Serum levels of brain-derived neurotrophic factor in drug-naïve obsessive-compulsive patients: A case-control study

SERUM LEVELS OF BRAIN-DERIVED NEUROTROPHIC FACTOR IN DRUG-NAÏVE OBSESSIVE–COMPULSIVE PATIENTS: A CASE–CONTROL STUDY

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ABSTRACT

Background
There is lack of data regarding BDNF serum levels in patients with obsessive–compulsive disorder (OCD). The aims of the present study were: 1) to assess the serum BDNF content in a sample of drug-naïve patients with OCD and 2) to assess whether putative alterations in peripheral BDNF may be associated to OCD severity and clinical characteristics.
Methods
Twenty-four drug-naïve patients with a principal diagnosis of OCD were recruited. In parallel, a control group of 24 unrelated volunteers matched for gender and age was enrolled. Serum BDNF levels were measured by ELISA method.
Results
The results showed that BDNF levels were decreased in OCD patients when compared to controls (36.90 ± 6.42 ng/ml versus 41.59 ± 7.82 ng/ml; $p = 0.043$). No correlations were evidenced between serum BDNF content and the severity of OCD symptoms measured as Y-BOCS scores or other clinical variables.
Limitations
The choice of drug-naïve patients with obsessive–compulsive disorder had limited the size of the sample and excluded the recruitment of patients with a severe symptomatology.
Conclusions
Our findings reveal for the first time in OCD patients a decrease in serum BDNF levels. These data corroborate the hypothesis of a dysfunction in the neurotrophin expression in the OCD pathogenetic mechanism and provide the rationale for further investigations directed to the identification of novel biomarkers and new therapeutic strategies for antiobsessional treatments.

KEYWORDS
Obsessive–compulsive disorder; OCD; Serum; Drug-naïve; Brain-derived neurotrophic factor; BDNF

1. INTRODUCTION

Obsessive–compulsive disorder (OCD) is a neuropsychiatric condition affecting an estimated 1% to 3% of the population worldwide (Rasmussen and Eisen, 1994). Genetic epidemiology studies have indicated for OCD a multifactorial model of inheritance where multiple genetic and biological risk factors act together with environmental stressors causing the disease onset (Hettema et al., 2001 and Grisham et al., 2008). The biological determinants that contribute to the pathogenesis are poorly defined, although it has been hypothesized that neurodevelopment and immune alterations as well

as dysfunctions in serotonergic and glutamatergic neurotransmitter pathways may underlie the disease (Goodman and Lydiard, 2007). The phenotypic heterogeneity of OCD, that occurs often in comorbidity with mood disorders, may complicate the identification of the specific etiological mechanism (Fineberg et al., 2007).

Brain-derived neurotrophic factor (BDNF) promotes neuronal proliferation, regeneration, and connectivity shaping during brain development and participates in the synaptic plasticity maintenance of the adult brain (Huang and Reichardt, 2001). In particular, BDNF plays a key role in the neural functions that regulate response to environmental stimulations as stress events during life and studies in human post-mortem brains have shown an involvement of BDNF in the pathophysiology of stress-related human psychopathologies, such as depressive and anxiety disorders (Carola et al., 2008 and Duman and Monteggia, 2006).

The BDNF gene and, in particular, the functional Val66Met polymorphism in the propeptide region was extensively studied in relation to mood and anxiety disorders including obsessive–compulsive disorder (OCD) susceptibility, reporting conflicting results (Alonso et al., 2008 and Wendland et al., 2008). However, a role of the BDNF gene in anxiety disorders has been supported by studies on the transgenic mouse carrying the human BDNF Val66Met polymorphism: the Met/Met carrier mouse, that reproduces the phenotypic functional hallmarks observed in humans exhibiting an increased anxiety-related behaviour in different experimental settings (Chen et al., 2006).

In the last years, biochemical studies in patients affected by psychiatric disorders provided intriguing findings on the involvement of BDNF in the disease aetiology and treatment. In particular, major depression has been consistently associated with low BDNF serum levels (Sen et al., 2008) whereas both pharmacological and non-pharmacological antidepressant therapies are able to normalize the neurotrophin levels (Brunoni et al., 2008, Zanardini et al., 2006 and Bocchio-Chiavetto et al., 2006). To date, only one clinical study has examined serum concentration of BDNF in OCD patients: the authors reported on the addition of risperidone in three OCD patients treated with fluvoxamine and indicated that serum BDNF levels were not altered after the recovery of OCD symptoms (Yoshimura et al., 2006). There are no data regarding serum levels of BDNF in OCD patients without pharmacological treatment compared to control subjects.

