

## Serum Brain-derived Neurotrophic Factor Levels among Euthymic Adolescents with Bipolar Disorder Type I

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### ABSTRACT

**Introduction:** Bipolar disorder (BD) has been increasingly associated with abnormalities in neuroplasticity and cellular resilience in brain regions that are involved in mood and that affect regulation. Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family that regulates neuroplasticity. The aims of the current study were to compare serum BDNF levels in euthymic adolescents with BD type I with those in controls and to investigate the relationship between clinical variables and serum BDNF levels in adolescents with BD type I.

**Methods:** Twenty-five adolescents diagnosed with BD type I and 17 healthy control subjects within the age range of 15–19 years were recruited. Diagnoses were made by two experienced research clinicians using the Kiddie and Young Adult Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version and the affective module of Washington University in St. Louis Kiddie and Young Adult Schedule for Affective Disorders and Schizophrenia-Present State and Lifetime. Blood samples were taken during euthymia, which was defined

as Young Mania Rating Scale and Hamilton Depression Rating Scale scores below 7.

**Results:** The comparison of BDNF serum levels between the case and healthy control groups revealed no significant differences. In the case group, BDNF levels were significantly lower in patients being currently treated with lithium.

**Conclusion:** Similar to normal BDNF levels in adult patients with BD, the normal BDNF serum levels that we found in the euthymic state in adolescents and early adulthood may be related to the developmental brain stage in our study group. It may also show a common neurobiological basis of pediatric and adult BD. Further investigations evaluating BDNF levels in different mood states could help identify the role of BDNF in the underlying pathophysiology of BD.

**Keywords:** Brain-derived neurotrophic factor, adolescent, bipolar disorder, neurotrophin

### INTRODUCTION

Bipolar disorder (BD) is a chronic and seriously debilitating illness affecting every age group. Pediatric BD (PBD) differs from the adult form of the disorder with significantly longer episodes, higher rates of mixed episodes, rapid cycling, prominent irritability, psychotic symptoms, and high rates of comorbid attention deficit hyperactivity disorder. It is unclear whether differences in clinical presentation between youth and adults with BD are due to differences in underlying etiologies or developmental differences in symptom manifestation (1). Although genetic and familial studies strongly suggest that a neurobiological basis underlies the pathophysiology of BD, its etiology is poorly understood (1).

Bipolar disorder has increasingly been associated with abnormalities in neuroplasticity and cellular resilience in brain regions that are involved in mood and that affect regulation (2) Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family and is involved in promoting synaptic efficacy, neural connectivity, and neuroplasticity (3). BDNF regulates neuronal development and survival and controls the activity of many neurotransmitters, including serotonergic, dopaminergic, and glutamatergic systems (3). The expression of BDNF is higher in the cerebral cortex and hippocampus, brain areas that are known to regulate complex brain functions such as memory and emotion (3). BDNF crosses the blood–brain barrier, and animal studies have indicated that its levels in the serum and plasma are highly correlated with its levels in the cerebrospinal fluid (4) Therefore, it is likely that peripheral BDNF levels provide important information about BDNF alterations in the brain.

There are several studies that have evaluated BDNF levels in adult patients with BD during different mood states with an aim of understanding the pathophysiology of BD. Although these studies have found serum and plasma BDNF level changes across different mood states, there are discrepancies among these studies. Two recent meta-analyses were performed to evaluate peripheral BDNF protein levels in adult patients with BD according to mood state. In these meta-analyses, it was shown that BDNF levels decreased during manic and depressive states and were neg-



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actively correlated with symptom severity (5,6). Although the frequency of normal levels decreased with age and duration of illness, BDNF levels were found to be normal in euthymia. In addition, pharmacological treatment for manic state increased BDNF levels (5,6). These results suggest that BDNF level changes can be used as a potential state-related biomarker for BD (5).

The main mood stabilizers lithium and valproic acid enhance the expression of BDNF, while the effects of typical and atypical antipsychotic agents on neurotrophic factor expression remain less well defined. The chronic administration of lithium or valproate has been shown to increase the expression of BDNF in the rat brain. This suggests that these mood stabilizers produce a neurotrophic effect mediated by the upregulation of BDNF in the brain (3).

