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Nitric Oxide and Asymmetrical Dimethylarginine Levels in Acute Mania

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ÖZET:

Akut mani nöbetinde nitrik oksit ve asimetrik dimetilarjinin düzeyleri

Amaç: İki uçlu duygudurum bozukluklarının (İDB) biyokimyasal boyutu üzerine olan çalışmalar yakın zamanda artış göstermiştir. Nitrik oksitin (NO) ve NO'nun sistem içi baskılayıcısı olan asimetrik dimetil arginin (ADMA)'nin işlevi, duygudurum bozuklukları, şizofreni, otizm, obsesif kompulsif bozukluk ve Alzheimer hastalığında incelenmiş ve anlamlı sonuçlar bulunmuştur. Bu çalışmada, İDB duygudurum bozukluğu hastalarının akut mani dönemlerinde, plazma NO ve eş zamanlı plazma ADMA seviyelerinin sağlıklı kontrollerle karşılaştırılması amaçlanmıştır.

Yöntem: Çalışmaya DSM-IV-TR'ye göre İDB-I mani nöbeti tanısı konulan 30 hasta alınmıştır. Sağlıklı kontrol grubu olarak hasta grubu ile yaş, cinsiyet, sigara kullanımı açısından eşleştirilmiş aynı sayıda kişi alınmıştır. Hasta grubuna tanı koymak, hasta ve çalışma gruplarında ilave ruhsal bozuklukları dışlamak için, SCID-I, hastalık şiddetini değerlendirmek için Hamilton Depresyon Ölçeği, Young Mani Ölçeği, Montgomery Asberg Değerlendirme Ölçeği kullanılmıştır. Çalışma ve kontrol grubundan, plazma NO seviyesi ve eş zamanlı ADMA seviyesi tayini için, 2 tüp plazma örneği alınmıştır.

Sonuçlar: Hasta ve kontrol gruplarının plazma NO ve ADMA seviyeleri karşılaştırıldığında, hasta grubunda kontrol grubuna göre plazma NO seviyelerinin istatistiksel olarak anlamlı derecede düşük, ADMA seviyelerinin ise istatistiksel olarak anlamlı derecede yüksek olduğu bulunmuştur.

Tartışma: Çalışmamız, İDB-I etiyopatogenezinde, NO'nun ve ADMA'nın işlevi ve karmaşık nörotransmitter sistemleri arasındaki ilişkiyi anlamaya katkıda bulunabilir.

Anahtar sözcükler: Bipolar bozukluk, mani, nitrik oksit, asimetrik dimetilarjinin

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ABSTRACT:

Nitric oxide and asymmetrical dimethylarginine levels in acute mania

Objective: Changes in NO synthesis have been shown in studies regarding NO function in mood disorders, schizophrenia, autism, obsessive compulsive disorder and Alzheimer's disease. The aim of this study was to compare plasma NO and simultaneous plasma ADMA levels of bipolar patients in acute mania with healthy controls.

Methods: A group of 30 patients experiencing a manic episode and diagnosed as having bipolar disorder according to the DSM-IV TR criteria were included in the study. The healthy control group consisted of the same number of age and sex-matched individuals with a similar smoking status. The SCID-I, Hamilton Depression Scale, Young Mania Scale, and Montgomery Asberg Assessment Scale were used to evaluate clinical condition and to exclude any concurrent mental disorders in both groups. Two tubes of blood were collected from all participants to examine plasma NO and ADMA levels.

Results: Plasma NO levels of patients were found to be significantly lower, whereas the ADMA levels were significantly higher than the control group.

Conclusions: The results of this study can contribute to a better understanding of the role of inflammatory processes in acute mania in relation to NO and ADMA, which are suspected to be involved in the pathogenesis of various neuropsychiatric disorders.

Key words: Bipolar disorder, mania, nitric oxide, asymmetrical dimethylarginine

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INTRODUCTION

Bipolar affective disorder (BAD) is a chronic and common mental disorder that increases morbidity and mortality and results in a serious decrease in functioning (1-3). Even though the underlying mechanism for BAD has not been completely understood, studies about the biochemical mechanisms in this disorder have increased recently (4-7). Although oxidative and antioxidative molecules have been studied in many mental disorders, studies about them in BAD are scarce (8-10).

Nitric oxide (NO) is defined as an endothelium-derived

relaxing factor. It is produced endogenously by NO synthase enzyme from the amino acid L-arginine. It acts as a messenger molecule in biological systems and plays a role in morphogenesis of the nervous system, synapse formation, neurotransmitter release, and gene expression (11).