On this basis, the aims of the present study were: 1) to assess the BDNF serum content in drug-naïve OCD patients without any recent severe psychological distress compared to age and sex-matched controls; 2) to determine if the putative alteration of the neurotrophin content is correlated to the clinical features in the patient sample.

2. METHODS

2.1 SUBJECTS

Subjects for this study were recruited from all patients with a principal diagnosis of OCD consecutively referred to the Mood and Anxiety Disorders Unit, Department of Neurosciences, University of Turin (Italy).

Inclusion criteria were: (a) principal diagnosis of OCD according to DSM-IV criteria; (b) minimum total score of 16 on the Yale–Brown Obsessive Compulsive Scale (Y-BOCS) (Goodman et al., 1989); (c) at least 18 years of age.

The following exclusion criteria were considered: (a) current or previous diagnosis of organic mental disorder, schizophrenia or other psychotic disorder, bipolar disorders, substance-related disorders; (b) current diagnosis of depressive disorder and a maximum total score of 7 on the Hamilton Depression Rating Scale 17-item (HAM-D-17); (c) uncontrolled or serious medical condition; (d) any current or past psychopharmacological treatment; (e) any severe stressful event within the year prior to inclusion.

In parallel a control group of 24 unrelated volunteers matched for gender and age with the patient group was enrolled. None of these subjects presented a positive personal and familial anamnesis for psychiatric DSM-IV-TR axis I disorders according to the clinical interview – and confirmed by the MINI – or was affected by any medical diseases or was in pharmacological treatment (including oral contraceptives).

Written informed consent was obtained from each subject after complete description of the study, which was approved by the local ethics committees.

2.2 ASSESSMENT

Patient data were obtained through the administration of a semistructured interview that we developed and used in previous studies (Maina et al., 2004 and Maina et al., 2008), with a format that covered the following areas:

a) Socio-demographic characteristics

b) BMI

c) Diagnostic evaluation: principal diagnosis and axis I and axis II comorbidities were recorded by means of the Structured Clinical Interview for DSM-IV Axis I and II Disorders (First et al., 1996 and First et al., 1997).

d) Onset and course of OCD

e) Stressful life events assessment: patients were asked whether they had experienced a stressful life event within the year prior the inclusion in the study (61 items list by Paykel et al., 1971).

In addition, the following rating scales were included in the assessment of patients: the Yale–Brown Obsessive Compulsive Scale (Y-BOCS); the Hamilton Rating Scale for Anxiety (HAM-A); the 17-item Hamilton Rating Scale for Depression (HAM-D) and the Clinical Global Impression (CGI).

Moreover, health-related quality of life was assessed using the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) (Ware and Sherbourne, 1992).

In the early phase of the study, inter-rater agreement between rater pairs on the diagnosis of axis I and axis II disorders was ascertained. The inter-rater reliability of DSM-IV diagnoses was found to be good: Kappa coefficients were greater than 0.80 for the presence of any lifetime axis I disorder and greater than 0.75 for the presence of any personality disorder.

2.3 SERUM BDNF DETERMINATION

Venous blood samples for patients and controls were collected after an overnight fast (between 8.00 and 9.00 a.m.) in anticoagulant-free tubes. Tubes were kept at room temperature for 1 h followed by 1 h at 4 °C before serum separation by centrifugation (3000 rpm for 15 min at 4 °C). Serum samples were stored at − 80 °C till the time of assay. BDNF levels were measured by the ELISA method (R&D system, Minneapolis, USA) according to the manufacturer's instructions. BDNF concentrations were assessed in serum samples diluted 1:100. Inter-assay variances were below 8%. The analyses were conducted in duplicate and the BDNF content was expressed as equivalent of human recombinant proteins and the data were expressed as ng of protein/ml of serum.

