



## Brain-derived neurotrophic factor serum levels before and after treatment for acute mania

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### ABSTRACT

Accumulating evidence suggests that reduced levels of brain-derived neurotrophic factor (BDNF) in acute mood episodes may play an important role in the pathophysiology of bipolar disorder (BD). In order to assess changes in BDNF serum levels in BD patients before and after treatment for acute mania, ten bipolar patients were prospectively examined at inpatient unit admission and discharge. Diagnoses were made using the Structured Clinical Interview for DSM-IV, SCID-I. Serum BDNF levels were measured by sandwich ELISA. The results showed that BDNF levels were decreased in BD patients during mania when compared to controls ( $p=0.013$ ) but this difference was no longer significant after treatment ( $p=0.126$ ). A sharp increase in BDNF levels was found after treatment of the episode of acute mania ( $p=0.010$ ). These findings suggest that the changes in BDNF serum levels may be associated with treatment response in acute mania. Further studies designed to validate the use of BDNF as a marker of treatment response in bipolar disorder are warranted.

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Bipolar disorder (BD) is among the most disabling medical disorders and is associated with high mortality rates due to suicide and other medical illnesses [8]. Notably, some authors reported neuroanatomical changes in BD patients that tend to be more pronounced with repeated episodes and length of illness [15,6]. Consistently, recent studies suggest that those patients who had their first manic episode present minimal alterations in brain structures [14]. Furthermore, there is evidence that patients with BD have persistent cognitive impairment and that the extent of impairment is greater in those with multiple episodes as compared with those who presented their first manic episode [3].

It has been suggested that reduced levels of neurotrophins described in acute episodes may play an important role in the brain changes related to cumulative mood episodes [9]. Accordingly, deficient expression of BDNF may contribute to, or be a consequence of, the pathophysiology of BD. In addition, Sen et al. [10] in a recent meta-analysis examined the difference in serum BDNF of unipolar depressed patients and suggested a potential utility of serum BDNF levels as a biomarker for illness and antidepressant efficacy. In bipolar disorder, serum studies have shown decreased serum

BDNF levels in BD patients in manic as well as in those with depressive symptoms, being normalized in euthymia [17,18]. In a study of patient assessed during a first episode of psychosis (including BD) plasma levels of BDNF increased about two-fold after 6 months of treatment among BD patients [7]. The present study was designed to assess changes in BDNF serum levels of BD patients during acute mania and after treatment of acute episode.

Ten patients with BD I in acute mania and 10 healthy controls, matched for age and gender, were recruited. We compared BDNF serum levels of BDNF of the same group of manic patients during acute mania and after treatment of acute episode. An additional comparison group of ten non-bipolar healthy subjects was included. BD manic patients were recruited at the Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre, Brazil. All subjects had a comprehensive clinical interview by a board-certified psychiatrist. The diagnosis of BD was established based on all the available clinical information and confirmed with a Structured Clinical Interview for DSM-IV – Axis I (SCID-I) and a standard protocol to assess psychopathology and clinical features. Subjects enrolled received open-label treatment for BD according to available clinical guidelines [8,16]. Patients did not have significant comorbid medical conditions and they were not on medication other than those prescribed to treat acute mania. Psychiatric status was assessed during and after treatment for acute mania using the Young Mania Rating Scale [2] and the Hamilton Depression Rating Scale, 21-item version [5].

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Controls, matched for age and gender, were screened to rule out current use of clinical and psychiatric medication, any history of psychiatric disorder, neurodegenerative disorder, mental retardation, cancer or chronic/acute infection. All procedures described in this study received approval from the local ethics committee. Written informed consent was obtained from all patients and healthy subjects prior to conducting any study procedures.

Five milliliters of blood were withdrawn from each subject by venipuncture into a free-anticoagulant vacuum tube. The blood was immediately centrifuged at  $3000 \times g$  for 5 min, and serum was kept frozen at  $-80^\circ\text{C}$  until assayed. BDNF serum levels were measured with sandwich-ELISA, using a commercial kit according to the manufacturer's instructions (Chemicon, USA). Briefly, microtiter plates (96-well flat-bottom) were coated for 24 h with the samples diluted 1:2 in sample diluents and standard curve ranged from 7.8 to 500 pg of BDNF. Plates were then washed four times with wash buffer, monoclonal anti-BDNF rabbit antibody was added (diluted 1:1000 with sample diluents), and incubated for 3 h at room temperature. After washing, a second incubation with anti-rabbit antibody peroxidase conjugated (diluted 1:1000) for 1 h at room temperature was carried out. After addition of streptavidin-enzyme, substrate and stop solution, the amount of BDNF was determined (absorbance set in 450 nm). The standard curve demonstrates a direct relationship between optical density (OD) and BDNF concentration. The intra-assay and inter-assay variations were 3.7% and 8.5%, respectively. Total protein was measured by Lowry's method using bovine serum albumin as a standard.

Statistical analyses were performed using SPSS software version 16.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics are used to report sociodemographic and clinical characteristics of the sample. Association between dichotomous variables was assessed with  $\chi^2$  test, as indicated. Continuous demographic/clinical/biochemical variables were compared between patients and their respective controls using paired sample *t* test, as indicated. All statistical tests were two-tailed and were performed using a significance level of  $\alpha = 0.05$ . Data are presented as means and standard deviation (S.D.), or percentage, as indicated.

