doi: 10.1111/sji.12158

Changes in Serum Levels of Brain Derived Neurotrophic Factor and Nerve Growth Factor-Beta in Schizophrenic Patients Before and After Treatment

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Received 11 December 2013; Accepted in revised form 29 January 2014

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Abstract

Schizophrenia is one of the most debilitating diseases among psychiatric disorders. Recent studies suggest the existence of effective immunological changes in the pathophysiology of this disease. The purpose of the current study was to determine the changes in serum levels of Brain Derived Neurotrophic Factor (BDNF) and Nerve Growth Factor-beta (NGF) in schizophrenic patients before treatment and 40 days after treatment. In this case-control study, serum levels of BDNF and NGF were measured by ELISA in 26 patients with schizophrenia and 26 healthy controls. All patients were treated with clozapine or risperidone for 40 days. A positive and negative syndrome scale (PANSS) questionnaire has been used to recognize the severity of the disease and to assess the response to treatment. Neurotrophin concentrations were compared before and after the treatment and with control groups using paired *t*-test and ANOVA test. BDNF and NGF levels in the case group were more than levels after treatment, but these differences were significant only for NGF. Concentrations in both neurotrophins were higher than the control group. The statistically significant difference was observed between changes in the NGF levels in the case and the control group, while no significant difference was seen in changes of BDNF. The main conclusion to be drawn from this study was that the increase in BDNF and particularly NGF may have an important role in causing schizophrenia. And possibly drugs clozapine and risperidone help to treat the disease by reducing the concentration of Neurotrophins.

Introduction

Schizophrenia is a disorder of the executive function of both sensory and central nervous system (CNS). Although schizophrenia is characterized by a single disease, it is composed of a group of disorders that have heterogeneous causes [1]. Approximately 1% of the general human populations are affected. It is estimated that adverse financial effects of schizophrenia in the United States are being more than total compensation caused by all cancers. About 75% of people with schizophrenia are severely disabled and unemployed. On the other hand the percentage of suicide is so high among these patients [2]. Various hypotheses are proposed for the pathogenesis and pathophysiology of the disease, but the most accepted one is dopaminergic system disorder, which is based on the hyperactivity of dopaminergic neurotransmitters [1]. There are some evidences suggesting that serum Neurotrophic levels [3] and neurodevelopment [4] are impaired in schizophrenia. Neurotrophins are a large family of dimmer polypeptides including: nerve growth factor (NGF), brain-derived Neurotrophic factor (BDNF) and the neurotrophins 5, 4, 3 and 6 [5]. BDNF is known as a regulator of dopamine GABA and serotonin receptors, which act through the TrK B tyrosine kinase receptor and has an important role in the survival and function of neurons. NGF is present in the cerebral cortex; especially in the hippocampus and is important for the maintenance of cholinergic neurons function in the CNS [6]. Shoval and Weizman in 2005 reported the protective effects of these factors. Neurotrophins are effective for growth, differentiation and coordination of neural responses to emotional stimuli [6,7]. Also neurotrophins are typical regulators through monominergic, GABAergic and cholinergic systems. All neurotrophins have the same basic structure, but specific connections to specific receptors will lead to different biological effects [8]. Neurotrophins effect on growth and differentiate of developing neurons in the central nervous system and protect neuronal cells in response to stress.

SCANDINAVIAN JOURNAL OF Immunology AN INTERNATIONAL MONTHLY JOURNAL

Studies have shown that neurotrophins have an important role in the transmission of neural messages in the CNS and nerve regeneration [9]. So it may have relevance in the pathophysiology of central nervous system disorders such as schizophrenia. Several conducted studies showed different conflicting results. For example, in study of Autry and Monteggia reported that serum BDNF levels in schizophrenic patients were lower than controls [10]. Also in a study conducted by Maria *et al.* [11] serum levels of NGF was reported to be increased in people with schizophrenia. Knowing whether or not there is a relationship between the lacks of these molecules and disease and whether the treatment could change these molecules and recurrence of disease could change them or not, has such a great importance. So we got to check serum levels of neurotrophins in the acute phase of the disease before and after treatment, in order to investigate the possible role of these molecules in the disease process.

