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Asymmetric dimethylarginine (ADMA) and treatment response relationship in male patients with first-episode schizophrenia: A controlled study

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ABSTRACT

Nitric oxide (NO) is thought to be involved in the pathogenesis of schizophrenia as well as many neuropsychiatric disease. Asymmetric dimethylarginine (ADMA) reduces the level of NO by inhibiting nitric oxide synthase (NOS) enzyme. In this study it is aimed to be investigated ADMA in patients with first-episode schizophrenia. In this study, according to DSM-IV diagnostic criteria for schizophrenia-like psychotic disorder, 49 male first-episode schizophrenia patients—whose mean age was 23.4 ± 3.5 year—and age and education matched 30 healthy male subjects were included for comparison. ADMA levels of the patients were measured before and after 2 months of therapy. In order to rule out the conditions that may affect the levels of ADMA, people whose physical examination and laboratory findings were within normal range were included in the study. In this study plasma ADMA levels of first-episode schizophrenia patients and control group were 3.6 ± 1.5 μmol/L and 1.02 ± 1.02 respectively. After 2 months of antipsychotic treatment plasma ADMA levels of the schizophrenia patients decreased compared to baseline. There was no relationship between the ADMA levels and the clinical severity of the disease. It is considered to be the role of ADMA in the etiopathogenesis of schizophrenia.

1. Introduction

Nitric oxide (NO) is a special molecule which serves as free oxygen radical, neuromodulator and neurotransmitter in peripheral and central nervous systems. It is thought that NO has an important role in the pathogenesis of schizophrenia and many other neuropsychiatric disorders. NO is synthesized by the enzyme nitric oxide synthase (NOS). Asymmetric dimethylarginine (ADMA) is synthesized by the enzyme protein arginine methyl transferase (PRMT) while the methylation of arginine amino acid (Vallance et al., 1992) decreases the production of NO by competing the L-arginine for nitric oxide synthase (NOS) (Boger et al., 2000; Beltowski and Kedra, 2006).

Limited number of studies have been published about the role of ADMA in psychiatric disorders. Das et al. (1996) demonstrated in their study that drug naive 16 schizophrenia patients had higher plasma ADMA level than 12 healthy control group. In the same study, it was also demonstrated plasma nitrate levels of the patients with schizophrenia lower than the control group (Das et al., 1996). In another study, plasma ADMA levels of schizophrenia patients were three fold higher than those of healthy controls and schizophrenia patients with multiple episodes have had the highest ADMA levels in the same study. (Celik et al., 2011). Aykut et al. (2012) studied with 30 patients diagnosed with bipolar manic episode and 30 healthy control group and they found ADMA levels of the patient group were higher but nitric oxide (NO) levels were lower than the healthy control group (Aykut et al., 2012).

The studies regarding the role of ADMA in psychiatric disorders are limited. Das et al. (1996), in a study of patients with schizophrenia, showed that plasma ADMA levels of patients were higher than the control group. In the same study, plasma nitrate levels of the patients with schizophrenia were detected lower compared to the control group (4). In another study, it has been shown that plasma ADMA levels of patients with schizophrenia were three times higher than in healthy controls and the patients who had suffered multiple schizophrenic exacerbations had higher plasma ADMA levels (5). In a

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study conducted in patients with bipolar mood disorder, plasma ADMA levels of the patients have been found to be higher than the control group whereas plasma NO levels were determined to be low (6).

Some of the studies reported that NOS or NO metabolites were higher in plasma of patients with schizophrenia than healthy control. Hence, the role of NO and ADMA in the etiopathogenesis of schizophrenia is not well elucidated. Though recent findings support the etiolopathological role of NO in schizophrenia, studies are cross-sectional.

In this study, it is intended the comparison of the ADMA levels in patients with first-episode schizophrenia like psychotic disorders with healthy controls and monitoring of the alteration after 8 weeks treatment period in order to rule-out any dilemma about the role of NO metabolism in schizophrenia etiopathogenesis. It will be the first study related to plasma ADMA levels and treatment response.

2. Methods

2.1. Study sample and procedure

Forty-nine patients—diagnosed with first-episode schizophrenia-like psychotic disorder according to DSM-IV diagnostic criteria—have been recruited into the study, and were compared with age and education matched 30 healthy control group. 49 patients were followed-up for 2 months.

Plasma ADMA levels were measured before treatment and after 2 months treatment period. For the measurements of ADMA levels, a High-Performance Liquid Chromatography (HPLC) method, which is defined by Chen et al. (1997), was used. Samples were prepared as follows: 5 mg of 5-sulphosalicilic acid (SSA) was added to 1 mL of plasma sample and this mixture was waited for 10 min at temperature of −20 °C. After that, in a refrigerated centrifuge at 4 °C, sample was centrifuged for 5 min at 7000 rpm. Supernatant was filtered through the 0.2 μL of filter into the violin. Samples have been studied as described below by the automized injection program.

ADMA	Method	Injection program	
89	Violin	OPA	90 μL, 89 (OPA) draw
91	Violin	HCL	9 μL draw from sample
92	Violin	Waste	99 μL mix 6 times
93	violin	Waste	Wait 3 min
			Inject to system

After this stage, system performed A–B gradient mobile phase in the following scheme.