There is no difference between patients and their respective control groups regarding gender (50% Female, 50% Male, in both group) and age (Controls  $34.41 \pm 3.97$ ; Patients  $34.9 \pm 13.85$ ; paired  $t = -0.655$ ;  $p = 0.529$ ). The clinical characteristics of the patients are presented in Table 1. BDNF levels were decreased in BD patients during mania ( $0.26 \pm 0.10$ ) when compared to controls ( $0.31 \pm 0.05$ ; paired  $t = 3.092$ ;  $p = 0.013$ ) but this difference was no longer significant after treatment ( $0.38 \pm 0.14$ ; paired  $t = -1.682$ ;  $p = 0.126$ ) (Fig. 1). There was a sharp increase in BDNF levels after effective treatment of acute manic episode (paired  $t = -3.230$ ;  $p = 0.010$ ) (Fig. 1). The BDNF levels either in acute episode or after treatment did not presented correlation with the clinical scales (GAF, YMRS and HAMD).

As far as we know, this is the first study designed to examine BDNF levels during acute mania and after treatment of the episode. Results suggest that BDNF levels may be associated with improvement of acute symptoms and may offer a biological marker of clinical response to treatment in acute mania. These results were obtained using a small sample size and replication is warranted. However, given that the present results are inline with previous studies [17,18,7] it is unlikely that a larger sample would change the direction of the results.

BDNF is a member of the neurotrophin family, and plays an important role in neuroplasticity and neuroprotection [9]. In BD patients, serum BDNF is decreased in both manic and depressive episodes [17] and has been negatively correlated with severity of episodes [17,18]. In addition, three independent studies reported that serum BDNF levels were reduced in unipolar depressive patients and were negatively correlated with the severity of

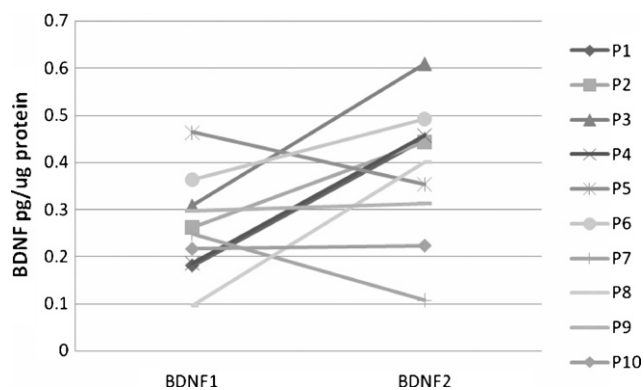
**Table 1**  
Clinical characteristic of patients with BD at baseline (before treatment) and follow-up (after treatment).

Patient	Time of illness (years)	Age of onset (years)	Treatment <sup>†</sup>	Duration of treatment <sup>‡</sup>	YMRS before treatment	YMRS after treatment	HAMD before treatment	HAMD after treatment	GAF before treatment	GAF after treatment
1	1	17	Lithium, haloperidol	78	16	4	8	2	50	75
2	0	22	Lithium, risperidone	24	40	10	2	0	31	70
3	11	18	Lithium, olanzapine, haloperidol, chlorpromazine	42	33	9	2	1	35	35
4	1	28	Lithium, risperidone	21	26	4	0	0	40	65
5	15	15	Electroconvulsive therapy (ECT)	20	28	18	3	2	35	50
6	12	19	Lithium, haloperidol, clonazepam	18	24	0	10	0	40	70
7	6	27	Lithium	72	18	6	5	8	40	80
8	10	30	Lithium	48	19	8	3	1	35	70
9	18	30	Lithium, clonazepam	27	16	0	7	2	40	65
10	36	30	Lithium, risperidone	170	42	0	2	1	35	80
Mean	11.00	23.60		52.00	26.20	5.90	4.20	1.70	38.10	66.00
S.D.	10.74	6.02		46.75	9.55	5.67	3.19	2.36	5.22	13.90
<i>t</i> Value*	-	-		-	6.268	2.179	2.179	0.057	-6.644	<0.001
<i>p</i>	-	-		-	<0.001					

<sup>†</sup> Patients 7 and 10 were medication-free (at least 14 days without medication) and the remaining patients were at described treatment for no longer than 10 days at blood draw.

<sup>‡</sup> Number of days from admission until discharge.

\* Paired samples *T*-test.



**Fig. 1.** BDNF levels in patients. Nine out of ten patients assessed at admission were discharged after resolution of the manic episode. One patient (patient five) was a refractory case and was treated using electroconvulsive therapy. This patient was discharged still within a manic episode and BDNF levels of this patient were decreased. Patient seven also presented a decrease in BDNF levels but was not manic at discharge. Overall out of nine responders BDNF levels were sharply increased in six patients. BDNF 1: before treatment BDNF 2: after treatment.

depressive symptoms [13,11]. The extent to what peripheral BDNF reflects brain changes remains a topic of debate. Although it is possible that peripheral BDNF levels may not reflect brain changes, BDNF has been shown to cross the blood–brain-barrier [4] and has been associated with many of the crucial pharmacotherapeutic interventions for bipolar illness (lithium, valproate, carbamazepine, quetiapine, and ECT) [12].

Some limitations should be considered when interpreting the results of this study. First, our findings might have been strengthened with a larger number of study participants, particularly in regard to increasing the power of statistical analyses. Second, the patient received open-label maintenance treatment, which does not permit to analyze the specific treatment effect on BDNF levels. In conclusion our findings suggest that the changes in BDNF serum levels may be associated with treatment response in acute mania. Further studies designed to validate the use of BDNF as a marker of treatment response in bipolar disorder are warranted.

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