Materials and methods

A case-control study conducted in patients with a diagnosis of schizophrenia, which confirmed by administration of interviews as SCID (Structured Clinical Interview for DSM-IV) who referred to the Zare Hospital-Iran during July 2008 to January 2011. All patients were asked to complete a written consent form, before entering the study. Also the project approved by the Mazandaran Medical University ethics committee. Individuals whom disease were being diagnosed for the first time or people whose disease relapsed due to not using the drugs and the doctor has used second generation antipsychotic drugs for their treatment, were interred the study. Based on these, 30 patients have had the eligibility criteria and selected for the study. Due to the lack of enough serum samples of second sampling stage four patients were excluded and finally the results of 26 patients were studied. Those patients who had used drugs in addition to the second generation drugs or suffered from other psychiatric disorders were excluded too. Of 26 individuals were selected as controls. Control groups were blood donors who referred to the blood transfusion organization Sari-Iran and had no history of antipsychotic drug taking and past history of any psychiatric disorders. These people were similar to the case group patients as an age and sex and had normal CRP and ESR levels. Data were collected by using two questionnaires for evaluating the schizophrenic symptoms, demographic features, socioeconomic status and also the medication data. An International PANSS questionnaire [12] was used to assess positive and negative symptoms in patients. The demographic questionnaire included 13 questions about demographic data and three questions related to the history of drug use. After confirming the diagnosis of schizophrenia in patients, the treatment with risperidone and clozapine was initiated based on the patient's condition. Clozapine used when their previous treatments for the disease have not been successful or when the treatments have caused adverse side-effects. Moreover risperidone administered once or twice daily in other cases. Before the treatment 5 ml of venous blood was taken and serum was isolated. All sampling was conducted during the morning. The serums were immediately sent to a central laboratory and stored in a freezer of −70 °C. Sampling was repeated 40 days after the start of treatment again. Also 5 ml of venous blood samples was taken from the individuals of the control group in the same conditions as case group and the serum was separated. Serum levels of NGF_beta and BDNF were measured using of Sandwich ELISA method and the commercial kit according to the manufacturer's instructions (Glory science Co., Ltd, Hangzhou, China). Laboratory workers were not aware of samples that were belonging to case group or the control group.

Statistical analyses. Several statistical methods were used for data analysis in this study: All data analyzed using SPSS Ver. 18.0 software (SPSS Inc. Released 2009. SPSS for Windows, Chicago, IL, USA). Serum levels of Neurotrophins in patients before treatment and 40 days after onset, and also changes in PANSS scale data were compared using paired-*T*-test. Pearson test was used to determine the correlation between serum levels of BDNF and NGF before and after treatment. The correlation was significant at the 0.01 level (2-tailed). ANOVA test used to determine the differences between the mean serum levels of factors of case group before and after treatment with the control group. P value <0.05 were considered statistically significant for all results. As well to determine which factor has the most significant relationship, multiple comparisons (Dunnett Test) were used. Spearman test was used for evaluating the relationship between BDNF and NGF levels with PANSS scale. The independent *t*-test was used for examining the relationship between disease relapse, times of hospitalization, disease duration with BDNF and NGF levels and also for differentiating the efficacy of the clozapine and risperidone on BDNF and NGF levels.

Results

Of 52 patients participated in the study, 26 patients were selected as case group and 26 patients were considered as a control group. Patients and controls were matched for age and sex. The mean age of the case group was 9.49 ± 33.61 and 8.86 ± 33.92 for the control group. In total, 40 (76.92%) were male and 12 (23.08%) were female. Their socioeconomic status was evaluated based on education, job, car, home and health insurance. Patients divided into three groups based on the total points assigned to each of the above items: Low, medium and high socioeconomic status. According to the results, 13 patients (50%) had low socioeconomic status, nine patients (34.62%) had moderate and four patients (15.38%) had a high socioeconomic status. An international PANSS questionnaire was used for

detecting positive and negative symptom of schizophrenic patients and to assess the response to treatment in this study. The mean scores of the evaluated variables in this questionnaire are mentioned in Table 1.