Recent findings from a genetic study has suggested that the BDNF val66val genotype is a potential risk factor for the development of BD (7) and could increase the risk of developing rapid cycling BD (8). Although Geller et al. (9) found a significant relationship between BD and BDNF val66val genotype in prepubertal and early-onset BD probands and their parents, the report in the general literature linking BDNF polymorphisms and BD is inconsistent (10).

Limited research has been conducted on BDNF in youths with BD. In early-onset BD, the only study found in the literature found that BDNF mRNA levels in lymphocytes and BDNF protein levels in platelets of drug-free patients were significantly lower than those in normal control subjects. In addition, long-term treatment with mood-stabilizing drugs significantly increased the levels of BDNF mRNA in subjects with BD (11). These results are consistent with those in the adult literature.

In light of these studies, we designed this study to provide further data about the neurotrophin hypothesis in BD by evaluating serum BDNF levels in euthymic adolescents with BD type I. We investigated the relationship between clinical variables, such as the duration of illness and treatment, and serum BDNF levels in adolescents with BD type I. In this study, our case group comprised adolescents between the ages of 15 and 19 years as we aimed to investigate a more homogenous group regarding the neurodevelopmental stage and age-related changes in BDNF levels. Furthermore, we considered that the data originating from different developmental age groups is important for pathophysiologically determining age-specific differences. The assessment of serum BDNF levels in the euthymic state may answer whether changes in BDNF levels are state-related rather than trait-related in BD.

## METHODS

### Subjects

Twenty-five adolescents aged between 15 and 19 years with BD type I according to DSM-IV criteria and who were either already being followed up or who had received the diagnosis after admission to the university hospital Department of Child and Adolescent Psychiatry between June 2008 and June 2009 were included. Seventeen adolescents between the ages of 15 and 19 years and without any psychiatric diagnosis were included in the healthy control group and were selected from the epidemiologic catchment area of the university. Exclusion criteria in both groups included a history of seizures, severe head trauma causing a loss of consciousness for more than 10 min, history of pregnancy, mental retardation [ $\leq 70$  intelligence quotient (IQ)], or the presence of a chronic medical disorder. In the patient group, a history of drug, psychostimulant, antipsychotic, or antidepressant use within three months before diagnosis; pervasive developmental disorders; or schizophrenia were the exclusion criteria, while

patients who had comorbid anxiety or disruptive behavior disorder and those who received medical treatment were included.

### Clinical Assessment

Diagnoses were made by two experienced research clinicians using the Kiddie and Young Adult Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version (and the affective module of Washington University in St. Louis Kiddie and Young Adult Schedule for Affective Disorders and Schizophrenia-Present State and Lifetime (12). The diagnoses were reached by consensus. These interviews were translated into Turkish, and reliability was established (13). Manic and depressive symptoms were assessed using the Young Mania Rating Scale (YMRS) and the Hamilton Depression Rating Scale (HDRS), respectively. Patients were considered euthymic if they scored  $< 7$  on both YMRS and HDRS. The WISC-R intelligence scale was applied to all participants. Data regarding the socio-demographic features of the participants were collected by means of a form prepared by the researchers. The study protocol was approved by the institutional ethics committee of Dokuz Eylül University, and informed consent and assent were obtained from all adolescents and their parents.

### BDNF Assessment

To measure BDNF levels, 10 mL of blood was withdrawn from each subject by venipuncture into a free-anticoagulant vacuum tube between 09.00 and 10.00 am after at least 12-h fasting. The blood samples were kept in the tubes with an anticoagulant at room temperature for 30 min. Then, they were centrifuged at  $3000 \times g$  for 10 min at room temperature. After that, the serum samples were aliquoted and kept at  $-86^{\circ}\text{C}$  until they were assayed further. For the measurement of BDNF levels, a commercial sandwich ELISA kit was used (Millipore, Chemikine, and CYT306) according to the manufacturer's instructions (Millipore, Chemikine, CYT306). The samples from the case and control groups were run in random order, with a biochemist blind to the clinical diagnoses.

