Original article / *Araştırma*

A potential biomarker for bipolar I disorder: serum arginine vasopressin levels

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ABSTRACT

Objective: *The neuropeptide arginine vasopressin (AVP) has effects on behavior and stress regulations which are impaired in bipolar disorder (BD). Only a very limited number of studies have investigated AVP levels in bipolar disorder in contrast to depressive disorders. The study aimed to investigate serum AVP levels during the manic, depressive, or remission periods and after treatment response in patients with bipolar I disorder (BD-I) and healthy controls.* ***Methods:*** *The study consisted of 67 patients with BD-I and 24 healthy controls. The patients were in the manic, depressive, or remission periods of BD-I. Serum AVP levels were assayed in the three groups of patients with BD-I and the controls at the study onset. Then, a second measurement of the AVP levels were carried out in the manic or depressive periods after treatment response. The treatment response was defined as a 50% decrease in the young mania rating scale and the Hamilton Depression Rating Scale scores for manic and depressive episodes, respectively.* ***Results:*** *The main finding was the significantly lower serum AVP levels in BD-I during manic, depressive, or remission periods compared to healthy controls. After-treatment-response serum AVP levels in depressive BD-I patients increased to the levels of healthy controls and became higher than in the remission period of BD-I.* ***Conclusions:*** *The global reduction in serum AVP levels may be an indicator of impaired neuronal function and neuroprogressive deterioration seen in BD. Notably, given the increased AVP levels in major depressive disorder, serum AVP levels may contribute to distinguishing depressive BD-I from major depressive disorder.* ***(Anatolian Journal of Psychiatry 2017; 18(3):195-202)***

Keywords: *bipolar I disorder, arginine vasopressin, manic episode, depressive episode, bipolar remission, treatment response*

Bipolar I bozukluğu için potansiyel bir biyomarker: Serum arjinin vasopressin düzeyleri

ÖZ

Amaç: *Bir nöropeptid olan arjinin vasopressin (AVP), davranış ve stres düzenlenmesi üzerinde etkiler gösterir. Bu düzenlenme bipolar bozuklukta hasar görmüştür. Depresif bozuklukların aksine bipolar bozuklukta çok az sayıda çalışma AVP düzeylerini araştırmıştır. Bu çalışmada manik, depresif ve remisyon dönemleri sırasında ve tedaviye yanıttan sonra bipolar I bozukluğu (BB-I) olan hastalarda ve sağlıklı kontrollerde serum AVP düzeylerinin araştırılması amaçlanmıştır.* ***Yöntem:*** *Çalışmaya BB-I olan 67 hasta ve 24 sağlıklı kontrol alınmıştır. Hastalar BB-I'in manik, depresif ve remisyon dönemlerindeydi. BB-I olan hastaların üç grubunda ve kontrollerde çalışma başlangıcında serum AVP düzeyleri ölçülmüştür. Daha sonra manik ve depresif atakta olan hastalarda tedaviye yanıttan sonra ikinci kez serum AVP düzeyleri ölçülmüştür. Tedaviye yanıt, manik ve depresif hastalar için sırasıyla Young Mani Derecelendirme Ölçeği ve Hamilton Depresyon Derecelendirme Ölçeği puanlarında %50 azalma olarak tanımlanmıştır.* ***Bulgular:*** *Sağlıklı kontrollerle karşılaştırıldığında BB-I'in manik, depresif ve remisyon*

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dönemlerinin tamamında anlamlı şekilde daha düşük serum AVP düzeyleri çalışmanın temel bulgusudur. Tedaviye yanıt sonrasında depresif BB-I olan hastalarda serum AVP düzeyleri sağlıklı kontrollerin düzeyine yükseldi ve BB-I'in remisyon dönemindekinden daha yüksek duruma gelmiştir. ***Sonuçlar:*** *Serum AVP düzeylerindeki global azalma bipolar bozuklukta görülen bozulmuş nöronal işlevin ve ilerleyici nöronal yıkımın bir göstergesi olabilir. Özellikle majör depresif bozukluktaki artmış AVP düzeyleri dikkate alındığında, serum AVP düzeyleri depresif BB-I'in majör depresif bozukluktan ayırt edilmesine katkı sağlayabilir.* ***(Anadolu Psikiyatri Derg 2017; 18(3):195-202)***