In the central nervous system, NO functions as a major messenger molecule regulating neurotransmission and vasodilatation. In the brain it regulates noradrenaline (NA) and dopamine (DA) release, memory, learning, awareness, the sense of smell, and food and liquid intake (12). In addition to regulating the release of NA and DA, NO interacts with them and changes their regulating influences in synaptic transmission. There are studies which report that NO facilitates calcium-induced DA flow, especially in the basal ganglia. It has been demonstrated that in rat striatum, there is a relation between NO-releasing neurons and DA-releasing neurons (13). Also, it has been found that NO changes serotonin (5-hydroxytryptophan; 5-HT) into an inactive form, and this transformation has an influence on neuromodulation. Similarly NA also has been reported to react with NO (14).

In studies on the function of NO in mood disorders, schizophrenia, autism, obsessive compulsive disorder, and Alzheimer's disease, quantitative changes in the NO production have been observed, that consequently showed a correlation between NO function and neuropsychiatric disorders (15-17) .

Asymmetric dimethylarginine (ADMA) is an endogenous competitive inhibitor of the nitric oxide synthase (NOS) enzyme. Observations show that ADMA accumulation may have an important role in the regulation of signal transduction in the NO system and this accumulation gives a new mechanism for studying NO production in the brain (18). ADMA has been shown to increase in many medical conditions and the function of ADMA in the pathogenesis of mental disorders has been investigated in Alzheimer's disease and depressive disorders (19,20).

NO is suggested to play a role in mood disorders, especially in the pathogenesis of depression (16,21). The occurrence of interferon-induced depression mediated through the NOS gene supports the NO hypothesis in the pathogenesis of depressive disorders. Selley (2004) showed that the plasma NO level was lower in patients with depressive disorder (20).

In a study by Savaş et al. (2002) in which patients with acute mania were compared with a healthy control group, plasma NO levels were demonstrated to be increased in patients with acute mania compared to the control group and abnormalities were present in the NO/NO synthase pathway (12). The researchers, who showed a negative relation between ADMA and NO levels, reported that elevated ADMA levels may have an influence on signal transduction by decreasing the production of NO and may have a role in the pathogenesis of depression (20,22,23).

Previous studies have suggested that BAD and schizophrenia share many epidemiological and clinical characteristics (24). Studies reporting that schizophrenia and BAD have common underlying mechanisms support the fact that either NO production and/or NOS system damage may play a role in both disorders (15,25). In various studies in which schizophrenic patients were compared to control groups, it has been shown that the nitrite levels of polymorphonuclear leucocytes in these patients were decreased and remained stable; hence it was concluded that a functional disorder in NO/NOS system might be contributing to the psychopathology of schizophrenia (17,25,26). In contrast to these findings, another study indicated that significantly high NO levels in the erythrocytes of schizophrenic patients, who were receiving antipsychotic treatment, suggests a potential function of NO in the pathogenesis of schizophrenia (27). The functions of NO have been extensively investigated in mood disorders and in psychiatric disorders other than schizophrenia, but controversial results were obtained (14).

The aim of this study was to compare the plasma NO and simultaneous plasma ADMA levels in patients with BAD during a manic episode with those of a healthy control group to understand the role of NO and ADMA, an endogenous inhibitor of NO and NOS.

METHODS

Sampling Groups

Thirty patients with acute mania, who were diagnosed with BAD by using the Structured Clinical Interview for DSM- IV Axis I Disorders (SCID-I) and who presented to the psychiatry outpatient clinic or emergency room of

Karadeniz Technical University Farabi Hospital between November 2008 and November 2009, were included in the study.

Manic patients, who had not taken any kind of psychotropic medication during the previous month, were recruited into the study. The severity of the manic episode was determined by the Young Mania Rating Scale (YMRS), scores higher than 12, the Montgomery Asberg Rating Scale (MADRS), scores lower than 12, and the Hamilton Depression Rating Scale (HAM-D), scores lower than 7.

The patients, who were diagnosed with any mental disorder other than BAD by the SCID-I, any neurological and physical disease history of a head trauma leading to unconsciousness, mental retardation, any drug or alcohol abuse or dependency or who were using any psychiatric medication were excluded from the study.

The SCID-I was also applied to the control group, consisting of 30 volunteers who were matched with the patient group with respect to age, sex, and smoking status. Participants with severe physical or neurological disorders, concussion of the head, mental retardation, current use of any psychotropic medication, or any drug or alcohol abuse or addiction were excluded from the study.