Brain-derived Neurotrophic factor and NGF levels were measured and compared before and after treatment in the patient group and the control group (Table 2). The relationship between pre- and post-treatment group with control group were examined using an ANOVA test. Results showed no significant change between BDNF concentrations which were measured in the three groups statistically ($P = 0.368$, $F = 1.014$). Findings revealed no significant difference between the mean serum levels of BDNF pre-treated with the control group ($P = 0.35$) and its level after treatment BDNF with control group ($P = 0.36$).

Comparison of NGF concentrations between the three groups showed statistically significant changes. $F = 3.525$, (2, 75), $P = 0.034$. The mean difference in NGF concentration prior to treatment with the control group was also statistically significant. ($P = 0.01$). While this difference was not significant in the post treatment group compared to the control group ($P = 0.09$). To determine which groups have more significant differences as a concentration of NGF; the multiple comparison test (Dunnett Test) was used. The result suggests that mean serum levels of NFG before the treatment and control group was more statistically significant ($P = 0.019$). Atypical antipsychotics were used for the treatment of patients. Among the 26 studied patients, 16 patients (61.53%) treated with risperidone and 10 patients (38.47%) were also treated with clozapine. For evaluating the comparative effect of the above drugs on the BDNF and NGF concentrations before and after treatment, the independent *T*-test was used. The results showed that risperidone has more efficacy than clozapine in decreasing of BDNF levels before and after the treatment. But in the case of NGF, the clozapine was more effective than risperidone; however, no significant difference existed statistically as an effect of these results. The correlation between BDNF and NGF concentrations before and after treatment were analyzed by the Pearson correlation test. Evidence indicates that a positive correlation between serum concentrations of these two factors before treatment ($R = 0.726$) (Fig. 1) and after treatment exists ($R = 0.835$) (Fig. 2).

The relationship between the frequency of relapses, hospital admissions, duration of the illness and the drugs used with the mean serum levels of BDNF and NGF before and after treatment were examined in this study. The results showed no significant difference between the variables and changes in NGF and BDNF levels (Table 3).

Table 1 Mean scores of positive and negative symptoms before and after the treatment.

PANSS questionnaire scores	Before the treatment	After the treatment	t	df	*P*-value
Mean total score	87.61 ± 22.99	52.93 ± 12.63	9.50	25	0.002
Mean of positive symptom scores	21.46 ± 8.44	11.46 ± 4.07	7.09	25	0.000
Mean of negative symptom scores	25.46 ± 7.77	15.92 ± 6.79	7.16	25	0.000

Discussion

The results of this study showed a significant relationship between mean concentration of NGF before and after treatment, levels of serum NGF before treatment and control; BDNF and NGF concentrations before treatment with the PANSS scale after treatment and *vice versa*. Also a positive correlation was observed between NGF and BDNF after treatment. BDNF and NGF concentrations were higher in patients rather than in the control group.

Changes in BDNF and NGF in case and control group

Recent studies in patients with schizophrenia leads to different results in association with Neurotrophins levels, and certainty of these changes has not been fully established yet [13]. BDNF levels were increased compared to controls in our study that was similar to the results of the study of Durany and Takahashi [14, 15]. One of the factors that is attributed to the increase of BDNF in these patients is aging, which can be the cause of similarity seen in the results of this study and other studies [16]. Studies of animal model showed that haloperidol, clozapine and risperidone significantly reduced BDNF levels in the frontal and occipital cortex and hippocampus, also lead to decrease of BDNF gene expression [17–19]. The results were in line with our study, which BDNF serum level is decreased following treatment. It seems that the decrease of BDNF gene expression might be due to the block of the 5-HT receptor.