Anahtar sözcükler: *Bipolar I bozukluk, arjinin vasopressin, manik nöbet, depresif nöbet, bipolar remisyon, tedavi yanıtı*

INTRODUCTION

The neuropeptide arginine vasopressin (AVP) has modulatory effects on homeostasis and behavior. AVP, which is abundantly available in the brain, is mainly synthesized in the magnocellular and parvocellular neurons of the paraventricular nucleus (PVN) and supraoptic nucleus (SON) of the hypothalamus. AVP is also expressed in the hypothalamic suprachiasmatic nucleus (SCN), the central nucleus of the amygdala (CeA), the bed nucleus of the stria terminalis (BNST), and other regions of the brain.[1] AVP has widespread physiological effects on the hypothalamo-pituitary-adrenal (HPA) axis, social behaviors (e.g., pair-bonding, parental behavior, and social interaction and communication), learning, memory, aggression, anxiety, sensorimotor gating function, and circadian rhythmicity.[2-4]

Because of its abundant availability in the brain and having effects on behavior, AVP has been investigated in a number of psychiatric disorders including schizophrenia, schizoaffective disorder, major depressive disorder (MDD), bipolar disorder (BD), anxiety disorders, post-traumatic stress disorder, personality disorders, dementia, autism spectrum disorders, eating disorders, and attention deficit hyperactivity disorder.[3,5-8] However, few studies have investigated AVP levels in patients with BD, although these patients display a variety of behavioral problems, such as aggression, unusual sexual behavior, decreased sleep, impaired social interaction and communication, distractibility, and excessive involvement in pleasurable and risky activities,[9] and also have a dysfunctional HPA axis.[10] The reason for the small number of studies may be the heterogeneous nature of BD characterized by a relapsing and remitting course with different episodes including mania, hypomania, or depression.

In the literature, there are conflicting findings regarding AVP levels in BD. Early studies of AVP levels in affective disorders have led to a hypothesis that AVP function is decreased during depression and augmented during mania.[11] This hypothesis was supported by some studies reporting increased cerebrospinal fluid (CSF) AVP levels[12] and increased plasma vasopressin-neurophysin (hNPI) levels[13] in manic patients, whereas a contradictory study reported increased CSF hNPI levels in the depressive episode of BD.[14] However, these studies suffered from methodological problems such as a very small number of subjects and lack of healthy controls. On the other hand, CSF AVP levels in euthymic BD and healthy controls have been reported to be similar.[15] Yet, a recent study found lower serum AVP levels in BD with psychotic features compared to healthy controls.[5] The different findings among the studies may stem from the different sample sizes, the heterogeneous groups of patients and controls, and the various assay methods used.

With regard to measurement of peripheral AVP levels, two criticisms may arise. First, peripheral AVP levels have a close correlation with plasma osmolality. In contrast, clinical studies in patients with MDD, BD, and schizophrenia showed no correlation between plasma AVP levels and osmolality.[12,16] Consistent with these studies, another study repeatedly measured urine osmolality and assayed plasma AVP lev-els in patients with BD, and no correlation was reported.[17] Second, peripheral AVP levels do not correlate with central AVP levels. A recent study in patients without psychiatric disorders supported this criticism,[18] but a high correlation between CSF and plasma AVP levels in depressive and manic patients was also found.[12] More recently, using the enzyme immuno-assay (EIA) method, some studies demonstrated that peripheral AVP levels show reliable correlations with CSF AVP levels.[5,19] Consequently, evidence suggests that measurement of peripheral AVP levels with the EIA method is reliable and reflects the central AVP function.

Given the heterogeneous nature of BD, inves-

tigating AVP levels in BD during active epi-sodes and after treatment may provide useful information. To our knowledge, no research has used this study design in the literature to ex-plore AVP levels in BD. Hence, we planned to investigate serum AVP levels in BD type I (BD-I) during manic, depressive, or remission peri-ods and after treatment response in a sample of subjects in whom we previously reported serum oxytocin levels.[20] We hypothesized that serum AVP levels might show differences between different periods of BD-I and healthy controls and also between active periods of BD-I and after treatment response.