The study was financially supported by the Research Projects Coordination Unit of Karadeniz Technical University. The assessment procedures were initiated after the approval of the protocol by the Ethics Committee of Karadeniz Technical University, Faculty of Medicine. Prior to being enrolled in the study the participants gave written informed consent after being provided standard education about the study. Two fasting blood serum samples were obtained from the patient and healthy controls to measure NO and simultaneous ADMA levels before initiating mood stabilizing treatment. Clinical interviews, the SCID-I, HAM-D, YMRS, and MADRS scales and collection of plasma samples were performed by the same psychiatrist.

Equipment

Socio-Demographic Data Form: This form was used to evaluate the socio-demographic variables (age, sex, marital status, etc.) and clinical characteristics (number of episodes, type of episode, duration of episode etc.) of the participants.

Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I): The SCID-I, was developed in 1987 for the purpose of diagnosing DSM-III-R axis I disorders (28). It was later updated for the DSM-IV (29).

Montgomery Asberg Depression Rating Scale (MADRS): This is a scale developed to measure the severity and the change in severity of core symptoms of depression in patients diagnosed with depression. It consists of 10 items where each item is scored between 0 and 6. In this study, the MADRS score was determined to be <12 for a pure manic episode. The validity and reliability study of the Turkish version was performed by Özer et al. (2001) (30).

Young Mania Rating Scale (YMRS): This scale covers the core symptoms of the manic episodes of bipolar disorder as rated from mild to severe. The validity and reliability study of the Turkish version was performed by Karadağ et al. (2002) (31). Euthymia is considered to be a YMRS score <12. In this study, the YMRS score was taken as >12 for acute mania.

Hamilton Depression Rating Scale (HAM-D): The HAM-D is commonly used to determine the severity of symptoms in depression. The highest possible score is 53 and scores of 14 and above indicate depression. In this study, the HAM-D score was determined to be <7 for a pure manic episode. The validity and reliability of the Turkish version was performed by Akdemir et al. (1996) (32).

Sample Collection and Preparation

Biochemical assessments were carried out by the Department of Biochemistry of Karadeniz Technical University Farabi Hospital. The participants were asked not to consume food, alcohol, or drugs 12 hours before the blood collection procedure. Blood samples were centrifuged for 10 minutes at 3000 rpm right after collection in the biochemistry research laboratory. The separated serum and plasma samples were stored at -80ºC. The collected samples were examined in a single measurement session.

NO level measurement: Serum NO level determination was performed using the Griess method with a commercial "Nitric Oxide (NO_2^- / NO_3) Assay Kit" (Assay Designs, Cat. No: 917-010). Absorbance values were measured

spectrophotometrically at 540 with a VERSA brand microplate reader (Molecular Devices in California, USA). The results were expressed in mmol/L unit.

ADMA activity measurement: ADMA serum levels were determined by using the ADMA ELISA (Immune Diagnostic, K7828-090417) commercial kit. Absorbance values were measured spectrophotometrically at 450 nm by taking the reference wavelength as 620 nm, with a VERSA brand microplate reader (Molecular Devices in California, USA). The results were expressed in mmol/L unit.

Statistical Analysis

Data analysis was performed by using SPSS for Windows, version 11.5 (SPSS Inc., Chicago, IL, United States). Whether the distributions of continuous variables were normal or not was determined by the Kolmogorov-Smirnov test. Data were shown as mean ± standard deviation or median (minimum-maximum), where applicable. While, the mean differences between groups were compared by Student's t test, the Mann Whitney U test was used for comparisons of median values. Nominal data were analyzed by Pearson's Chi-square test. The degree of association between NO and ADMA values was evaluated by Spearman's Rank Correlation test. A p value less than 0.05 was considered statistically significant.

RESULTS

Thirty patients diagnosed with a BAD manic episode were included in the study. As the healthy control group, 30 volunteers were matched with the patient group with respect to age, sex, and smoking status.

The mean age of the patient group was 37.67±13.67 years and for the control group was 37.63±13.57 years.

Table 1: Demographic data of the groups

	Patient group (n=30)	Control group (n=30)	p
Sex (n, %)			
Male: n (%)	15 (50.0)	15 (50.0)	1.000*
Female: n (%)	15 (50.0)	15 (50.0)	
Age (years)	37.6±13.6	37.6±13.5	0.992**
Smoking (n, %)			
No: n (%)	17 (56.7)	17 (56.7)	1.000*
Yes: n (%)	13 (43.3)	13 (43.3)	

n=number of patients, %=percentage,* Pearson Chi-square test, ** Student's t test.

