



RESEARCH ARTICLE

Investigation of the effect of electroconvulsive treatment on serum glial cell line-derived neurotrophic factor levels in patients with schizophrenia and bipolar disorder

Mustafa Akkus¹, Tefvik Kalelioglu², Hicret Kan³, Nesrin Karamustafalioglu⁴, Mehmet Cem Ilnem⁴

¹Erzincan Binali Yildirim University Faculty of Medicine, Mengucek Gazi Training and Research Hospital, Department of Psychiatry, Erzincan, Turkiye

²Virginia University, Department of Psychiatry and Neurobehavioral Sciences, Virginia, USA

³Dr. Ersin Arslan Training and Research Hospital, Department of Psychiatry, Gaziantep, Turkiye

⁴Bakirkoy Prof. Mazhar Osman Training and Research Hospital for Psychiatry, Neurology, and Neurosurgery, Department of Psychiatry, Istanbul, Turkiye

ABSTRACT

Objective: A relationship between glial cell line-derived neurotrophic factor (GDNF) and the etiology of schizophrenia (SCH) and bipolar disorder (BD) has been reported. GDNF, in addition to the other neurotrophic factors, may play a role in the mechanism of action of electroconvulsive treatment (ECT). The primary objective of this study was to investigate the effect of ECT on the serum GDNF levels before and after the administration of ECT.

Method: Thirty male inpatients undergoing treatment for SCH (n=20) or BD (n=10) and 28 age- and sex-matched healthy control subjects were included in the study. The serum GDNF levels of the patients were measured both before and after the ECT administration using the commercially available enzyme-linked immunosorbent assay kits.

Results: The serum GDNF levels of the patients with BD (p=0.013) but not SCH (p=0.998) showed a statistically significant change after ECT. The mean serum GDNF level of all patients (SCH and BD) was not statistically significantly different from the healthy control subjects prior to the ECT administration (p=0.177).

Conclusion: The current study is the first to report a comparison of the serum GDNF levels after ECT in patients with SCH and BD. The findings of this study do not support the hypothesis of a definitive relationship between serum GDNF levels and outcomes of ECT in patients with SCH, but do support such a relationship in patients with BD.

Keywords: Bipolar disorder, electroconvulsive treatment, GDNF, schizophrenia

How to cite this article: Akkus M, Kalelioglu T, Kan H, Karamustafalioglu N, Ilnem MC. Investigation of the effect of electroconvulsive treatment on serum glial cell line-derived neurotrophic factor levels in patients with schizophrenia and bipolar disorder. *Dusunen Adam J Psychiatr Neurol Sci* 2022;35:86-92.

Correspondence: Mustafa Akkus, Erzincan Binali Yildirim University Faculty of Medicine, Mengucek Gazi Training and Research Hospital, Department of Psychiatry, Erzincan, Turkiye

E-mail: drmustafaakkus@gmail.com

Received: February 08, 2022; **Revised:** March 27, 2022; **Accepted:** April 22, 2022

INTRODUCTION

Schizophrenia (SCH) is a chronic disease that manifests itself in emotional, cognitive, and behavioral impairments (1), while bipolar disorder (BD) is a chronic mood disorder with recurrent manic, depressive, or hypomanic episodes (2). Glial cell line-derived neurotrophic factor (GDNF), a neurotrophic factor from the transforming growth factor- β family, was shown to be one of the most potent factors for the survival of dopaminergic neurons (3). The pathogenesis of SCH has been associated with changes in GDNF function (4). An increase in serum GDNF levels was observed after atypical antipsychotic drug treatment in patients with SCH, suggesting that GDNF may play a role in the etiology and pharmacological treatment of SCH (5). A decrease in GDNF levels was reported in patients with SCH compared with the healthy control subjects, most likely due to dopaminergic dysfunction in SCH (6).

Serum GDNF levels were reported to show an increase in both manic and depressive episodes in patients with BD; however, no statistically significant difference was found between the patient group at the euthymic phase and a healthy control group (7). These findings suggest that GDNF may play a role in the pathophysiology of BD or increased adaptive response (7). Of note, other studies have reported a decrease in GDNF in BD patients during the acute manic and depressive phase (8). Patients with mood disorders were found to have significantly lower serum GDNF levels than controls suggesting that low GDNF levels might play a role in the pathophysiology of mood disorders (9). More importantly, the same study reported that serum GDNF levels showed a significant increase after drug treatment (9). A relationship between polymorphisms in the potential regulatory sites of GDNF and BD has been suggested, indicating that there may be a genetic basis for the observations reported (10).