METHODS

Ethics

This study was approved by the Ethics Committee of Erciyes University Faculty of Medicine. The objectives and procedures of the study were explained to the patients and controls, and their written informed consents were obtained. The study was carried out in accordance with the Declaration of Helsinki.[21]

Subjects

The study consisted of 67 (39 males and 28 females, age range: 18-64) patients with BD-I and 24 (14 males and 10 females, age range: 24-52) healthy individuals. The patients enrolled in the study while they were in the manic (10 males and 12 females), depressive (13 males and 8 females), or remission (16 males and 8 females) periods of BD-I. The patients were diagnosed independently by two psychiatrists using clinical interviews according to DSM-IV-TR diagnostic criteria, although they had an established diagnosis and were receiving treatment with at least one drug on an inpatient or outpatient basis at the Psychiatry Clinic of Erciyes University Faculty of Medicine. These medications used by the patients are presented in Table 1.

The patients and controls were selected by performing physical, psychiatric and neurologic examinations, routine blood chemistry (e.g., complete blood counts, electrolyte levels, glucose levels, lipid profile), and liver, thyroid, and renal function tests.

Exclusion criteria for the patients included the following: electroconvulsive therapy within the last six months, any known metabolic or endocrine disorder, a current or past substance use disorder other than cigarette smoking, and neurological conditions such as epilepsy or head trauma that could result in organic brain disorder. Additional exclusion criteria for female patients were as follows: menstrual irregularity, confirmed or suspected pregnancy, being in the lactation or parturition period, and receiving oral contraceptives or hormone therapy. Exclusion criteria for the controls were as follows: a current or past psychiatric, neurologic, endocrine or metabolic disorder, and the same additional criteria for the female patients.

Table 1. Medications used by the bipolar I disorder patients

	Manic (n=22)	Depressive (n=21)	Remission (n=24)
MSA[a]	1	-	8
MSA+AAP[b]	12	9	13
MSA+AAP+CAP[c]	3	8	-
MSA+AD[d]	-	-	2
AAP	-	2	-
AAP+CAP	3	-	-
AAP+AD	-	2	1
CAP	3	-	-
BDZ[e]	3	1	-

[a]Mood stabilizing agent; [b]Atypical antipsychotic; [c]Conventional antipsychotic; [d]Antidepressant; [e]Benzodiazepine

The sociodemographic characteristics of all subjects and clinical course characteristics of the patients are presented in Table 2.

Design

The study was designed to investigate serum AVP levels at two time points. At the study onset, the three groups of patients with BD-I and the healthy controls were evaluated. At the second time point, the patients in the manic or depressive episodes were evaluated when they responded to the treatment within the 6-month follow-up (Figure 1). The treatment response was defined as a 50% decrease in the Young Mania Rating Scale (YMRS)[22] and the Hamilton Depression Rating Scale (HDRS)[23] scores for manic and depressive episodes, respectively.

Procedure

Blood samples for AVP assays were obtained from an antecubital vein between 08:00 and 09:00 hours in the morning after fasting during the previous eight hours. The samples were collected in standard plain vacuum tubes and centrifuged at 1000 rpm for 15 min at 4°C within 30 minutes of collection to obtain serum

Table 2. Sociodemographic characteristics of all subjects and clinical course characteristics of the bipolar I disorder patients