2.4 STATISTICAL ANALYSES

Demographic and clinical characteristics in the patient and control samples were described either in terms of mean ± SD if quantitative or in terms of proportions. Two-tailed student t tests were used to evaluate differences in BMI values. Since studies in large samples indicated that BDNF serum concentrations were not normally distributed (Lang et al., 2009), non-parametric tests were used for comparing BDNF means in patients versus controls and to evaluate the correlations with clinical variables (Mann–Whitney test, Spearman test). Statistical analyses were performed using SPSS, version 13.0 (website: http://www.spss.com).

3. RESULTS

A total group of 28 drug-naïve patients with OCD were screened: 4 patients (13.8%) were excluded from the following analyses for concomitant depressive disorder (n = 2), for lifetime diagnosis of bipolar disorder (n = 1), and for the presence of a severe stressful life event in the year prior to the investigation (n = 1). The remaining 24 subjects were enrolled in the study. Of these 24 patients, 13 had been previously treated with psychotherapies and 11 patients had never been treated and 8 of 24 patients had at least one depressive episode.

In each patient and control group 15 subjects were males (62.5%) and 9 were females (37.5%). The mean age (± SD) of the patients and the healthy controls was respectively 37.7 ± 12.2 years and 38.2 ± 10.6 years. The mean BMI value (± SD) was not different between patients and controls (respectively 24.2 ± 3.5 and 23.1 ± 3.4; $p = 0.258$).

The socio-demographic and clinical features of the OCD sample are presented in Table 1. According to the Y-BOCS Symptoms Checklist the more frequent obsessions were of symmetry/order (41.6%), contamination (37.5%) and aggressive (37.5%); the more frequent compulsions were of cleaning (45.8%) and checking (25%). Eight patients (33.3%) showed a lifetime comorbidity for depressive disorders and, of those, six (25%) for major depressive disorder.

Table 1. Socio-demographic and clinical characteristics of *N* = 24 OCD patients.

	OCD (*N* = 24)	
	***N*/mean**	**%/SD**
Marital status		
Married	12	50
Divorced	0	0
Never married	11	45.8
Widowed	1	4.2
Educational level	13.7	4.2
Working for pay		
Yes	15	62.5
No	9	37.5
Age at onset, years	19.42	5.54
Length of illness, years	18.96	12.70
Type of onset		
Insidious	18	75
Abrupt	6	25
Type of course		
Episodic	4	16.7
Chronic	20	83.3
Positive family history		
At least one axis I disorder	11	45.8
OCD	4	16.7
Other anxiety disorders	6	25
Mood disorders	5	20.8
Other psychiatric disorders	2	8.3
Y-BOCS		
Total score	22.17	4.63
Obsession subscore	11.50	2.28
Compulsion subscore	10.67	3.10
HAM-D-17 item	5.29	1.49
HAM-A	13.38	5.65
SF-36 subscales		

	OCD (*N* = 24)	
	***N*/mean**	**%/SD**
Physical functioning	89.16	10.70
Role limitations due to physical health	63.33	43.95
Bodily pain	76.87	20.25
General health	56.58	26.68
Vitality	43.33	15.99
Social functioning	43.31	20.39
Role limitations due to emotional problems	33.27	43.91
Mental health	44.91	21.47
Physical summary score	51.84	8.48
Mental summary score	31.27	13.10

Serum BDNF levels were decreased in drug-naïve OCD patients (36.90 ± 6.42 ng/ml) toward controls (41.59 ± 7.82 ng/ml) and the difference was statistically significant (p = 0.043) (Fig. 1).

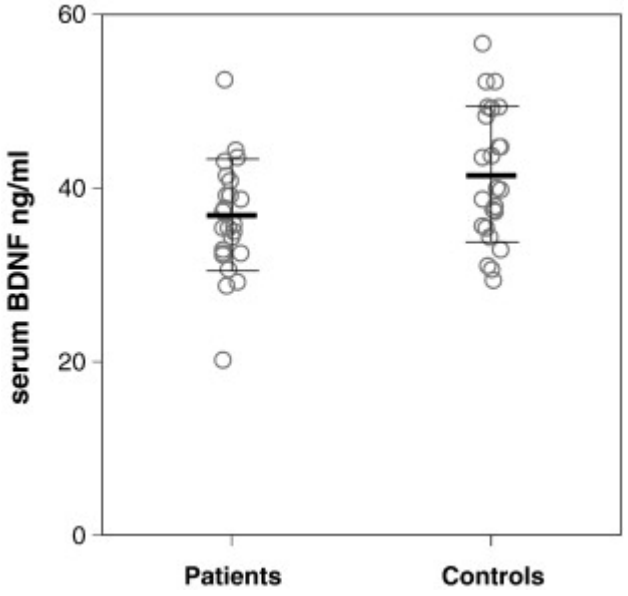

Fig. 1. BDNF serum levels: differences between OCD patients and healthy controls ($p = 0.043$).