Electroconvulsive treatment (ECT) is one of the treatment options used in patients with SCH and BD (11). The possible mechanisms of action of ECT include an acceleration in serotonin and dopamine cycles in the brain, activation of monoaminergic pathways (12,13), deceleration of cerebral metabolism (14), and increasing the threshold of seizures, anticonvulsant effects (15,16), and neuroplasticity (17). However, the exact mechanism of action of ECT is still not fully known.

Very few studies have been conducted on the relationship between ECT and GDNF. One such study

conducted on depressive patients reported increased GDNF levels in patients undergoing manic shifts following ECT (18). Serum GDNF levels were also reported to be significantly increased after administering ECT in patients with drug-resistant depression; additionally, ECT was shown to provide clinical benefit by increasing GDNF levels (19). In animal studies, electroconvulsive seizures were shown to reduce GDNF concentrations in the hippocampus and striatum (20). In another study in which the acute and chronic effects of electroconvulsive stimulation in rats were investigated, changes in messenger RNA expressions of GDNF and its receptors [GDNF family receptor alpha-1 (GFR α 1), GDNF family receptor alpha-2 (GFR α 2), and receptor tyrosine kinase] were evaluated, and an increase in the expression of GFR α 1 and GFR α 2 was found in the dentate gyrus in both acute and chronic periods. Thus, the GDNF receptor complexes might play a role in the adaptive response to stimulation (21).

Given the available data, the primary objective of the current study was to investigate the effect of ECT on the serum GDNF levels and whether the change in serum GDNF levels reflected a response to ECT treatment. For this purpose, the serum levels of GDNF were measured both before and after the ECT administration in patients with SCH and BD. We also aimed to compare the serum GDNF levels of the patient and healthy control groups.

METHOD

Participants

The patients included in the current study were consecutively selected from a cohort diagnosed with BD or SCH based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnostic criteria. Those patients who were experiencing a manic episode of BD or an acute exacerbation of SCH were considered. These patients had been receiving inpatient treatment at a male psychiatry clinic in Bakirkoy Prof. Dr. Mazhar Osman Training and Research Hospital for Psychiatry, Neurology, and Neurosurgery, taking antipsychotic drugs (daily doses of more than 600 mg of chlorpromazine equivalent), and were recommended to undergo ECT treatment. Ethical committee approval of the study was obtained from Şişli Hamidiye Etfal Training and Research Hospital Clinical Research Ethics Committee (Decision number: 741, Date: January 24, 2017). Exclusion criteria were as follows: having an intellectual disability, using alcohol or

substance, having a neurological disease, and having a documented abnormality in blood screening.

ECT was planned for patients at risk of suicide or homicide or who refused to undergo medical treatment. Thirty-three patients with acute exacerbation of SCH or at the manic episode BD, who were recommended to undergo ECT treatment, met the study inclusion criteria and were included in the study. Three patients were excluded from the study because they terminated the ECT or their blood samples were not suitable for analysis. The final study group, therefore, consisted of thirty patients. Twenty-eight age- and sex-matched healthy volunteers were included as the control group in the study. After a thorough explanation of the study objectives and aims, written informed consent forms were obtained from all participants or their legal representatives. A form containing questions about sociodemographic information was filled out for each participant by an experienced clinician. The patients were clinically assessed both before and after the administration of ECT. The severity of affective symptoms of BD patients was assessed using the Young Mania Rating Scale (YMRS) (22,23), whereas the Positive and Negative Syndrome Scale (PANSS) (24,25) was used for assessing the severity of psychotic symptoms in patients with SCH.

ECT Procedure

ECT was performed in patients with BD and SCH between 08:00 a.m. and 11:00 a.m. after fasting for 8 h. None of the patients used dentures, contact lenses, or any ornament. The ECT room was equipped with a defibrillator and drugs necessary for cardiopulmonary resuscitation. Technical procedures were performed according to the standard routines of the laboratory. Electrodes were placed bilaterally on the temporal areas for the conduction of electrical stimulus. Propofol 1 mg/kg was administered as a short-acting anesthetic. Atropine was not used as a preanesthetic because it affects the heart rate and could mask possible bradyarrhythmia during the procedure. Curarization was performed with succinylcholine (0.5 mg/kg). Guedel airway was used to optimize oxygen ventilation with a mask and Ambu bag during the convulsive crisis, and a protective device was placed between the dental arches. The ECT device generated waves of fixed, biphasic, and short pulses. The electrical charge ranged from 250 to 350 mC, a current of 550–800 mA, and a frequency of 0.5–2.0 s. Seizures lasting more than 20 s were considered to be effective. Blood pressure, ECG tracing, and oxygen saturation index were monitored

before and during each convulsive seizure because ventilation was not interrupted. After the seizures, all the patients were provided with medical and nursing care until complete recovery.