	Manic Comparison n=22 Mean±SD	Depressive n=21 Mean±SD	Remission n=24 Mean±SD	Controls n=24 Mean±SD
Age (years)	33.14±12.40	36.19±12.51 χ^2=1.92, df=3, p=0.589	36.00±11.40	34.42±8.30
Duration of education (years)	11.41±2.94	11.38±2.99 χ^2=2.87, df=3, p=0.413	10.67±3.94	12.25±4.19
BMI[a] (kg/m2)	26.01±5.94	27.41±4.96 χ^2=0.89, df=3, p=0.828	26.78±4.25	25.78±3.04
Number of cigarettes smoked per day	8.23±11.78	6.86±8.88 χ^2=0.18, df=3, p=0.981	7.13±9.17	9.96±13.79
Gender (male/female)	10/12	13/8 χ^2=2.29, p=0.513	16/8	14/10
Duration of disease (months)	107.68±119.26	116.00±66.74 χ^2=2.17, df=2, p=0.338	123.08±94.05	-
Number of manic episodes	3.86±4.14	2.57±2.71 χ^2=3.03, df=2, p=0.220	3.50±3.71	-
Number of depressive episodes	1.18±1.40	2.76±2.45[b] χ^2=8.90, df=2, p=0.012	1.75±2.07	-
Number of mixed episodes	0.73±1.03	0.52±0.60 χ^2=0.41, df=2, p=0.980	0.79±1.25	-
Duration of last episode	1.66±0.68	1.95±0.76 χ^2=1.78, df=2, p=0.410	1.75±0.71	-

[a] Body mass index, [b] Number of previous depressive episodes are higher in depressive patients than in manic patients

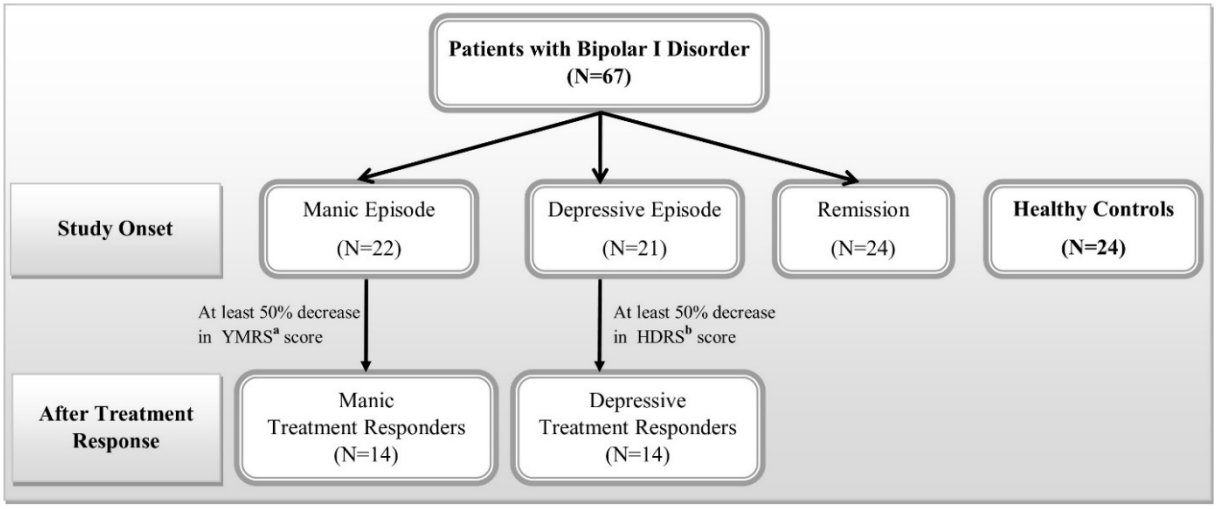

Figure 1. The study design
[a] The Young Mania Rating Scale, [b] The Hamilton Depression Rating Scale

samples, which were stored at -70° C until analyses were performed. After a 50% de-crease was achieved in the YMRS and HAM-D scores during follow-up, a second blood sam-pling was carried out in manic or depressive BD-I patients.

Biochemical analysis

Serum samples were evaluated by using an ELISA test device (Sunrise Basic Tecan, Tecan Austria GmbH) at the Biochemistry Research Laboratory of Erciyes University Faculty of Medicine. Serum AVP levels were assayed with EIA [PHONEIX Pharmaceuticals, Inc. (Arg8)-Vasopressin (Human, Rat, Mouse, Ovine) EIA Kit, Catalog No. EK-065-07 (assay range: 0-100 ng/ml, sensitivity; minimum detectable con-centration=0.06 ng/ml)]. The intra-assay and the inter-assay coefficients of variation were <10% and <15%, respectively. All samples were run at the same time. The obtained optic density values were converted into serum concentration values according to the formula calculated from linear regression analysis.