Briefly, the serum samples were added on 96-well microplates coated with BDNF monoclonal rat antibodies. The plates were incubated at  $4^{\circ}\text{C}$  for 17 h. To remove factors other than BDNF, four respective wash-outs were performed by an automatic equipment. After that, for the detection of the antigen-antibody complex [BDNF (antigen)-BDNF-rb (antibody)], a biotin-coated monoclonal antibody was added to the samples. Afterwards, streptavidin-tagged horseradish peroxidase was also added in this solution. Because each streptavidin molecule was bound to a biotin molecule (i.e., the BDNF molecules coming from the samples), every BDNF molecule was represented by an enzyme. As the number of BDNF molecules increases, the number of enzymes bound to them increases too. To detect the BDNF molecules bound to enzymes, tetramethylbenzidine, the substrate of peroxidase, was added to the samples. The color as a result of the addition of the substrate was measured by a spectrophotometer at 450 nm. The quantitative measurement of the BDNF molecules in the samples is shown in a graph drawn using BDNF standards that were treated in the same way as the samples.

### Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS Inc.; Chicago, IL, USA) 15. The Mann-Whitney U-test was employed for continuous variables, and chi-square tests were employed for categorical demographic variables. The Kolmogorov-Smirnov test showed that BDNF were normally distributed. Pearson's correlations were calculated based on whether there was any relationship between two variables in the bipolar groups. Pearson correlations were measured for the age at onset, treatment duration, illness duration, and BDNF. For all tests used in the statistical analyses, p-values of  $< 0.05$  were considered significant.

## RESULTS

The gender and other clinical features of 25 bipolar subjects and 17 healthy control subjects are presented in Table 1. The case and healthy control groups were statistically similar regarding age and gender but differed by full IQ scores. The patients with PBD had received different combinations of mood stabilizers and atypical antipsychotics, and only two patients were drug free.

The comparison of BDNF serum levels between the case and healthy control groups revealed no statistically significant difference ( $Z=-1.734$ ,  $p=0.170$ ).

In the case group, BDNF levels were significantly lower in patients currently being treated with lithium ( $Z=-0.197$ ,  $p=0.031$ ) (Table 2).

In order to evaluate the effects of illness duration, treatment duration, and the number of mood episodes on BDNF levels, we separated bipolar adolescents into two groups (for illness duration and treatment duration lasting a year and less than one year versus more than a year; for number of mood episodes of three and less than three versus more than three episodes). In the case group, when we compared BDNF levels in terms of gender ( $Z=-0.222$ ,  $p=0.824$ ), family psychiatric disorder history ( $Z=-0.383$ ,  $p=0.702$ ), diagnosis prior to the age of 15 years ( $Z=-1.360$ ,  $p=0.174$ ), number of mood episodes ( $Z=-0.109$ ,  $p=0.913$ ), duration of illness ( $Z=-0.218$ ,  $p=0.828$ ), and duration of drug treatments ( $Z=-1.271$ ,  $p=0.204$ ), we found no significant differences.

There were no positive or negative relationship between BDNF levels and the duration of illness, age at first mood episode, and duration of drug treatments (for duration of illness:  $r=0.173$ ,  $p=0.409$ ; for age at first mood episode:  $r=-0.218$ ,  $p=0.296$ ; for duration of drug treatments:  $r=0.135$ ,  $p=0.520$ ) (Table 3).

## DISCUSSION

As far as we know, this is the first study in subjects with euthymic PBD that has evaluated BDNF serum levels and their possible role in the pathophysiology of PBD. The major findings of this study were that BDNF serum levels of euthymic patients with BD are similar to normal control levels and that patients treated with lithium, had significant lower BDNF levels compared to patients not treated with lithium.

Recently, in two meta-analysis in adults with BD, BDNF serum levels were shown to be decreased in depressive and manic states, but returning to normal levels in euthymia. Our findings of normal serum BDNF levels in euthymic BD-I patients are consistent with the results of these meta-analysis (5,6).