Some studies have indicated that the concentration of this factor is increased in the central nervous system. BDNF is also expressed outside the central nervous system; in the blood and its blood levels is representative of the level in the central nervous system [20–22].

However, other studies have shown that serum BDNF levels are decreased. One hypothesis is that reduced BDNF levels may occur in 20 years and in response to limited neurodegenerative processes in patients with chronic schizophrenia. Some studies have reported that there is no difference between BDNF levels of case and control groups. Toyooka *et al.* in their study investigated the changes in serum levels of neurotrophins in patients

Table 2 Serum neurotrophin levels in patients (before and after treatment) and control group.

Factors	Before treatment ($N = 26$)	After treatment ($N = 26$)	t	df	P-value*[a]	Control group ($N = 26$)	P-value*[b]
BDNF (pg/ml)	4.128 ± 4.017	4.065 ± 3.648	0.273	25	0.787	3.18 ± 3.32	0.368
NGF (pg/ml)	344.5 ± 215.731	289 ± 167.794	2.072	25	0.049	209.8 ± 163.47	0.019

[a]Comparison of mean serum concentrations of BDNF and NGF-beta before and after treatment (paired t-test).
[b]Comparison of mean serum concentrations of BDNF and NGF-beta before and after treatment with control group (ANOVA test).
*P-value <0.05 considered significant.

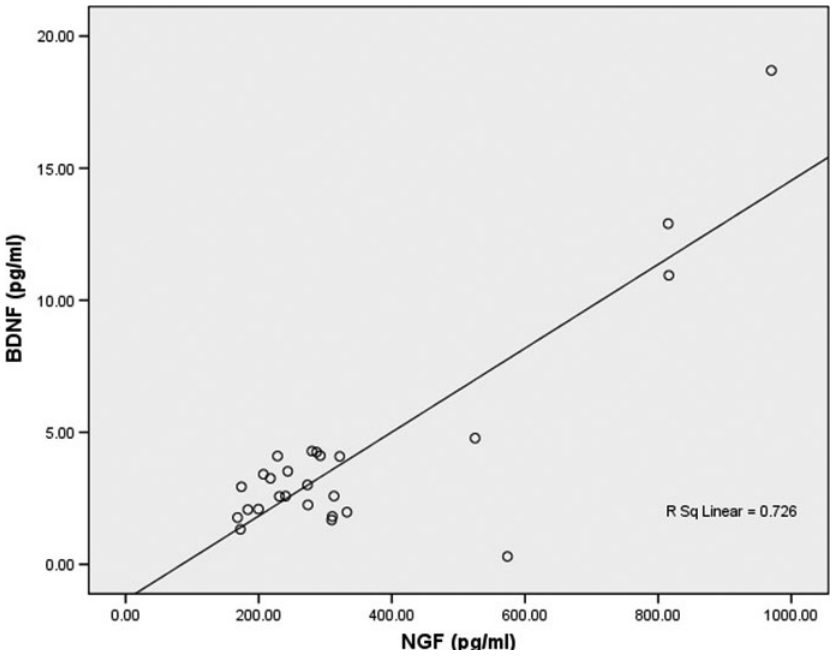

Figure 1 Correlation of BDNF and NGF serum concentration before treatment.

receiving Haloperidol that provided no positive results [23].

In the present study, the mean serum NGF in patients after treatment than before treatment and the control group had a statistically significant reduction.

This may indicate that NGF plays an effective factor in the pathophysiology of schizophrenia. Xiong and colleagues in 2011 reported in their study that NGF levels were higher than controls, which is the same as our data [24]. The findings of some studies showed lower levels of this Neurotrophins before treatment that is contrary to the hypothesis proposed in the present study [25–27].

All these differences in the changes of serum levels of BDNF and NGF indicate the absence of a proven theory about these changes. These differences could be due to the complexity of symptoms in schizophrenia and the lack of biological homogenicity of patients and particularly differences in the last studies that examine cases who were treated chronically.