Table 2: Mean rating scale scores of the study groups

	Patient group (n=30)	Control group (n=30)	p
MADRS	5 (0-11)	0 (0-5)	<0.001
YMRS	30 (14-45)	0 (0-2)	<0.001
HAM-D	3 (0-7)	0 (0-3)	<0.001

n=number of patients

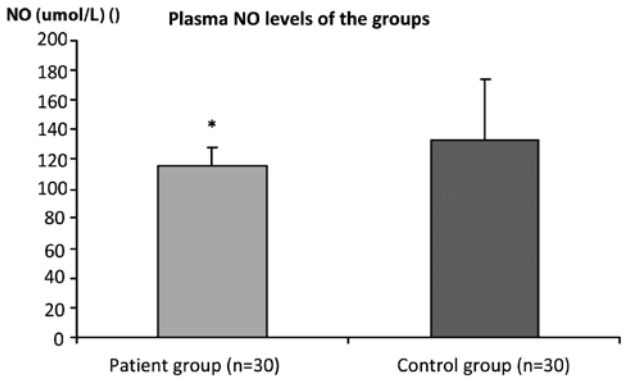

Figure 1: Comparison of NO levels between the control and patient groups (*: p<0.05)

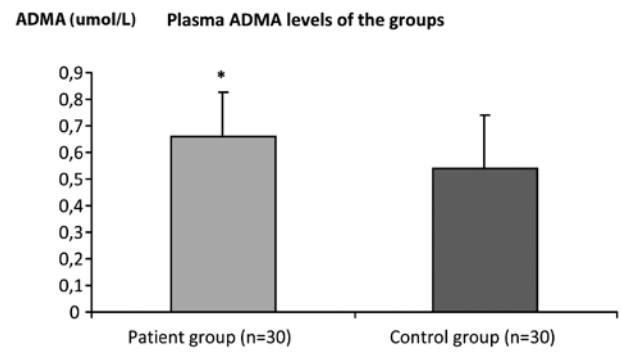

Figure 2: Comparison of ADMA levels between the control and patient groups (*: p<0.05)

Fifty percent of the patient and control groups were male and 50% (n=15) were female. Both in the patient and control groups, 43.3% of the participants (n=13) were current smokers. There was no statistically significant difference between the groups with respect to mean age, sex, or smoking status (p≥0.05) (Table 1).

The median MADRS total score was 5 (min 0 - max: 11) in the patient group, and 0 (min: 0 - max: 5) in the control group. The median YMRS score was 30 (min: 14 - max: 45) in the patient group, and 0 (min: 0 - max: 2) in the control group. The median HAM-D score was 3 (min: 0 - max: 7) in the patient group, and 0 (min: 0-max: 3) in

the control group. The MADRS, YMRS, and HAM-D scores were higher in the patient group compared to the control group. A statistically significant difference was found between the groups with respect to MADRS, HAM-D, and YMRS scores ($p<0.001$) (Table 2). Psychotic features besides mania were detected in 86.7% of the patient group (n=26).

Mean plasma NO levels were 115.47±12.26 μmol/L in the patient groupand 132.82±40.61 μmol/L in the control group. The NO level was significantly lower in the patient group compared to the control group ($p=0.032$) (Figure 1).

Mean plasma ADMA levels were 0.66±0.17 μmol/L in the patient group and 0.54±0.20 μmol/L in the control group. ADMA was significantly higher in the patient group compared to the control group ($p=0.014$) (Figure 2).

No statistically significant correlation was found between ADMA and NO levels of the patient group ($r=-.343$, $p=0.064$).

DISCUSSION

In this study, NO levels of the patients during acute mania were found to be statistically significantly lower, however ADMA levels were found to be statistically significantly higher compared to the healthy controls.

Hoekstra et al. (2006) investigated NO production and/or NOS function in patients with mood disorders. In his study, NO production and/or NOS function and tetrahydrobiopterin (BH4) levels were measured in a total of 4 patient groups consisting of 20 with BAD-I manic episodes, 12 with BAD-I depressive episodes, 20 with depressive disorder with melancholic features, 19 with depressive disorder with seasonal features, and a healthy control group. The citrulline-arginine ratio (Cit-Arg ratio) was used to demonstrate NO production and/or NOS function and the neopterin ratio was used for BH4 measurement. Cit-Arg and neopterin ratios in manic depressive, and euthymic periods after lithium treatment of BAD patients were found to be significantly lower as compared to both healthy control groups (15). The results of this study that are related to mania, in which NO production and/or NOS function were found to be lower than those of the normal controls, support the results of our study.

