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Serum brain-derived neurotrophic factor in bipolar and unipolar depression: A potential adjunctive tool for differential diagnosis

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ABSTRACT

The differential diagnosis of Bipolar Disorder (BD) and Major Depressive Disorder (MDD) is a diagnostic challenge during depressive episodes. Noteworthy, the proper differentiation between BD depressive state and MDD has important treatment implications. BDNF levels may be valuable adjunctive tool for this differential diagnosis. Ten subjects with MDD, forty with BD type I and thirty healthy comparison subjects were recruited. All subjects had BDNF serum levels measured and, in patients, BDNF serum levels were assessed during acute depressive episode. Optimal sensitivity and specificity of serum BDNF for the differential diagnosis of unipolar and bipolar depression were determined by the receiver operating characteristic (ROC) curve analysis, using a nonparametric approach. Serum BDNF levels in depressive BD patients were lower compared to MDD patients and controls (0.15 ± 0.08, 0.35 ± 0.08, and 0.38 ± 0.12, respectively, $p < 0.001$). The area under the curve (AUC) of the ROC analysis in BD depression vs. MDD was 0.95 (ranged from 0.89 to 1.00). Overall, the AUC of the ROC analysis (BD depression vs. MDD and controls) was 0.94 (95% CI 0.89 to 0.99, $p < 0.001$). A proposed "best" cutoff of 0.26 resulted in 88% sensitivity and 90% specificity. Serum BDNF levels appear as a promising tool to discriminate bipolar from unipolar depression. Our results suggest the role of BDNF as an adjunctive tool to promote prompt and accurate diagnosis of BD. However, further investigation and replication of these results are warranted.

1. Introduction

Bipolar disorder (BD) and major depression disorder (MDD) are two highly prevalent and disabling disorders in psychiatry (Yatham et al., 2009). Despite clear phenomenological criteria, the differential diagnosis of unipolar and bipolar depression remains a clinical challenge. The differential diagnosis between BD depressive episodes and MDD is critical to prevent misdiagnosis, delay in appropriate treatment and poor prognosis. Several potential biological markers have been recognized lately. Mood disorders have been widely recognized as disorders that affect neurotrophins, particularly brain-derived neurotrophic factor (BDNF). BDNF is involved in promoting synaptic plasticity and neuronal connectivity (Berk et al., 2008; Kapczinski et al., 2008a,b,c). The idea that changes in BDNF levels may be involved in the pathophysiology of BD depressive episodes and of MDD have been extensively reported (Duman et al., 1997, 2000; Cunha et al., 2006; Gama et al., 2007; Machado-Vieira et al., 2007; Guimaraes et al., 2008; Kapczinski et al., 2008b,c; Kauer-Sant'Anna et al., 2008; Fernandes et al., 2009; Oliveira et al., 2009). However, as far as we are aware, BDNF has not been examined as a potential blood diagnostic test for depressive episodes. BDNF have not been examined as a potential blood diagnostic test.

The aim of this study was to investigate the properties of serum BDNF as a potential diagnostic biomarker. To this purpose, we assessed serum BDNF levels during depressive episode, and compared the levels between BD and MDD patients.

2. Methods and materials

BD type I and MDD inpatient and outpatient subjects, currently in acute depressive episode, were recruited from Bipolar Disorders Program and Psychiatry Inpatient Unit – Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil. Diagnosis of depressive episodes and of BD and MDD were established according to Structured

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Clinical Interview for DSM-IV-Axis I Disorders (SCID-I) (APA, 2000) by trained psychiatrists. Severity of depressive episodes was evaluated using the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960). Our sample was powered to analyze the difference between BD and MDD using a ROC curve with a power of 80% and an alpha one-tailed of 0.05 for an accuracy of 0.8 with a ratio between MDD and BD of 2.0. For this purpose a minimum of eight per group would be necessary; and we have included 10 patients with MDD and 40 with BD.

We conducted an exploratory study with 10 MDD and 40 BD type I patients in acute depressive episode, and 30 healthy controls. All patients were taking psychiatric medication. Psychiatric assessment in controls was carried out using SCID-I, non-patient version. Control subjects were not on medication, and had no history of major psychiatric disorders, dementia or mental retardation in their first-degree relatives. Patients and controls with drug abuse or untreated or uncontrolled major medical illness were excluded. The Hospital de Clinicas de Porto Alegre Ethics Committee approved the study protocol and all subjects provided written informed consent before entering in the study.

