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Diagnostic accuracy of serum brain derived neurotrophic factor concentration in antidepressant naïve patients with first major depression episode

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ABSTRACT

Diagnosing major depressive disorder (MDD) continues to be based on meeting phenomenological and descriptive criteria. As of yet, there is still no non-invasive, peripheral biomarker that would allow for a certain diagnosis of MDD. The objective of this paper is to use the receiver operating characteristic (ROC) analysis to test the diagnostic value of serum concentrations of brain derived neurotrophic factor (BDNF) in diagnosing the first episode of MDD.

Among 1014 patients admitted for an initial psychiatric evaluation, antidepressant naïve patients diagnosed with first episode MDD were separated into the test group. Only patients signing an informed consent form were included in the study. Using DSM-IV-TR diagnostic criteria, those patients meeting the MDD criteria ($N = 122$) and patients not meeting MDD or other psychiatric disorder criteria ($N = 142$) were differentiated. Subjects with repeated episode MDD ($N = 121$) and other psychiatric comorbid illnesses ($N = 138$) in the MDD group were excluded from the study. In the group without MDD or other psychiatric illnesses, patients with physical comorbidities ($N = 59$) were excluded. The serum concentration of BDNF was determined in all patients using the ELISA assay.

Subjects with first episode MDD showed differences in serum BDNF concentrations (ng/mL) in comparison to the control group of patients not meeting the criteria for first episode MDD (mean ± SD; 37.5 ± 13.3 vs. 56.8 ± 6.3; $t = 1.372$; df = 262; $p < 0.01$). The ROC analysis established a discriminant diagnostic value of serum BDNF in diagnosing MDD. The area under the curve (AUC) was 0.892 with a 95% confidence level (0.826–0.939), which was statistically significant at $p < 0.01$. The serum BDNF had a high diagnostic sensitivity of 83.9% and a specificity of 93%. Serum BDNF concentrations appear to be a promising tool in discriminating subjects with MDD from those without MDD.

1. Introduction

Diagnosing major depressive disorder (MDD) is based on relatively unobjective phenomenological and descriptive methods (Lakhan et al., 2010). It would be ideal to identify a biological marker to improve the diagnostic procedure. The term biomarker implies a specifically marked individual state that helps in distinguishing the presence or absence of a state of illness (Perlis and Duman, 2007). Numerous studies have been conducted to date in search of a biomarker for MDD, the majority of which have focused on the concentration of monoamines, growth factors and/or pro-inflammatory cytokines (Castren and Rantamaki, 2010; Schmidt and Duman, 2007; Karlović et al., 2012; Silić et al., 2012). In addition, there is a long history and evidence for altered endocrine factors (eg, hypothalamic–pituitary–adrenal (HPA), thyroid, sex steroids) and metabolic dysregulation (eg, insulin resistance) in mood disorders (Silić et al., 2012). Despite decades of research, a non-invasive, quantitative test that could be useful in diagnosing MDD has not yet been confirmed, primarily due to the lack of specificity and sensitivity of the tested potential biomarkers (Lakhan et al., 2010).

In recent years, the MDD neurotrophic hypothesis has been highlighted, by which reduced levels of brain derived neurotrophic factor (BDNF) in MDD underlie depression, and antidepressives

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achieved their effects via restoration of central BDNF activity (Duman and Monteggia, 2006). A large number of clinical studies have reported that BDNF levels in serum (Aydemir et al., 2006; Gervasoni et al., 2005; Karege et al., 2005; Shimizu et al., 2003; Jevtović et al., 2011) and plasma (Kim et al., 2007; Lee et al., 2007) are significantly decreased in depressed patients, and that this decrease is normalized with antidepressant treatments (Aydemir et al., 2005; Bocchio-Chiavetto et al., 2006; Gervasoni et al., 2005; Gonul et al., 2005; Huang et al., 2008; Okamoto et al., 2008; Yoshimura et al., 2007; Zanardini et al., 2006), this has been also confirmed by metaanalysis (Brunoni et al., 2008; Sen et al., 2008). These findings indicate that serum BDNF could have functional significance in the pathophysiology and/or treatment of mood disorders. Though some studies to date have confirmed a significant difference between serum BDNF between groups with MDD and the control, this was insufficient for serum BDNF to be considered a clinical diagnostic test for MDD. Our hypothesis is that the serum concentration of BDNF can be a clinically useful diagnostic test for MDD.

The objective of this study was to use receiver operating characteristic (ROC) analysis to investigate the potential of serum BDNF as a diagnostic biomarker for major depressive disorder. In order to achieve this objective, specificity, sensitivity, and percentage of correctly classified patients were evaluated using serum BDNF of patients with MDD.