Enzyme-Linked Immunosorbent Assay (ELISA) Procedure

A human GDNF ELISA kit (ELABSCIENCE, E-EL-H1495, USA) was used to determine serum GDNF levels. Venous blood samples from patients and healthy controls were transported to the laboratory at +4°C in tubes (13 × 100 5 mL Vacutainer plastic SST gel tube, Code VT 367955 Becton Dickinson) and centrifuged for 5 min at 4000 × g. The separated serum samples were transferred to sterile Eppendorf tubes and stored at -80°C until use. The serum GDNF levels were determined once in the healthy control subjects and twice in the patients before and after ECT. Quantitative measurement of serum GDNF levels was carried out in a spectrophotometer. The unit of serum GDNF levels was ng/mL, and the detection range was 0.31–20 ng/mL.

Statistical Analyses

Before the study, a power analysis was performed with the G*Power 3.1.9.2 program to determine the difference between groups in terms of measurements. The minimum sample size was calculated as 52, with 26 individuals in each group (type 1 error: 0.05, type 2 error: 0.80, and effect size=0.80). Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 22 software package for Windows. Categorical variables were expressed as percentages, whereas the continuous variables were expressed as mean±standard deviation. The Chi-squared test was used to compare the categorical variables. The Kolmogorov–Smirnov test was used to assess whether the data conformed to a normal distribution. In the case of parametric variables, Student's t-test was used to compare continuous variables between groups. The comparison of the continuous variables before and after treatment was carried out using the dependent sample t-test. Pearson's and Spearman's correlation analyses were performed to evaluate the relationship between variables. Probability (p) value <0.05 was accepted to indicate statistical significance.

RESULTS

Table 1 demonstrates the sociodemographic characteristics of the patient and control groups.

Table 1: Demographic properties of the patients and healthy controls

| | Patient group (n=30) | Control group (n=28) | χ^2 | t | p |
|----------------------------|-------------------------|-------------------------|----------|--------|--------|
| Age, mean \pm SD (years) | 36.27 \pm 9.77 | 36.60 \pm 9.00 | | -0.137 | 0.891 |
| Marriage status | | | 15.785 | | <0.001 |
| Single, n (%) | 24 (80%) | 7 (25%) | | | |
| Married, n (%) | 6 (20%) | 21 (75%) | | | |
| Working status | | | 40.941 | | <0.001 |
| Working, n (%) | 5 (16.7%) | 28 (100%) | | | |
| Not working, n (%) | 25 (84.3%) | 0 (0%) | | | |

χ^2 : Chi-squared test value; t: Student's t-test value; SD: Standard deviation.

Table 2: Serum GDNF levels (ng/ml)

| | Patient group Pre-ECT (n=30) Mean \pm SD | Post-ECT (n=30) Mean \pm SD | Control group (n=28) Mean \pm SD | t/p ¹ | t/p ² | t/p ³ |
|---------------------------|---|-------------------------------------|---|---------------------------|---------------------------|---------------------------|
| Serum GDNF levels (ng/mL) | 3.56 \pm 1.14 | 3.89 \pm 1.44 | 4.03 \pm 1.42 | -1.368/0.177 ^a | -0.383/0.703 ^a | -1.481/0.149 ^b |

p1: Comparison of the pre-ECT serum GDNF levels of the patient group and the control group; p2: Comparison of the post-ECT serum GDNF levels of the patient group and the control group; p3: Comparison of the pre-ECT and post-ECT serum GDNF levels of the patient group; GDNF: Glial cell line-derived neurotrophic factor; ECT: Electroconvulsive treatment; SD: Standard deviation; a: Student's t-test; b: Paired sample test.

Table 3: Comparison of GDNF levels of patients with BD and schizophrenia before and after ECT (specific for each disease)

| | | Pre-ECT Mean \pm SD | Post-ECT Mean \pm SD | t | p |
|-----|---------------------------|--------------------------|---------------------------|--------|-------|
| BD | Serum GDNF Levels (ng/mL) | 3.96 \pm 0.68 | 4.91 \pm 1.01 | -3.077 | 0.013 |
| SCH | Serum GDNF Levels (ng/mL) | 3.38 \pm 1.28 | 3.38 \pm 1.39 | 0.002 | 0.998 |

Paired sample test is used. GDNF: Glial cell line-derived neurotrophic factor; BD: Bipolar disorder; ECT: Electroconvulsive treatment; SD: Standard deviation; SCH: Schizophrenia.