Relationship between BDNF, NGF and PANSS total score questionnaire

Severity and treatment response in schizophrenic patients are measured by PANSS. In this study, a significant relationship between serum BDNF and NGF pre-treatment, with post-treatment PANSS score were seen, and *vice versa*, which is indicative of improvement of patients with treatment. Some findings suggest a lack of correlation between BDNF levels and PANSS negative symptoms [28, 29]. Also, Xiong noted that there is no relationship between NGF levels and score of PANSS [24], although there are some results that indicate that there is a significant relationship between the levels of BDNF and positive symptom scale PANSS [30]. The complexity of schizophrenia symptoms, short duration of the disease in some patients and the relatively low mean age, may be able to explain this lack of correlation. These results and observations can be followed by the interaction between dopamine and Neurotrophins.

Drug and neurotrophins

The results of this study showed that risperidone can significantly decrease BDNF levels after treatment, while clozapine effectively reduces the amount of NGF. Chen [31] showed that risperidone can effectively increase serum levels of BDNF in contrary to clozapine. In a study of Tan *et al.*, treatment with risperidone had no effect on serum

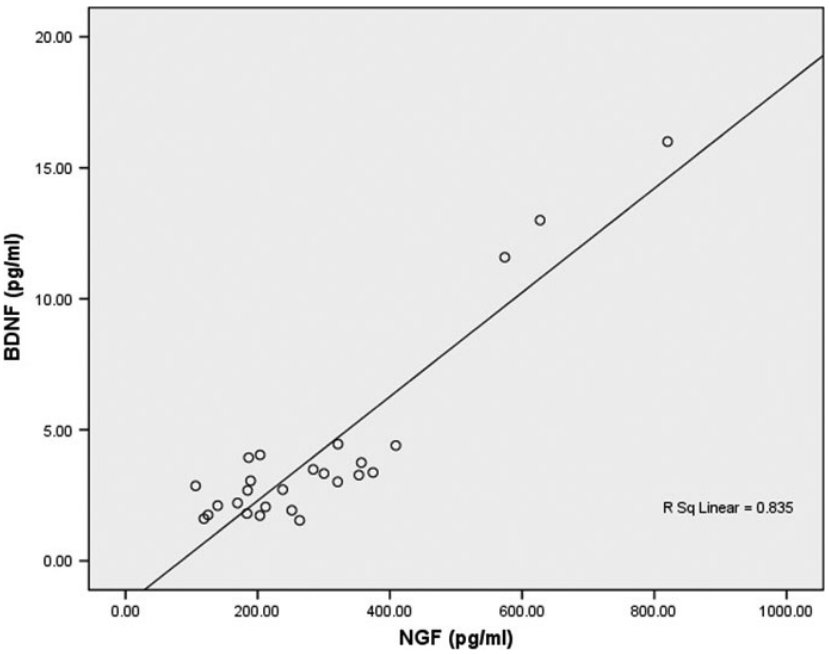

Figure 2 Correlation of BDNF and NGF serum concentration after treatment.

Table 3 Relationship between the clinical features and neurotrophin levels before and after the treatment.

Variables	BDNF level concentration before treatment	BDNF level concentration after treatment	*P*-value	NGF level concentration before treatment	NGF level concentration after treatment	*P*-value
Frequency of relapses						
Less than 5 times	4.01	4.05	0.97	3.50	2.88	0.31
More than 5 times	4.50	4.09	0.81	3.23	2.91	0.79
Frequency of hospital admissions						
Less than 7	4.33	4.39	0.96	3.69	2.97	0.24
Between 7 and 15	2.99	2.23	0.34	2.08	2.43	0.51
Duration of the illness (year)						
Less than 5	3.78	3.80	0.98	3.82	2.49	0.08
More than 5	4.38	4.25	0.95	3.16	3.17	0.98
Medication						
Clozapine	5.63	5.62	0.99	438.25	359.47	0.49
Risperidon	2.80	2.91	0.76	2.75	2.37	0.24