Considering the relationships between serum BDNF and OCD clinical features, no significant correlations emerged with total Y-BOCS and obsession/compulsion subscale scores, age at onset of OCD and of symptoms, length of illness, family history, HAM-A, CGI and SF-36 total score. Only a trend for a decrease in serum BDNF was observed in patients with a lifetime history of major depression (MD) (32.38 ± 6.78 ng/ml) compared to those without (38.40 ± 5.71 ng/ml) (p = 0.09).

4. DISCUSSION

To our knowledge, this is the first case–control study investigating serum concentrations of BDNF in non-treated OCD. Our first aim was to assess if BDNF peripheral levels in a sample of drug-naïve OCD patients were different from those of controls.

The data obtained evidenced a significant reduction of serum BDNF levels in OCD patients: this finding corroborate the hypothesis of an alteration in the BDNF expression in the disease pathogenesis. In fact, this result is in line with the reported observations in studies who have addressed a BDNF involvement in the regulation of anxiety-related behaviours (Chen et al., 2006) and particularly in OCD (Alonso et al., 2008 and Hall et al., 2003). A decrease in the BDNF peripheral levels has been consistently evidenced in major depression (Sen et al., 2008) and also in anorexia nervosa (Monteleone et al., 2005 and Saito et al., 2009) a disorder that shares common features with obsessive–compulsive disorder, such as a high level of harm avoidance and neuroticism. Moreover, a negative correlation between the BDNF serum concentration and neuroticism has been observed also in subjects not affected by psychiatric disorders (Lang et al., 2004) suggesting that low BDNF levels might constitute a risk marker that is linked to vulnerability to several mood and anxiety disorders. At this regard the data obtained on the putative association of the neurotrophin content with the clinical features do not support a specific effect for OCD: firstly, the decreased serum BDNF levels in OCD did not correlate with an increased severity of OCD symptoms or with other clinical characteristics and, secondly, a trend for a greater serum BDNF decrease was observed in OCD subjects with a lifetime history of MD.

It is now clear that antidepressant drugs and in particular selective serotonergic reuptake inhibitors (SSRIs), that are commonly used in the therapy of OCD, beyond the action on their specific pharmacological targets play a role in the mechanisms of synaptic plasticity reactivation through the potentiation of BDNF signalling in the brain (Racagni and Popoli, 2008) and increase serum BDNF in depressed patients (Sen et al., 2008). This suggests that the BDNF serum measurement might be useful to screen for novel antidepressant-antiobsessional agents or possibly even become a predictive marker of individual response if a relationship can be established between the change in BDNF levels and the clinical improvement in longitudinal studies. Additional work will be required to determine whether peripheral BDNF levels also correlate with antiobsessional response to SSRIs in OCD patients.

Some limitations of the current study should be mentioned. First, it was carried out in a small sample of patients, but they were all drug-naïve, without concomitant depression and any recent severe life stressor. Second, this study is also limited by the mild obsessive–compulsive symptomatology that could have influenced our results; the choice of drug-naïve patients had probably excluded the recruitment of patients with more severe symptomatology.

In conclusion, our findings reveal for the first time that serum BDNF levels are decreased in drug-naïve patients with OCD and support the hypothesis of alterations in the neurotrophin regulation in this disorder providing a rationale for further investigations aimed to the identification of novel biomarkers and new therapeutic strategies for antiobsessional treatments.

ROLE OF FUNDING SOURCE

Funding for this study was provided by the Italian Ministry of Health and Cariplo Foundation; they had no further role in the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

CONFLICT OF INTEREST

All authors declare that they have no conflicts of interest.

ACKNOWLEDGMENT

We would like to specially acknowledge the contribution of Jorge Perez who passed away in October 2007 for the constructive suggestions in the preliminary phases of this study.

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