functions (Czobor et al., 2007).

Czobor et al. (2007), investigated the six neurocognitive areas (attention, working memory, learning, verbal information, non-verbal functions, thought fluency/processing) of BD patients that are impaired in patients with schzophreania, and found that impairment in those neurocognitive fields occur both in patients with BD and (those) with schizophrenia. They also reported that impairment in attention and non-verbal functions is more distinct in patients with schizophrenia.

Stroop test is (a tool that is) used to measure attention, cognitive set (construct), ability to change reactions against an interference, maintenance of goal-directed behaviour and processing speed (concentration and attention)

(Thursina et al., 2015). In a study, Soni et al. (2017), categorised (grouped) BD patients in sub-groups as (with) low and high functional with global functional assessment scale, forming then three groups with healthy volunteers, and subjected them to a series of neuropsychological tests. They demonstrated (based on the tests they performed) that while the group with low functions had the lowest scores in Stroop tests, the group with high functions, on the other hand, had scores lower than healthy volunteers. The results they observed match the Stroop test results (delivered in) of our study.

Frontal Assessment Battery (FAB) is a quick test used to assess frontal lobe functions consisting of six sub-tests with total scores ranging from 0 to 18. Higher scores (obtained in the test) indicate better performance. In our study, the patients had statistically significant lower scores than healthy individuals in FAB (Table 5).

In their study performed on 25 patients with BD in euthymic episode and a healthy control group, Barbosa et al. (2012), found that the patient group had FAB results significantly lower than the control group, and the results we observed in our study are consistent with this study.

In a study performed with BD patients, Pavuluri et al. (2009), reported that cognitive impairment progresses along with the (developmental course) process of the disease. At the beginning, the patients obtained lower scores in verbal memory, visual memory, visual perception, process /working memory, attention and executive functions in BD patient group than the healthy control group. This study suggests that cognitive impairment can get worse over time if corrective or preventive treatment options cannot be offered. There are (have also been) some studies which argue that if pharmacotherapy affects neuropsychological functions in patients or if it cannot rehabilitate cognitive impairments (Goldberg and Chengappa 2009). As no sufficient data is available concerning the neuropsychological effects of antipsychotics, mood stabilisers and antidepressants on our sample (that received pharmacotherapy), it would not be reasonable to attribute the impairments observed in patients solely to the disease process.

There have also been a number of studies (that have) reported that pharmacotherapy and especially polypharmacy can/may lead to cognitive impairments in patients with BD. As a polypharmacy, increased number of antipsychotic (especially typical) use which may result in tardive dyskinesia could lead to an increased cognitive impairment (Goldberg and Chengappa 2009; Waddington et al., 1990). (Given that) As (more than one) multiple drugs were used in the treatment programmes of the patients with BD participating our study, it should be taken into account that besides the disorder itself polypharmacy might have also played a role in the impairment of cognitive functions.

Previous research has reported that typical and atypical antipsychotics used in psychiatric disorders have effects on neurotoxicity, resulting in neurodegeneration. (as a result of which neurodegenerative disorder might occur) (Gil-ad et al., 2001). This suggests that this neurodegeneration would increase (the level of) the cognitive impairment. (that occurs during the course of the disease).

A large number of studies have provided evidence about oxidative stress increase and cognitive impairment in psychiatric diseases such as bipolar disorder, schizophrenia and depression (Martinez-Aran et al., 2004; Martinez-Cengotitabengoa et al., 2012). This led to

a hypothesis about that, in case where antioxidants reduce the oxidative stress, they could lead an improvement in cognitive functions.

Although some experimental research on rats has argued that an improvement yielded in oxidative stress by using antioxidants could also lead to an improvement in cognitive functions; the results of such studies have, however, not been confirmed in research on humans. A study conducted with N-Acetyl Cystein (NAC) which is an antioxidant agent reports that antioxidant use does not improve cognitive functions in patients with BD (Alzoubi et al., 2013; Rajasekar et al., 2013).

In another randomized, double-blind and placebo-controlled study, added NAC 2000 mg/day (n=21) and placebo (n=25) to the regular treatments of the patients, and conducted cognitive function tests, one at the beginning and another at the end of the study. Following a six-month period of treatment, they found no significant difference in cognitive functions of the patients treated with NAC compared with those who received placebo (Dean et al., 2012).

Consequently, (As it follows from the studies indicated above), the impairment in cognitive functions, which occurs along with an increase in oxidative stress over the process of disease, cannot be reversed by reducing the oxidative stress. (by means of antioxidant therapy) Further studies are needed about new/various pharmacotherapy methods or life style changes to provide insights into improvement of cognitive functions.

CONCLUSION

In conclusion, our study suggests that: /Our study has reached the following conclusions:

The patients with BD receiving treatment had an oxidative stress level lower than the control group. We believe that this lower level might be associated with the pharmacotherapy (the drug therapies used). (The results of FAB (that are consistent with those observed in previous research show that) The patient group had statistically significant lower FAB scores than healthy individuals. Compared with the control group, the patient group had lower scores in the sub-scores of the Stroop test. The study found a negative correlation between the FAB results and TOL and OSI values. This explains why the impairment of cognitive functions in patients did not respond to antioxidant treatment. As a result, further studies with larger samples need to be performed to obtain more comprehensive results.

LIMITATIONS

As is the case in all cross-sectional studies, our study was also limited by the lack of information on the previous cognitive performances of the patients. To obtain more sound results concerning the impairments in cognitive functions of patients with BD, and changes in the parameters of oxidative stress that occurs as a result of the disease, further longitudinal studies need to be conducted that enable us to monitor, from the first attack onwards, the correlation of these data with the duration of the disease and attack frequency.

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