levels of BDNF and NGF. Also, results of some studies indicated that treatment of 6–8 weeks with atypical antipsychotics such as risperidone, olanzapine and clozapine does not have any effect on serum levels of BDNF [32, 33]. Better effectiveness of drugs on serum neurotrophin concentration in our study could be justified by the items such as: interaction between dopamine and BDNF, BDNF effect on synaptic plasticity and its structure in the CNS and the protective effect of BDNF against the neural damage. The exact mechanism of this effectiveness is not yet known. Although some scholars believe that the effect of these drugs on cell viability and neurogenesis induce changes in Neurotrophins; these effects are almost modulator but not stimulatory [34, 35].

The relationship between the number of relapses, hospitalizations, duration of illness, with BDNF and NGF concentrations

One of the main purposes of the long-term treatment of schizophrenia is the consistent improvement of the disease and prevention [36, 37]. The few studies conducted to determine the relationship between factors such as number of relapses, hospitalizations, duration of illness with neurotrophin concentrations. In our study, no relationship between the mentioned factors and the serum levels of neurotrophins were observed. Heigsberg not reported any significant relation as our study [38]. Xiu *et al.*, reported a significant relationship between duration of illness and changes of BDNF serum concentrations [35].

These differences could be associated with clinical phenotypes including: gender, antipsychotic treatment, and patient's psychotic symptoms.

Study limitations and strengths

One limitation of the present study was to measure serum levels of Neurotrophins. So that most of these factors are released in the CNS and small amounts of them are released into the peripheral cells. Since the BDNF can pass the blood-brain barrier so blood level representative of its level in the CNS [39]. Numerous studies have also shown that intraventricular injection of NGF can affect the activity of peripheral cells and *vice versa* peripheral injection of NGF could affect the CNS [40]. In our study, all measurements were carried out simultaneously in the morning. Circadian variations in concentration of Neurotrophins previously mentioned in some studies [41]; sampling of some factors such as BDNF is reduced in the evening. Therefore, in our studies the effects of circadian variation have been eliminated as a confounding factor. In addition, matching of groups as age and sex and eliminating of patients treated with antipsychotic drugs could give more credibility to the results. Another limitation of the study was to measure the neurotrophin levels in the control group. It was better that the measurements would be implemented in two stages (before and 40 days later) and were compared with the other groups.

Conclusion

According to the findings of this study indicating that NGF and BDNF levels decreased in patients after treatment and also The amount of these two molecules before the treatment of patients is more than its levels in the control group; it can be concluded that changes in these two factors are involved in the pathophysiology of schizophrenia.

In other words, unconventional increasing of these two molecules, particularly the NGF has an important role in the evolution and development and function of the central nervous system. So far, very few studies performed prospectively to evaluate the relationship between the prognostic relevance of neurotrophins and consequences of psychiatric disorders, particularly schizophrenia; therefore, further investigation and experimentation into this field is strongly recommended.

Acknowledgment

This manuscript is the result of research project approved by the research council of Mazandaran University of Medical Sciences (MAZUMS). In this way, we thank the president, deputies and all staff of painstaking research and technology deputy of Mazandaran University of Medical Sciences, for their assistance in all process of ratifying and implementing the research project. The authors gratefully acknowledge all educational authorities for operating the implementation process of this thesis. Also, thank all Zare hospital staff members specially laboratory department for helping us with blood sampling and acknowledge with grateful appreciation the kind assistance the Dr Fazlali and Dr Nazemi (Residents of psychiatrics) for helping with data collection. The authors would like to thank the personnel of the Immunology Laboratory of MAZUMS for contributions in laboratory studies. Finally the corresponding author of the manuscript has special thanks to the Mrs Mina Rostami, Dr Mehran Taghipour and Dr Sovaid Taghipour for their editorial assistance in writing the manuscript.

Conflict of interests

None of the contributing authors have any conflict of interest, including specific financial interests or relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

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