Five milliliters of blood were withdrawn from each subject by venipuncture into a free-anticoagulant vacuum tube. The blood samples were drawn in the afternoon (around 5 pm). The blood was immediately centrifuged at 4000*g* for 10 min, and serum was kept frozen at −80 °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 1:25 in sample diluents and standard curve ranged from 7.8 to 500 pg of BDNF. Plates were then washed four times with wash buffer, added monoclonal anti-BDNF rabbit antibody (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. Total protein was measured by Lowry's method using bovine serum albumin (BSA) as a standard.

Statistical analysis was performed using Analyze-it for Excel Program and SPSS 16.0 for Windows. Most of the BDNF values were fitted in a standard distribution curve and were therefore subjected to parametric analyses. All values are presented as mean ± standard deviation (SD), except when indicated. For the comparisons between the groups, one-way analysis of variance (ANOVA) test with individual differences assessed using a Tukey post-test if the ANOVA was significant, and independent *t* test were employed. Pearson's correlation coefficient was also used. Optimal sensitivity and specificity of serum BDNF ratio for the diagnosis of depressive BD episode were determined by the receiver operating characteristic (ROC) curve analysis utilizing a nonparametric approach. The Youden index was calculated for each cutoff value as corresponding [(sensitivity + specificity) − 1] to find the cutoff values that maximize discriminating power of the test. *P* values <0.05 two-tailed were considered statistically significant for the ANOVA and χ^2, and for the ROC curve analysis $p < 0.05$ one-tailed were considered statistically significant.

3. Results

The characteristics of BD and MDD patients and controls are summarized in Table 1. BD and MDD patients were similar regarding gender, age, presence of psychosis, and HDRS score. BD and MDD patients and controls were similar regarding gender, and age. BDNF was not correlated to age or severity of depressive symptoms assessed by the HDRS (all $p > 0.05$). Use of medication was similar in both groups regarding antidepressants and antipsychotics; 60% of BD patients were using mood stabilizers (lithium or

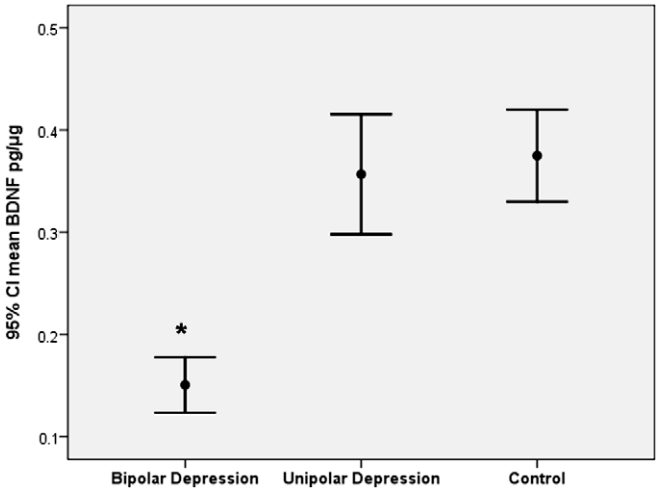

Fig. 1. Serum brain-derived neurotrophic factor (BDNF) levels in pg/µg ratio (mean ±95% CI) in bipolar and unipolar depression, and in healthy controls. * $p < 0.001$ for bipolar depression vs. unipolar depression/control (One-way ANOVA with Tukey post-test).

Table 1
Characteristics of the bipolar and unipolar depression patients, and controls.

Characteristics	Group*			*p* value
	Bipolar depression (*n* = 40)	Unipolar depression (*n* = 10)	Controls (*n* = 30)	
Male sex[a]	13/40	4/10	12/30	0.903
Age – years[b]	41.32 ± 8.45	44.80 ± 17.97	41.00 ± 11.99	0.562
Presence of psychosis[a]	25/40	4/10	–	0.170
Inpatient patients[a]	18/40	10/10	–	0.189
HDRS score[c]	23.40 ± 7.53	26.30 ± 5.50	–	0.284
Mood stabilizers[a]	24/40	0/10	–	0.001
Antidepressants[a]	17/40	7/10	–	0.360
Antipsychotics[a]	18/40	9/10	–	0.082
BDNF (pg/µg)[b,d]	0.15 ± 0.08	0.35 ± 0.08	0.38 ± 0.12	0.001

Abbreviations: HDRS (Hamilton Depression Rating Scale); BDNF (brain-derived neurotrophic factor).
* Columns show mean ± standard deviation (SD) for all categories except male sex, presence of psychosis, impatient patient, and medications.
[a] Qui-square test.
[b] One-way ANOVA test with Tukey post-test.
[c] Unpaired *t* test.
[d] BDNF in bipolar disorder depression < major depressive disorder ($p = 0.006$).