Clinical Data

Among the patients included in the study, 66.7% (n=20) had a diagnosis of SCH, while 33.3% (n=10) had a diagnosis of BD (Table 1). The mean PANSS scores in patients with SCH before and after ECT were 121.40 \pm 9.54 and 73.55 \pm 9.65, respectively, and the mean YMRS scores in patients with BD before and after ECT were 46.90 \pm 5.02 and 2.10 \pm 1.40, respectively. The average number of ECT sessions administered to the patients during the course of the current study was 7.16 \pm 1.31. The mean duration between the first and last ECT sessions was 14.16 \pm 3.10 days. Additionally, the average lifetime ECT sessions that the patients had undergone was 14.30 \pm 11.17. The patients underwent the ECT sessions under anesthesia with propofol (mean dose of 60.66 \pm 12.29 mg) and succinylcholine as a muscle relaxant (mean dose of 35.66 \pm 6.66 mg).

Serum GDNF Level Measurements

The mean serum GDNF level of the healthy control subjects was 4.03 \pm 1.42 ng/mL. The mean serum GDNF

levels of all patients (SCH and BD) before and after ECT were 3.57 \pm 1.13 ng/mL and 3.88 \pm 1.45 ng/mL, respectively (Table 2). Although the serum GDNF levels showed an increase after ECT administration, the difference did not reach statistical significance (p=0.149). The difference in the mean serum GDNF levels of all patients measured both before (p=0.177) and after ECT (p=0.703) with the healthy control subjects also did not reach statistical significance (Table 2). An ANCOVA test indicated the lack of any statistically significant difference when the effect of the age variable was evaluated on the relationship between post-ECT GDNF levels in the patient group and GDNF levels in the control group (p=0.707). The mean serum GDNF level of SCH patients before and after ECT was not significantly different (p=0.998). However, the mean serum GDNF levels of the patients with BD before and after ECT were significantly different (p=0.013) (Table 3).

Post-ECT serum GDNF levels as well as other parameters, such as the number of hospitalizations,

Table 4: Correlation between post-ECT GDNF levels and clinical data

| | Number of hospitalization | Duration of the psychiatric illness | Mean PANSS scores after ECT | Mean YMRS scores after ECT | Number of ECT sessions |
|----------------------|---------------------------|-------------------------------------|-----------------------------|----------------------------|------------------------|
| Post-ECT GDNF levels | | | | | |
| r | -0.043 | -0.109 | -0.232 | 0.284 | -0.312 |
| p | 0.820 ^a | 0.568 ^b | 0.325 ^b | 0.426 ^a | 0.094 ^a |
| n | 30 | 30 | 20 | 10 | 30 |

ECT: Electroconvulsive treatment; GDNF: Glial cell line-derived neurotrophic factor; PANSS: Positive and Negative Syndrome Scale; YMRS: Young Mania Rating Scale; a: Spearman's correlation; b: Pearson's correlation.

duration of the psychiatric illness, mean PANSS scores after ECT, mean YMRS scores after ECT, and the number of ECT sessions administered during the course of the study, were compared in the patient group after they were administered ECT. No statistically significant correlation was identified between the serum GDNF levels and any of these other parameters (Table 4).

DISCUSSION

The current study is the first to evaluate the relationship between ECT and serum GDNF levels in patients with SCH and BD. Serum GDNF levels increased after ECT in BD patients, but remained unchanged in SCH patients. Additionally, there was no statistically significant difference between the mean serum GDNF levels of all patients (SCH and BD) before and after ECT and the mean serum GDNF levels of the controls.

PANSS scores were shown to decrease by at least 20% in treatment-resistant patients with SCH after ECT (26). The efficacy of ECT was reported to range between 56% and 100% in the treatment of manic episodes (27). In comparison, we observed that the mean PANSS score of SCH patients decreased from a pre-ECT mean score of 121.40 ± 9.54 to a post-ECT mean score of 73.55 ± 9.65 , a decrease of approximately 40%. The mean YMRS score of BD patients also showed a substantial decrease (approximately 95%) from a pre-ECT mean score of 46.90 ± 5.02 to a post-ECT mean score of 2.10 ± 1.40 . A previous study reported administering an average of 8.9 ± 5.13 ECT sessions (range 7–12) to patients, excluding maintenance ECTs (28). In the current study, the average number of ECT sessions administered was 7.16 ± 1.31 , comparable to the results reported in the literature.