Conversely, our results differ from those reported by Monteleone et al. (14). That study showed a reduction in BDNF levels in euthymic BD-I patients as compared to healthy controls (14). We think that such a difference comes from the fact that their sample differs from ours in terms of illness duration ( $20\pm 12.9$  years in their study,  $1.9\pm 1.6$  years in our study), medication status (only six of 17 patients in their study, twenty-three of 25 patients in our study were receiving pharmacological treatment), and number of mood episodes ( $6.5\pm 4.6$  in their study,  $2.9\pm 1.7$  in our study).

Limited research has been conducted on BDNF in youths with BD. Geller et al. (9) found a significant relationship between BD and the BDNF val-66val genotype in prepubertal and early-onset BD probands and their parents. In the only research assessing BDNF levels in youths with BD, Pandey et al. (11) investigated BDNF mRNA levels in lymphocytes and BDNF protein levels in platelets in drug-free patients with manic and

**Table 1.** Characteristics of pediatric bipolar disorder and control groups

	PBD group	Control group	p
Sex (Male/ Female)	10/15	7/10	0.939 <sup>a</sup>
Age (years)	16.4±1.3	16.5±1.1	0.598 <sup>b</sup>
Total IQ	84.2±12.9	92.8±10.4	0.011 <sup>b</sup>
Age at onset	14.6±1.9	-	-
Number of mood episodes	2.9±1.7	-	-
Duration of illness (years)	1.98±1.6	-	-
Duration of drug treatment(years)	1.82±1.1	-	-

<sup>a</sup>Chi-square test was used,  $X^2:0.006$ , <sup>b</sup>Mann-Whitney U-test was used,  $p<0.05$  were considered significant. PBD: pediatric bipolar disorder.

**Table 2.** The comparison of serum brain-derived neurotrophic factor levels between patients treated with lithium and those not treated with lithium

	Lithium (Monotherapy/ Combined ) Treatment				p
	With lithium		Without lithium		
Case group	n	%	n	%	
	8	32	17	68	0.031 <sup>a</sup>
BDNF levels (pg/mL)	983.8±130.2		1236.4±287.6		

<sup>a</sup>Mann-Whitney U-test was used.  $Z:-0.197$ . BDNF: Brain-derived neurotrophic factor

**Table 3.** The relationship between the levels of brain-derived neurotrophic factor and the duration of illness, age at onset, and duration of drug treatments

Case group	r	p
Age at onset	-0.218	0.296
Number of mood episodes	0.135	0.520
Duration of illness (years)	0.173	0.409

Pearson correlation test was used.

mixed states. Then, they treated the BD youths with mood-stabilizing and second-generation antipsychotic drugs for 8 weeks till they became euthymic. They found that BDNF mRNA levels in lymphocytes and BDNF protein levels in platelets of drug-free subjects were significantly lower than in normal control subjects. After stabilizing the mood symptoms using long-term treatment with mood-stabilizing drugs, the levels of BDNF mRNA in the lymphocytes of youths with BD increased and reached normal control levels (11). Normal BDNF levels in euthymic BD subjects results are consistent with our study and also adult literature, which support the hypothesis of BDNF involvement in the pathophysiology of BD. In this study, the case group consisted of children and adolescents within the age range of 7–17 years with heterogeneous neurodevelopmental stages. We consider that age-related changes in BDNF levels may occur due to different neurodevelopmental stages. In a study evaluating the age-related

changes in serum BDNF levels in healthy individuals, it was found that serum BDNF levels within the first 10 years were the same as in the ages of 30–39 years, which is accepted as the adult level. However, the BDNF levels significantly started to decrease within 10–19 years (15). For that reason, our sample was limited to subjects between the ages of 15 and 19 years. During adolescence, brain neurogenesis and synaptogenesis activity are similar to adulthood and, concurrently, myelination still continues. The neurogenesis level is the highest in the prenatal period. In contrast to previous beliefs, it has been established that although it reduces, neurogenesis also continues in adolescence and adulthood. In brain development, starting from the prenatal period, programmed cell death (apoptosis) continues intensely in the first few years of life. Synaptogenesis occurs intensively during the prenatal period of life, and then begins to decrease with age. Between 2 and 7 years of age, synapse formation and synaptic pruning are in an equilibrium. Afterwards, during puberty, synaptic pruning becomes more prominent, synapse numbers gradually decrease, and synapse levels become similar to adulthood. Myelination also continues intensively during adolescence (16). The normal BDNF serum levels that we found in euthymic adolescents and early adulthood were similar to normal BDNF levels in adult patients with BD, which may be related to the neurodevelopmental stage in our study group.

