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Decreased Plasma BDNF Levels of Patients with Somatization Disorder

Nam-In Kang[1], Jong-Il Park[2,3], Yong-Ku Kim[4] ✉, and Jong-Chul Yang[2,3] ✉

[1]Department of Psychiatry, Maeumsarang Hospital, Wanju, Republic of Korea
[2]Department of Psychiatry, Chonbuk National University Medical School, Jeonju, Republic of Korea
[3]Research Institute of Clinical Medicine of Chonbuk National University-Biomedical Research Institute of Chonbuk National University Hospital, Jeonju, Republic of Korea
[4]Department of Psychiatry, Korea University Ansan Hospital, Korea University College of Medicine, Ansan, Republic of Korea

Objective Brain-derived neurotrophic factor (BDNF), one of the most abundant and important neurotrophins, is known to be involved in the development, survival, maintenance, and plasticity of neurons in the nervous system. Some studies have suggested that BDNF may play a role in the pathophysiology of several psychiatric illnesses such as depression and schizophrenia. Similarly, it is likely that the alteration of BDNF may be associated with the neuro-modulation that contributes to the development of somatization disorder.

Methods The purpose of this study was to determine whether there is an abnormality of plasma BDNF levels in patients with somatization disorder, and to analyze the nature of the alteration after pharmacotherapy using an enzyme-linked immunosorbent assay (ELISA).

Results The plasma BDNF levels of the patients with a somatization disorder were significantly lower compared with those of the control volunteers (83.61±89.97 pg/mL vs. 771.36±562.14 pg/mL); moreover, the plasma BDNF levels of those patients who received an antidepressant were significantly increased after the treatment (118.13±91.45 pg/mL vs. 72.92±88.21 pg/mL).

Conclusion These results suggest that BDNF may play a role in the pathophysiology of somatization disorder.

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Key Words Somatization disorder, BDNF, Neurotrophin.

INTRODUCTION

Somatization disorder is a chronic illness accompanied by numerous physical complaints regarding various parts of the body and lasts for more than 2 years, resulting in significant impairments of daily life and occupational function. The somatic symptoms usually involve gastrointestinal, cardio-respiratory, urogenital, musculoskeletal, and other internal systems.[1-3] The psychosocial disability of these patients leads to reduced productivity and an increased social health care burden.[4]

Brain-derived neurotrophic factor (BDNF) is a member of the nerve-growth-factor family, and plays a critical role in the growth, differentiation, maintenance, and synaptic plasticity of neuronal systems. It is the most abundant of the neurotrophins in the brain and serves as a neuromodulator.[5-9] There is some evidence of the association between BDNF and several psychiatric illnesses, and of a clinical severity that includes major depression, anxiety disorder, and psychosis.[10-15] Only a few investigations, however, have examined the relationship between serum BDNF and somatization disorder.

BDNF is also involved in various other mental and physical conditions such as stress,[16,17] allergic disease[18,19] and pain. BDNF which serves as a pain modulator plays an important role in pain sensation.[20-26] Although the pathophysiology of somatization disorder is not clearly identified yet, several studies have suggested that abnormal pain sensation is one of the possible pathogeneses of somatization disorder.[13,27-29] Moreover, BDNF influences the serotonin neurotransmitters that

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✉ **Correspondence:** Jong-Chul Yang, MD, PhD
Department of Psychiatry, Chonbuk National University Medical School, 20 Geonji-ro, Deokjin-gu, Jeonju 54907, Republic of Korea
Tel: +82-63-250-2580, **Fax:** +82-63-275-3157, **E-mail:** yangjc@jbnu.ac.kr

✉ **Correspondence:** Yong-Ku Kim, MD, PhD
Department of Psychiatry, Korea University Ansan Hospital, Korea University College of Medicine, 122 Jeokgeum-ro, Danwon-gu, Ansan 15355, Republic of Korea
Tel: +82-31-412-5140, **Fax:** +82-31-412-5144, **E-mail:** yongku@korea.ac.kr

are linked to somatoform disorder and hypochondriasis.[12,30-33] On these bases, we assumed that there may be some changes of the BDNF levels of the patients with somatization disorder compared with the healthy control volunteers. The aim of the present study was to clarify the magnitudes of the relationships between somatization disorder and serum BDNF.