Statistical analyses

The normality of the data was evaluated by the Kolmogorov-Smirnov test. The chi-square test was used to compare the gender distribution of the groups. For the demographic and clinical data, the Kruskal-Wallis test was applied for the data without normal distribution, and the post hoc Mann-Whitney U test was used when intergroup differences were found.

With the number of cigarettes smoked per day, age, gender, and body mass index (BMI) as the covariates, MANCOVA was performed to com-pare the AVP values of the groups. Bonferroni correction was used to avoid type 1 error. Then, with the same covariates, serial ANCOVAs were carried out to determine which group dif-fered from the other(s) when there were statis-tically significant differences. For the compari-son of the pre-treatment and post-treatment AVP levels of the manic and depressive BD patients, the paired t-test was used. Spear-man's or Pearson correlation analyses were carried out depending on the normality of the data. Results are presented as mean±standard deviation, and all p-values are two-sided. The statistical signifi-cance level was set at $p<0.05$.

RESULTS

Sociodemographic and clinical characteristics

Age, duration of education, body mass index (BMI), gender, and number of cigarettes smoked per day did not significantly differ be-tween the patient and control groups (Table 2). For the clinical course characteristics, the only significant difference was the higher number of previous depressive episodes in depressive BD-I patients than in manic BD-I patients ($z=-2.84$; $p=0.005$) (Table 2). In manic BD-I pa-tients, the mean YMRS score decreased by 70.7% after treatment response (25.73±6.08 and 7.53±2.48 before and after treatment re-sponse, respectively), and, in depressive BD-I patients, the mean HDRS score decreased by 82.7% after treatment response (25.00±4.47 and 4.33±1.59 before and after treatment re-sponse, respectively). The YMRS and HDRS scores of patients in the remission period of BD-I were 2.46±1.72 and 4.37±1.38, respec-tively.

AVP levels at the study onset

When age, gender, BMI, and the number of cigarettes smoked per day were included as covariates, significantly lower serum AVP levels were found in the manic, depressive, or remis-sion periods of BD-I patients as compared to controls [$F=18.04$, $df=(1, 44)$, $p<0.001$; $F=9.20$, $df=(1, 43)$, $p=0.004$; and $F=22.83$, $df=(1, 46)$, $p<0.001$, respectively] (Table 3 and Figure 2).

AVP levels after treatment response

With age, gender, BMI, and the number of cigarettes smoked per day as covariates, serum AVP levels were significantly lower in manic BD-I patients after treatment response than in controls [$F=10.20$, $df=(1,36)$, $p=0.003$]. After treatment response, the serum AVP levels of depressive BD-I patients were significantly higher than those of BD-I patients in the remission period [$F=5.17$, $df=(1,36)$, $p=0.030$] (Table 3 and Figure 2).

AVP levels before and after treatment response

In manic or depressive BD-I patients, paired comparisons of serum AVP levels did not show any significant difference between before and after treatment response (for manic patients during episode 0.891±0.195 ng/ml, n=14 vs. after treatment response 0.929±0.20 ng/ml, n=14, $t=-0.55$, $df=13$, $p=0.591$; for depressive patients during episode 0.907±0.20 ng/ml, n=14 vs. after treatment response0.985±0.16 ng/ml, n=14, $t=-1.25$, $df=13$, $p=0.233$).

Table 3. Comparisons of serum arginine vasopressin levels* among bipolar I disorder patients and healthy controls

Assessment at the study onset				
Manic n=22 Mean±SD	Depressive n=21 Mean±SD	Remission n=24 Mean±SD	Controls n=24 Mean±SD	Comparison**
0.905±0.184[a]	0.926±0.202[a]	0.844±0.195[a]	1.098±0.142	F=4.246; df=(3, 87); ***p=0.008******
Assessment after treatment response				
Manic n=14 Mean±SD	Depressive n=14 Mean±SD	Remission n=24 Mean±SD	Controls n=24 Mean±SD	Comparison**
0.929±0.197[a]	0.985±0.164[b]	0.844±0.195[a]	1.098±0.142	F=8.217; df=(3, 72); ***p=0.001******