	Mobile phase A %	Mobile phase B %
0 dk	95	5
6 dk	88	12
16 dk	60	40
28 dk	25	75
32 dk	0	100
34 dk	0	100
35 dk	95	5

Mobile A: 820 mL sodium acetate, 170 mL methanol, and 10 mL tetrahydrofurane.

Mobile B: 170 mL sodium acetate, 770 mL methanol, and 10 mL tetrahydrofurane.

Column Nova-pak C18 4 μL, 4.6 mm × 150 mm column were studied in the measurement. Flow rate was 1 mL/min, and working hours were given as 35 min.

The advantages of this method are that being specific for ADMA, not to cross-react with symmetric dimethylarginine (SDMA) or N^G-monometil-L-arginin (L-NMMA), having low detection limit and high reproducibility of the results. Disadvantages are demanding and costly (Siroka et al., 2007).

ADMA elevation caused by any medical condition was considered for exclusion and psychical examination was completed in patient and control groups. Serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic-pyruvic transaminase (SGPT) levels were measured for the assessment of liver functions; urea and keratin levels were measured for the assessment of kidney functions. By the way, to determine risky conditions for the vascular disease, triglyseride, cholesterol and blood pressure and to rule out of inflammatory diseases and infections, hsCRP measurements have been completed. Severity of the disease was evaluated by Brief Psychiatric Rating Scale (BPRS), the Scale for the Assessment of Negative Symptoms (SANS), the Scale for the Assessment of Positive Symptoms (SAPS) scales. The SANS was developed by Andreasen (1990). The BPRS was developed by Lukoff et al. (1993) and was translated into Turkish by Soykan (1989). The BPRS measures the severity of psychotic symptoms and some depressive mood symptoms in schizophrenia and in other psychotic disorders. This scale consists of 24 items. The SANS is scale designed to measure the level, distribution, and intensity of negative symptoms. İt is a 25-item instrument containing the following subscales: affective flattening, alogia, apathy, anhedonia and attention. The Turkish version was reported to be reliable by Erkoc et al. (1991a, 1991b). The SAPS was developed by Andreasen (1990). The SAPS is a scale designed to measure the level, distribution, and intensity of positive symptoms. İt is a 35-item instrument containing the following sub-scales: hallucinations, delusions, bizarre behavior, and formal thought disorder. The Turkish version was reported to be reliable by Erkoc et al. (1991a, 1991b).

Sociodemografic data collecting from BPRS, SANS, SAPS scales were applied all the patients that fulfill the inclusion criteria and Structured Clinical Interview for DSM-IV (SCID)-1 diagnosed with first episode schizophrenia-like psychotic disorder. After 12 h starvation, venous blood sample was collected from antecubital veins. After this procedure, antipsychotic medications were initiated to patients by their clinicians. A treatment process was conducted independently from research team. BPRS, SANS, SAPS scales were applied all the patients coming for the follow-up examination 2 months later, and second venous blood samples were collected after 12 h starvation from antecubital veins. All of the samples were centrifuged at 21 °C temperature, 2000*g* for 10 min and kept at −80 °C until the analysis time.

2.2. Statistical analyses

Data analyses were performed using SPSS 15.0 version (SPSS Inc., Chicago, IL, United States). Kolmogorov–Smirnov test was used to determine whether continues variables matched normal distribution or not. Investigating whether there is a difference in terms of discrete variables between groups Pearson chi-square test; whether there is a difference between continuous variables Student-*t* test was used when parametric conditions provided, otherwise Mann Whitney *U* test was used.

Table 1
Patient clinical scale scores before and after antipsychotic treatment.

	Before treatment ($N=49$)	After treatment ($N=49$)	Statistical	
			t	*p*
SANS	40.80 ± 13.63	20.25 ± 8.44	21.79	0.001*
SAPS	67.09 ± 12.79	23.56 ± 7.54	42.49	0.001*
BPRS	54.98 ± 8.97	18.63 ± 6.80	34.82	0.001*

t: dependent group *t* test.

* $p < 0.001$.

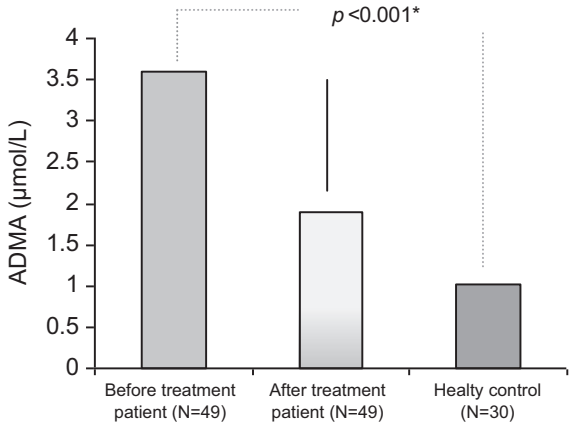

Fig. 1. Comparison of the ADMA levels of patient and control groups, before and after treatment.