METHODS

In this study, we examined the peripheral BDNF levels in the plasma of the following two independent groups: somatization-disorder patients and healthy volunteers. The 27 patients with somatization disorder (mean age: 46.33±9.73 years; 12 males and 15 females) who fulfilled the DSM-IV criteria for somatization disorder and the 27 healthy control volunteers (mean age: 46.81±6.81 years; 12 males and 15 females) were enrolled in the study. DSM-IV diagnoses were determined from a consensus procedure involving two psychiatrists who used all of the available clinical material including a semi-structured interview based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Revised (DSM-IV).[34] A complete medical history (including allergic history) and physical examination; laboratory tests including urine and blood screens; and an electrocardiogram were obtained from both the patients and the control volunteers. Patients were excluded from the study if a physical illness, comorbid psychiatric illness, any neurological disorder, or abnormal results appeared on the laboratory screening tests. The clinical assessment of the somatization disorder was measured by a Korean version of the Wahler physical symptom inventory (K-WPSI). Patients with major depressive disorder, diagnosed in accordance with the DSM-IV and Beck Depression Inventory (BDI, cut-off score ≥21), were excluded from this study. The age- and sex-matched normal control volunteers consisted of randomly selected healthy individuals who visited the University Hospital for regular health screenings. All of the subjects provided written, informed consent after receiving a complete description of the study. The study was approved by the hospital ethics committee (Korea University Ansan Hospital and Chonbuk University Hospital, Korea), and the study procedures were in accordance with Helsinki Declaration of 1975, as revised in 1983.

Between 8.00 and 9.00, 10 mL of fasting blood from each of the patients was withdrawn into a lithium heparin vacuum tube, and the blood was immediately centrifuged at 3800 rpm for 10 min. Plasma was stored at -70°C until it was thawed for assay. The human BDNF was assayed using the DuoSet ELISA Development System (Catalog number DY248, R&D Systems, UK). The assay had a detection range from 20 pg/mL to 4000 pg/mL. All of the assays were performed in duplicate using the manufacturer-recommended buffers, diluents, and substrates. The optical density of the color reaction in the wells was read using a microtiter plate reader (Bio-tek instruments) that was set for 450 nm. The concentrations of the samples in each plate were calculated according to a standard curve and the dilution factor.

All of the numerical values are expressed as the mean± standard deviation. The differences of the plasma BDNF levels between the patients and healthy controls were analyzed with a non-parametric Mann-Whitney test using the SPSS 15.0 software package; the statistical significance level was set at $p<0.05$. We assessed the alteration of the plasma BDNF levels after the pharmacotherapy treatment using the Wilcoxon Signed Ranks test. Of the 27 patients, 22 patients with somatization disorder took the antidepressant medication, most of which are selective serotonin reuptake inhibitors (SSRIs) (fluoxetine: n=13, paroxetine: n=8) but only one patient took the noradrenergic and specific serotonergic antidepressant (NaSSA) medication (mirtazapine). After the medication, the blood sampling was conducted when the Clinical Global Impression-improvement scale (CGI-I) was 3 which means 'minimally improved' between 9 to 16 weeks. The correlations between the BDNF levels and the clinical-assessment-scale scores were examined using the Spearman correlation coefficient.

RESULTS

The socio-demographic and psychopathological variables of the normal controls and the patients with somatization disorder are shown in Table 1. The groups were similar in age (p=0.897), sex ratio (p=0.414), and BMI (p=0.299). The BDI

Table 1. Socio-demographic and psychopathological variables of the normal controls and the patients with somatization disorder

Characteristics	Normal control (mean±SD)	Patients with somatization disorder (mean±SD)	p-value
Age (year)	46.81±6.81	46.33±9.73	0.897
Sex (M/F)	12/15	12/15	0.414
BMI (kg/m^2)	22.63±2.31	23.14±2.45	0.299
K-WSPSI	0.87±0.24	2.21±0.81	0.000

BMI: Body Mass Index, K-WPSI: Korean version of Wahler Physical Symptom Inventory

Table 2. Plasma BDNF level difference between the normal controls and the patients with somatization disorder

Variables	Normal control (N=27)	Patients with somatization disorder (N=27)	Z	p-value
BDNF (pg/mL)	771.36±562.14	83.61±89.97	-5.735	<0.000*

*p<0.01 (Mann-Whitney). BDNF: brain-derived neurotrophic factor

Table 3. Multivariate association between BDNF level (lower vs. higher)* and group (somatization disorder vs. normal control) of participants after adjusting age and gender

	OR	95% CI	p-value
Age	0.990	0.893–1.098	0.850
Gender			
Female	1.000	-	
Male	0.972	0.172–5.489	0.974
Group			
Somatization disorder	1.000	-	
Normal control	64.640	11.748–355.659	<0.001

*BDNF was median splitted into lower (≤201.44 pg/mL) vs. higher BDNF (>201.44 pg/mL) groups. BDNF: brain-derived neurotrophic factor

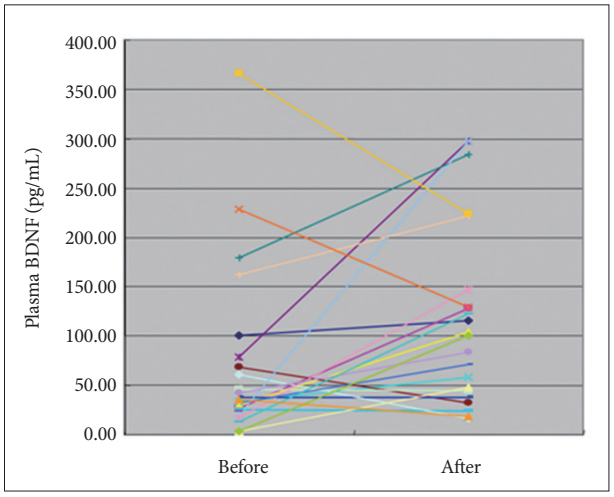

Figure 1. Changes of plasma BDNF level before and after treatment in patients with somatization disorder (N=22). BDNF: brain-derived neurotrophic factor.