2. Methods

2.1. Subjects and study design

This study was designed according to the protocol of the Standards for the Reporting of Diagnostic Accuracy Studies (STARD) (Bossuyt et al., 2003). The STARD protocol is a set of guidelines that outline how to design studies on the diagnostic significance of a tested marker (in the present case, of BDNF). According to this protocol, it is very important to include all patients successively attending a given clinical setting with specific symptoms in a set time period. In line with the DSM-VI-TR classification, patients gave their informed consent to participate in the study and were divided into those with the test diagnosis and those that did not meet the criteria for the test diagnosis. This study, therefore, encompasses all the patients making their first visit as outpatients to the Department of Psychiatry for psychiatric consultation for depressive symptoms ($N = 1014$) in the period from September 2009 to August 2010. Study groups were selected and included patients with the criteria for MDD ($N = 122$) and the control group without criteria for MDD ($N = 142$). Patients that did not given their informed consent ($N = 209$) were not included in the study. All patients were antidepressant naïve and with first MDD episode. Sociodemographic and clinical characteristics of all included subjects are presented in Table 1.

The DSM-IV-TR criteria were applied to all patients to identify patients with MDD and controls without MDD. Using the DSM-IV-TR criteria on the MDD group, those patients with repeated depressive episodes ($N = 121$) or depressive episodes in comorbidity with other psychiatric illness ($N = 138$) (47 with anxiety disorder, 13 with somatoform disorders, 32 with addictions to alcohol or other addictive substances and 46 with personality disorders) were excluded from further analysis. Patients having any physical comorbid illness ($N = 233$) were also excluded from this group (71 with hypertension, 42 with diabetes, 22 with thyroid disorders, 31 with neurological disorders, 9 with cancer, 19 with gastrointestinal disorders, 10 with renal disorders and 29 with cardiovascular disorders). Patients in the control group having a physical comorbid illness ($N = 59$) (14 with hypertension, 12 with neurological disorders, 9 with cardiovascular disorders, 8 with diabetes, 7 with gastrointestinal disorders, 6 with renal disorders, 3 with cancer) were also excluded from further analysis. Ultimately, the control group consisted of patients without any other confirmed psychiatric illness and which did not meet the criteria for the diagnosis of MDD or other psychiatric disorder, though they experienced some depressive symptoms. The overall diagnostic procedure and selection of patients is shown in Fig. 1.

The standards used for diagnosing MDD were the criteria of the DSM-IV-TR classification (APA, 2000). For this purpose, the Mini International Neuropsychiatric Interview (MINI) was used (Sheehan et al., 1998), which is also based on the DSM-IV-TR criteria, comorbid psychiatric disorders to MDD were also diagnosed. Episodes lasting more than two weeks and less than six months were considered. The duration of a minimum of two weeks was set according to the DSM-IV-TR criteria (APA, 2000) and a maximum episode duration of six months was set as it has been shown that the majority (up to 70%) of MDD episodes spontaneously regress after six months (Posternak et al., 2006). The severity of the depressive episode was assessed using the Hamilton depression rating scale (HAMD-17) (Hamilton, 1960). Trained and experienced psychiatrists administered the DSM-IV-TR criteria, HAMD-17 and MINI interview. The presence of a comorbid physical illness in both groups of patients was made based on the basis of medical history information provided by the patient, or a review of the patient's medical record forwarded from his or her general practitioner. The sociodemographic and clinical parameters of all included subjects are shown in Table 1. Informed consent was obtained from the patients in the test group and control group after a complete and extensive description of the study profile. The study was approved by the Hospital's Ethics Committee.

Table 1
Sociodemographic and clinical characteristics of patients with major depressive disorder (MDD) ($N = 122$), and control group without MDD ($N = 142$).

	MDD	Control group	Statistics
Sex: *N* (%)			$\chi^2 = 1.524$; df = 1; $p = 0.217$
Male	56 (45.9)	76 (53.5)	
Female	66 (54.1)	66 (46.5)	
Education: *N* (%)			$\chi^2 = 4.973$; df = 2; $p = 0.083$
Elementary	34 (27.9)	51 (35.9)	
High school	70 (57.4)	62 (43.7)	
University	18 (14.8)	29 (20.4)	
Marital status: *N* (%)			$\chi^2 = 4.690$; df = 2; $p = 0.096$
Single	20 (16.4)	39 (27.5)	
Married	88 (72.1)	90 (63.4)	
Divorced	14 (11.5)	13 (9.2)	
Working status: *N* (%)			$\chi^2 = 2.925$; df = 2; $p = 0.232$
Employed	51 (41.8)	51 (35.9)	
Unemployed	28 (23.0)	46 (32.4)	
Retired	43 (35.2)	45 (31.7)	
Place of living: *N* (%)			$\chi^2 = 2.087$; df = 1; $p = 0.149$
Urban	57 (46.7)	79 (55.6)	
Rural	65 (53.3)	63 (44.4)	
Age in years (mean ± SD)	46.5 ± 12.4	44.8 ± 14.2	$t = 1.014$; df = 262; $p = 0.311$
Hamilton rating scale for depression (mean ± SD)	27.3 ± 5.6	Not applicable	Not applicable