It is noteworthy that in our sample, patients treated with lithium had significantly lower BDNF levels than those not treated with lithium. This finding does not support the hypothesis of the association of the mood-stabilizing effects of lithium with increasing BDNF levels. However, when interpreting this result, it should be kept in mind that most patients were using multiple agents; thus, we could not assess the effects of a specific class of drug on BDNF levels. In the only lithium monotherapy study, Tsend et al. found decreased BDNF levels in patients with lithium monotherapy for a minimum of 3 years, with no affective episodes during the course of treatment (17). This finding is consistent with our result. Future prospective studies on patients with BD on lithium monotherapy should further investigate the relationship between lithium and BDNF.

In the present study, no relationship was found between BDNF levels and the duration of illness, age at first mood episode, or number of mood episodes. Additionally, we could not find any correlation in BDNF levels with the number of mood episodes and duration of illness. Kauer-Sant' Anna et al. (18) described that BDNF levels decreased in late-stage individuals with adult euthymic BD compared to those in early stages of the illness and in healthy controls. Moreover, BDNF serum levels were found to be negatively correlated with the duration of illness and number of mood episodes. Our case group consisted of young patients with a mean of  $2.9 \pm 1.7$  mood episodes and 1.98 years of duration of illness. These clinical variables are compatible with those of individuals in early stages (duration of illness  $2.1 \pm 2.9$ , number of mood episodes  $2.8 \pm 2.1$ ). The normal BDNF levels that we found in our case group are consistent with those of their early-stage individuals. In line with this study's findings, we may also explain the decreased BDNF serum levels in euthymic patients in Monteleone et al.'s (14) study due to the longer duration of illness (20 years).

It has been suggested that normal serum BDNF levels in the early stages of the illness, are a result of protective mechanisms. Additionally, in the later stages, a longer duration of illness and recurrent mood episodes may have cumulative effects on these protective mechanisms. The failure of compensatory mechanisms occurs with a reduction in BDNF levels. This may be a part of the physiopathology of the long-term outcome, with incomplete recovery between the episodes, less response to treatment, functional decline, and neuroanatomical changes in the brain that tend to

be more pronounced with repeated episodes with a longer duration of illness (19). Prospective studies are needed to test this hypothesis.

The differences in full-scale IQ between the case and healthy control group may be coincidental but may also be due to cognitive impairment in PBD. The meta-analysis of cognitive and neuropsychological functions in pediatric BD compared to healthy controls indicated moderate differences in the full-scale IQ (20).

Some limitations to the present study should be considered. The main limitation is the small sample size. Further, we measured BDNF levels in serum samples. Although the specific cellular sources of plasma BDNF are still unknown, it has been reported that platelets, vascular endothelial cells, and neurons may contribute to the circulating BDNF content (21). In addition, it has been demonstrated that BDNF can cross the brain–blood barrier and that there is a high positive correlation between serum and cortical BDNF levels (4). Therefore, it has been suggested that the changes in plasma BDNF levels partly reflect the changes in brain BDNF secretion. Another limitation is that we studied medicated BD subjects. Because it is well established that psychotropic medications change BDNF levels, we cannot rule out the effects of medications on the present findings.

In conclusion, we found normal serum BDNF levels in patients with PBD as compared with those in healthy controls. Long-term studies with larger sample sizes and patients in different mood states are needed. Further investigations evaluating BDNF levels in the early stages of BD in different mood states and BDNF level changes in different developmental stages could help identify the underlying pathophysiology of early- and late-onset BD and the role of BDNF in brain development in health and disease.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of Dokuz Eylül University School of Medicine (21.08.2008/decision number 334/2008).

**Informed Consent:** Written informed consent was obtained from patients and also from parents of the patients.

**Peer-review:** Externally peer-reviewed.

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