** (ng/ml), ** Age, gender, body mass index, and the number of cigarettes smoked per day were included as covariates*
**** p<0.05,*
[a] Lower than control group, [b] Higher than remission group

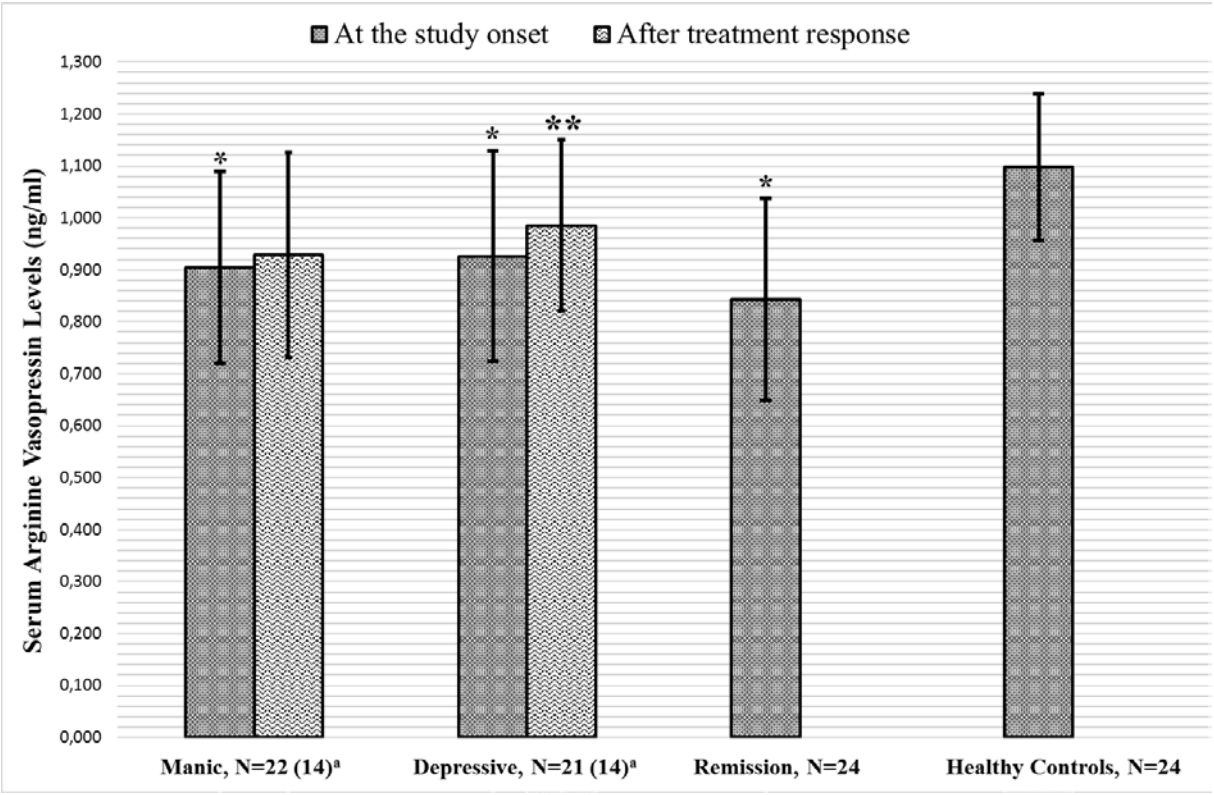

Figure 2. Comparison of serum arginine vasopressin levels among bipolar I disorder patients and healthy controls. Error bars represent standard deviations

** Lower than control group, p<0.05, ** Higher than remission group, p<0.05*
[a] After treatment response

DISCUSSION

Our main finding was the significantly lower serum AVP levels in BD-I patients during manic, depressive, or remission periods com-pared to healthy controls. After treatment re-sponse, there was a tendency towards an increase in serum AVP levels when compared with active periods in manic or depressive patients with BD-I, but this did not reach statistical significance. In manic patients after treatment response, serum AVP levels were still significantly lower than in healthy controls. On the other hand, in depressive BD-I patients after treatment re-sponse, serum AVP levels in-creased to the levels of healthy controls and became higher than those of BD-I patients in the remission period (Figure 2).