Selley (2004) demonstrated that the plasma ADMA and (E)-4-hydroxy-2-nonenal (HNE) levels significantly increased, however plasma NO level decreased to an significant extent in patients with major depression when compared to a healthy control group. This study, which also demonstrates a negative correlation between ADMA and NO levels, suggested that increased ADMA levels may decrease NO production and may decrease NO diffusion and NO dependent serotonin release to nerve cells from the endothelium; such a mechanism may explain the relationship between increased ADMA production and the onset of depression (20). In our study, plasma levels of ADMA were higher in the patient group. According to the results of our study, the decrease in NO production which is implicated in BAD etiology may be associated with increased ADMA levels. If these findings from both the study by Selley (2004) and our work, indicating increased ADMA, decreased NO levels, and the negative correlation between the two, are taken into consideration together, it might be claimed that these variables are related not only with a specific but also with all kind of mood disorders.

The efficacy of oxidative stress and the antioxidant enzyme activities were examined in another study in a pre- and post-treatment fashion. That study was performed in a heterogeneous sample consisting of a total of 30 patients with bipolar mania, bipolar depression, recurrent unipolar depression, and schizoaffective disorder. The NO level was lower in the pre-treatment group compared to the post-treatment group, and significantly lower compared to control group (33). Although the sampling was not homogenous, the results of this study support the findings of our study which was performed with only manic patients. In addition, there are some contradictory results that have reported higher NO levels in mania and bipolar depression (8,34). Controversial results have been obtained from studies in which the function of NO was extensively investigated in schizophrenia, mood disorders, drug addiction, and autism (14).

In a study in which the plasma ADMA levels of schizophrenic patients were compared with those of a healthy control group, plasma ADMA levels were shown to be significantly higher in drug-free schizophrenic patients compared to the healthy control group. Based on these results, researchers suggest that ADMA accumulation might be an intra-system control mechanism in the regulation of NO production in the brain, and might be associated with the pathophysiology of schizophrenia (18). Similarly, Srivastava et al. (2001) showed that the

nitrite levels of polymorphonuclear leukocytes from drug-free schizophrenic patients decreased, and in another study, that nitrate which is the metabolite of NO was shown to decrease in drug-free schizophrenic patients, however, a significant change was not seen in treated schizophrenic patients (26,35). In another study, plasma dimethylarginine levels and nitrate levels of drug-free first episode schizophrenic patients were higher and nitrate levels were significantly lower in the patient group compared to healthy controls. As a result, it was reported that a decrease in NO production with an endogenous NOS inhibitor may suppress signal transmission, and thus may have a role in the pathogenesis of schizophrenia (36).

In previous studies, it has been stated that BAD and schizophrenia share many epidemiological and clinical characteristics and both may have common neurobiological mechanisms (24,25). If we consider that 86.7% of our patient group had psychotic features, it may be suggested that NOS system damage may play a role in the emergence of mania with psychotic features. In this aspect increased the endogenous NOS inhibitor ADMA may decrease NO production in BAD just as it does in schizophrenia.

In our study, the importance of NO in the etiology of BAD and the effect of ADMA were investigated and the sample size was large enough to demonstrate dependable statistical analysis. Almost all previous clinical studies examining the inflammatory response in mood episodes included small sample sizes with various diagnoses that were not specific to an episode type. Controversial results obtained from all sort of studies depending on different type of mood episodes with different clinical conditions are not persuasive enough to make a final decision about the role of NO and ADMA. In studies using similar methodologies to ours, another limitation is whether or not the activity of peripheral NO production reflects the NO activity in the central nervous system. Some researchers have suggested that it does (17,37).

The results of our study point to a possible role of NO and ADMA in the emergence of psychotic mania. However, more studies examining the specificity of the mechanisms related to the type, clinical features, and the course of the episodes with larger and different homogeneous samples are needed for more reliable results on this subject.

The use of the SCID-I for the diagnostic evaluation in both groups and the stringent application of inclusion criteria for a single type of mood episode differentiate this study from many others. This study presents data that may be helpful in understanding the function of NO, ADMA, and their interrelation in the pathogenesis of BAD.

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