Xiao et al. (5) reported the administration of atypical antipsychotic monotherapy to 138 drug-free patients with SCH to investigate the relationship between serum GDNF levels and the consequent psychiatric symptoms. A significant increase in serum GDNF levels was reported after 8 weeks of treatment in the group that responded to treatment, whereas no increase in the

GDNF serum levels was observed in the nonresponders, suggesting that GDNF may play a role in the etiology of SCH. In another study including 33 SCH patients, 39 BD patients with manic episodes, and 78 healthy control subjects, GDNF levels were reported to be high in patients with mania and low in patients with SCH, suggesting that GDNF levels may be used to distinguish SCH patients from BD patients undergoing an episode of mania (6). Additionally, Takebayashi et al. (29) reported that blood GDNF levels were significantly lower in patients with major depression and BD patients under remission than in healthy controls. Furthermore, Barbosa et al. (3) reported that the plasma GDNF levels were significantly higher in BD patients in the euthymic phase ($n=35$) compared with BD patients undergoing an episode of mania ($n=35$) and healthy control subjects ($n=50$). The same study reported no significant difference in plasma GDNF levels between BD patients undergoing an episode of mania and healthy controls. Overall, the study suggested that plasma GDNF levels tended to decrease in BD patients undergoing an episode of mania. Along the same lines, serum GDNF levels were significantly lower in manic and depressive patients than in healthy control subjects, suggesting that peripheral release of GDNF may decrease during the acute episode of BD, thus highlighting the importance of GDNF in the pathology of BD (8). Contrary to these data, Rosa et al. (7) reported that serum GDNF levels increased in manic and depressive episodes compared with healthy control subjects. However, these authors did not report any difference in serum GDNF levels between BD patients in the euthymic phase and the healthy controls, suggesting a potential compensatory increase in GDNF levels in BD.

To summarize, most of the studies cited above reported that serum GDNF levels showed a decrease in SCH patients, while an increase or a decrease was seen in patients with mood disorders. The studies that reported an increase in serum GDNF levels attributed it to a compensatory increase in response to the pathophysiology of the disease. Studies that reported a

decrease in the serum GDNF levels suggested that GDNF may play a role in the pathophysiology of the disease.

We did not observe any statistically significant difference in serum GDNF levels of 30 patients, of whom 20 were SCH and 10 were BD patients, with the healthy control subjects. This lack of difference may be attributed to the relatively small sample size or the diagnostic heterogeneity of the patient groups. A review article on the role of glial cells in the efficacy of ECT suggested that ECT-induced changes in glial cells may ensure better functioning of neurons, which may play a role in response to treatment (30). Zhang et al. (8) reported a positive correlation between ECT response and increased serum GDNF levels in depressive patients who were resistant to medical treatment. In yet another study, it was observed that the serum GDNF levels were significantly increased in patients undergoing manic switch after ECT compared with their pre-ECT levels and healthy control subjects. The same study reported no statistically significant difference between the serum GDNF levels of patients with depression relapse and patients who responded to ECT compared with the serum GDNF levels of healthy controls. This result was attributed to the possible role of the glial system in the pathogenesis of mood disorders (18). Supporting this, we observed an increase in serum GDNF levels after ECT in BD patients in the current study, but no change was observed after ECT in SCH patients.

The current study had some limitations that need to be considered when interpreting the study results. First, our sample size is small. Second, the GDNF levels may have been affected by ongoing drug treatments during the administration of ECT. The third limitation was that the sample included different diagnostic groups, and we only included male participants in the patient and control groups. Hormonal changes in women are a confounding factor known to affect the serum GDNF levels (31). Thus, the inclusion of female participants in the study may have precluded us from evaluating the exact effect of ECT. We also did not evaluate the patients' body mass index, which can be considered another limitation.

CONCLUSION

The current study is the first to evaluate the relationship between ECT and serum GDNF levels in patients with SCH or BD. We reported that alterations in serum GDNF levels might play an important role in response to ECT in BD patients. Further studies with larger samples should be carried out to substantiate our findings.

| Contribution Categories | | Author Initials |
|-------------------------|-----------------------------------|-------------------------------|
| Category 1 | Concept/Design | N.K., M.A. M.C.I. |
| | Data acquisition | M.A., H.K. |
| | Data analysis/Interpretation | T.K., M.A. |
| Category 2 | Drafting manuscript | M.A., H.K., M.C.I. |
| | Critical revision of manuscript | T.K., N.K. |
| Category 3 | Final approval and accountability | M.A., T.K., H.K, N.K., M.C.I. |

Ethical Approval: The Sisli Hamidiye Etfal Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 24.01.2017, number: 741).

Informed Consent: Informed consent was obtained form all participants.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors declare that they have no conflict of interest.

Financial Disclosure: The authors declare that they have no financial support.

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