Showing overall lower serum AVP levels during manic, depressive, or remission periods in BD-I compared to healthy controls, our main finding may suggest a decrease in the function of and/or a decline in the number of AVP-producing neurons. Consistent with this idea, increased oxidative stress, which has been implicated as a biological marker in BD, can cause impaired neuronal function.[24] Additio-nally, postmortem explorations demonstrate smaller volumes of different brain regions including the basal ganglia, limbic areas, thalamus, and hypo-thalamus in patients with BD as compared to controls and patients with MDD.[25] Moreover, findings from neuroimaging studies indicate an atrophy in the hypothalamus and especially in the SON that is the major area for AVP-producing neurons.[26] Thus, an overall reduction in serum AVP levels may be an indicator of the neuroprogressive deterioration seen in BD.[27]

With regard to treatment effects, another im-portant finding of the present study is the increase in serum AVP levels after treatment response in manic or depressive BD-I patients. While this increase did not reach significance in manic BD-I patients, similar serum AVP levels were observed in healthy controls and depress-sive BD-I patients after treatment response, and depressive BD-I patients showed higher serum AVP levels as compared to BD-I patients in the remission period. The increase in serum AVP levels immediately after active episodes of BD-I may point towards an improvement in the neuronal functions due to the effects of medi-cations, especially mood stabilizers.[24] Further-more, these changes in serum AVP levels may be a mediator of treatment response or spon-taneous improvement in BD-I. Consequently, these changes may be useful clinical para-meters in BD-I. However, when the lower serum AVP levels during remission in BD-I are con-sidered, these immediate changes after treat-ment response may be temporary and restricted to the acute recovery period. This issue can be addressed by measurements of serum AVP levels at regular intervals in both treatment responders and non-responders.

With respect to other psychiatric disorders, our main finding is in agreement with the low AVP levels seen in schizophrenia in which neuro-degenerative features are more pronounced.[5] In contrast to BD-I, increased AVP levels have been demonstrated in MDD.[6] There are no reliable biological markers in differentiating depressive BD-I from MDD.[28] Thus, serum AVP levels together with oxytocin levels[20] may be a useful biological marker to differentiate de-pressive BD-I from MDD in clinical settings.

The results of the study must be interpreted with caution for several reasons. Mainly, because this study was carried out during a natural treatment course, it was not possible to exclude the effects of medications. Another limitation is the small number of manic and depressive BD-I patients after the treatment response because the researchers could not contact the patients.

In conclusion, we found lower serum AVP levels in different periods of BD-I compared to healthy controls. The overall reduction in serum AVP levels may be an indicator of the impaired neuronal function and neuroprogressive deteri-oration seen in BD. Serum AVP levels may be a useful parameter in the clinical follow-up of BD-I. Additionally, serum AVP levels may contribute to differentiating depressive BD-I from MDD. However, the number of clinical studies on serum AVP levels in BD-I is limited. Hence, prospective studies including all the periods of BD-I in large samples are needed to determine how AVP levels are related to the patho-physiology of BD-I and whether AVP levels are useful markers in clinical settings.

Teşekkür

Erciyes Üniversitesi Bilimsel Araştırmalar Birimi tarafından TSU-10-3046 proje numarasıyla desteklenmiştir.

Yazarların katkıları: *A.A.: Sorumlu yazar, çalışmanın tasarlanması, literatür araştırması, verilerin istatistiksel analizi ve yorumlanması, makalenin yazılması; T.T.: Çalışmanın danışmanlığı ve planlanması, verilerin yorumlanması, makalenin yazılması; C.U.: Çalışmanın projelendirilmesi ve yürütülmesi, materyalin toplanması, literatür araştırması, makalenin yazılması; E.K.: Çalışmanın planlanması, yöntem ve hizmet desteği, biyokimyasal ölçüm ve analizlerin yapılması, makalenin yazılması.*

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