score was not clinically severe in both of the groups (normal controls=3.56±3.68; patients with somatization disorder=12.89±3.84). There was a significant difference of the K-WPSI (p=0.000). The mean plasma BDNF levels of the 27 patients with somatization disorder were significantly lower compared with those of the controls (83.61±89.97 pg/mL vs. 771.36±562.14 pg/mL; Z=-5.735; p<0.001), as shown in Table 2.

In multivariate logistic regression analysis (Table 3), normal control (OR=64.640) was significantly associated with higher BDNF level even after controlling for age and gender. In the 22 patients who received pharmacotherapy, their plasma BDNF levels were significantly increased after the antidepressant treatment (118.13±91.45 pg/mL vs. 72.92±88.21 pg/mL; Z=-2.029; p=0.042), as shown in Figure 1; however, the clinical-assessment-scale scores did not reveal any significant correlations with the BDNF levels.

DISCUSSION

Many studies have addressed the clinical importance of BDNF in psychiatric diseases, and significant changes of the plasma BDNF levels for each condition have been demonstrated;[35-38] furthermore, some of the researchers also reported the recovery of lowered plasma BDNF levels, especially for depressive disorders, after proper treatment.[39-41] For somatization, however, investigation results regarding the implications of BDNF are extremely rare. The present study showed that somatization disorder was associated with significantly decreased plasma BDNF levels; therefore, a decrease of plasma BDNF levels could constitute a vulnerable marker for disease diagnosis. Our study did not, however, evaluate the relationship between the plasma BDNF levels and somatization-disorder-symptom severity, or whether any correlation with the specified clinical assessment subscale existed. Also, we did not conduct an experiment on the plasma BDNF levels in the treatment non-response group, and such experiments are still required to form a definite conclusion.

Somatic symptoms, one of the major features of somatization disorder, are very common in depressive and anxiety disorders,[42-46] and the comorbidity rate is also very high.[47-49] Decreased plasma BDNF levels in depressive and anxiety disorders have been observed in many previous studies.[11,50,51] In this context, our results were achieved in consideration of the previous studies. But, in spite of this meaningful result, we did not completely rule out the effect of stress on plasma BDNF level. As we previously mentioned, there are several reports about the relationship between BDNF and stress.[52-55] Sometimes, the BDNF reflects the stress condition but in another case, specific genetic status of BDNF also acts as a precipitating factor of stress. So we suggest that further investigations of BDNF in relation to somatization disorder in well controlled sample would be of interest in the future.

We also studied the efficacy of antidepressants in the treatment of 22 patients with somatization disorder, and the condition of the patients after the treatment was evaluated using neuropsychological scales and the plasma BDNF levels. Antidepressant treatment has been shown to enhance the production of plasma BDNF levels; however, despite its previous

positive results for clinical improvement, we failed to show a statistically significant association between the clinical-assessment-scale scores and the plasma BDNF levels after the antidepressant treatment. One of the possible reasons for why we were unable to produce this association is an insufficient clinical follow-up period; following treatment, we reassessed the plasma BDNF levels after a period that lasted from 9 weeks to 16 weeks. Considering that somatization disorder is a chronic disease that typically lasts for more than 2 years, 9 weeks to 16 weeks is not an adequate time frame for observing the relationship between the plasma BDNF levels and the clinical-assessment-scale scores, so this needs to be addressed in further studies. Also, the number of patients participated in our experiment was too small and the blood samples after the treatment were obtained at different time points between the individuals from 9 to 16 weeks. Furthermore most of the drugs used in this study were SSRIs but there are several other kinds of antidepressants are existed and there is a possibility that they would show another results. Therefore, further clinical investigations with a same and longer time frame and of a larger scale are needed to attain a more precise conclusion about the effect of SSRI treatment on the plasma BDNF levels and clinical-assessment-scale scores for somatization-disorder patients.

In addition to the previously described limitations, another limitation of this study was identified. The BDNF was apparently capable of crossing the blood-brain barrier,[56,57] and a positive relationship between the central- and peripheral-blood BDNF in rats has been reported[58] however, the cellular origin of human plasma BDNF has not yet been clearly defined.[39] Therefore, an assessment of plasma BDNF that is circulating in the body, which is not stored in the brain, cannot exactly reflect the BDNF level of the brain. Nevertheless, this study is worthy of notice, as it is the first study to find lower plasma BDNF levels in somatization-disorder patients.

In conclusion, BDNF may play a role in the pathophysiology of somatization disorder. Regarding somatization disorder, however, further studies are needed to clarify the role of BDNF more precisely and its interaction with other vulnerable factors.

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