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Serum Brain-derived Neurotrophic Factor Levels Following Electroconvulsive Therapy in Treatment-resistant Depressed Patients

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Abstract

Objectives: To determine whether serum levels of brain-derived neurotrophic factor (BDNF) are associated with response to electroconvulsive therapy (ECT) in treatment-resistant depressed patients with a relatively longer period of measurement.

Methods: This study included 30 Japanese unipolar depressed patients with current major depressive episode. Montgomery-Äsberg Depression Rating Scale (MADRS) score was ≥21 in all subjects. ECT was performed twice a week for a total of 4–10 sessions. Serum BDNF levels were measured before ECT (T0), the day after the last ECT session (T1), and 1 month after the last ECT session (T2). Patient response to treatment was defined as a ≥50% decrease compared with the pretreatment total MADRS score.

Results: Serum BDNF levels showed no significant variation among the patients during the entire study period. In responders, serum BDNF levels showed a progressive increase, and the differences between T0 and T1 and between T0 and T2 were significant (p=0.022 and p=0.007, respectively). In non-responders, serum BDNF levels showed a progressive decrease, and the difference between T0 and T2 was significant (p=0.012). No significant association was identified between change in serum BDNF level and change in total MADRS score in any of the patients following ECT.

Conclusions: The present results showed that serum BDNF levels after ECT increased progressively in responders, but not in non-responders. Our results provide important information for understanding the exact role of BDNF in the antidepressive effects of ECT.

Key Words

BDNF, electroconvulsive therapy, refractory depression, Montgomery-Äsberg Depression Rating Scale

Introduction

Electroconvulsive therapy (ECT) is an important option in the treatment of depressive disorders, particularly in patients with treatment-resistant disease. A recent review showed that controlled ECT studies published after 1978 still support the marked efficacy and superiority of ECT compared with antidepressants in the treatment of depression[1]. In one investigation of 38 treatment-resistant patients with depression, 65.8% responded to ECT and 55.3% achieved remission[2]. ECT is thus highly effective against severe treatment-resistant depression.

Brain-derived neurotrophic factor (BDNF), a nerve growth factor expressed in the central nervous system (CNS), has been considered responsible for cell growth and survival, and altered expression in BDNF in the hippocampus has been linked to depression[3]. In clinical patients with depression, lower plasma BDNF concentration was found when compared with that of control subjects[4),5]. A meta-analysis reported a significant increase in peripheral BDNF

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levels after antidepressant treatment in depressive patients[6]. Accordingly, BDNF activity in the CNS has been considered to represent neurophysiological changes associated with recovery of depression[3),6)]. Studies have measured peripheral (i.e., serum or plasma) levels of BDNF before and after ECT in depressive patients[7–18)]. A recent meta-analysis by Brunon[19)] found a significant increase in peripheral BDNF levels after ECT in depressive patients. Nevertheless, that meta-analysis showed no significant association between increases in BDNF and improvement of depressive symptoms, which were analyzed by calculating the total Montgomery-Äsberg Depression Rating Scale (MADRS) score and Hamilton Depression Rating Scale (HAM-D) score. As previous studies measured peripheral BDNF levels[8–15),17),18)] before ECT and within 1 week after the last ECT session, with the exception of two studies that measured 1 month after the last ECT session[7),16)], a need for studies with a longer measurement period has been suggested[19)].

On the other hand, a small number of studies have investigated changes in BDNF levels after ECT from the perspective of patient response or remission. Okamoto et al.[9)] found that patients whose HAM-D scores decreased by ≥50% (responders) experienced an increase in serum BDNF between the time before starting ECT and 1 week after finishing ECT; however, non-responders experienced no increase. Piccinni et al.[12)] reported that patients in whom total HAM-D scores decreased to <10 (remitters) showed significantly higher plasma BDNF levels at 1 week after the last ECT session when compared with non-remitters. These results suggest that changes in peripheral BDNF levels after ECT may be associated with patient response or remission, rather than changes in depression rating scores. Although changes in total MADRS or HAM-D scores after ECT provide important information, whether a patient responds or remits is more important for both patients and clinicians, since patients treated with ECT are usually treatment-resistant to antidepressant therapy. However, it must be noted that Fernandes et al.[11)] found no significant changes in serum BDNF level after ECT when data were analyzed according to response and remission at 1 day after the last ECT session.

The present study measured serum BDNF concentrations after ECT among unipolar depressive patients at various time points: T0, before ECT; T1, the day after the last ECT session; and T2, 1 month after the last ECT session. We analyzed changes in serum BDNF levels throughout the study period in responders and in non-responders separately. A patient's response to treatment was defined as a ≥50% decrease compared with the pretreatment total MADRS scores. We also analyzed the association between serum BDNF levels and changes in total MADRS score following ECT in all patients (both responders and non-responders). The aim of this study was to clarify the association between clinical response and change in serum BDNF level after ECT using a relatively longer measurement period.

Materials and Methods

Subjects

This study was conducted at St. Marianna University School of Medicine between March 2008 and December 2014. Participants in this study were 30 Japanese patients who fulfilled the Diagnostic and Statistical Manual of Mental Disorder-fourth edition criteria for the diagnosis of major depressive disorder, underwent assessment of illness severity and outcome of ECT treatment using the MADRS, and showed total MADRS score ≥21 at T0. Patients with other Axis I disorders (including schizophrenia, bipolar disorder, dementia, substance abuse, dysthymia, panic disorder, obsessive-compulsive disorder, and generalized anxiety disorder) or Axis II disorders as determined by a clinical interview were excluded. Patients with severe non-psychiatric physical diseases were also excluded. Cognitive deficits were evaluated using the Mini-Mental State Examination (MMSE). Patients with MMSE score ≤23 at T0 were excluded.

Patients who ranged in age from 40 to 85 years and had been planning to receive ECT were asked to participate in the study. Out of the 30 patients, none refused to participate in the study. An independent psychiatrist recommended ECT according to clinical judgment, because of drug resistance in the patients. Drug resistance was defined as a failure to respond to at least three courses of antidepressant medication of adequate dose and duration (i.e., the stage 3 definition of Thase and Rush[20)]). Concomitant use of mood stabilizers (lithium carbonate, sodium valproate, carbamazepine) was stopped before the start of ECT. Patients were maintained on the same drug treatment for at least 1 week before ECT and during the entire study period.

The protocol of this study was approved by the Bio-ethics Committee of St. Marianna University School of Medicine. (approval number: 2414) The

method and objectives of the study were explained to all patients and their families. Informed consent was obtained from either the patient or from their family members, if the patient was not capable of providing informed consent.

ECT

A medical history and physical examination as well as routine blood and urine examinations, electrocardiography, cerebral computed tomography or cerebral magnetic resonance imaging, and chest x-ray were performed on all patients to screen for general medical conditions. For each ECT session, patients were anesthetized with propofol (1.0–1.5 mg/kg), and muscle relaxation was achieved using suxamethonium (0.8–1 mg/kg). ECT was performed between 09:30 and 11:30 using a brief bipolar pulse and a constant-current Thymatron System IV machine (Somatics, Lake Bluff, IL,U.S.A.). ECT conditions were set in a preset stimulation program (Low 0.5; Somatics) during which a fixed 0.5-ms pulse width automatically varied in frequency to maximize duration. Seizure threshold was determined at the first treatment using the empirical titration procedure. For initial treatment, we set the percent energy to half the age of the patient (e.g., 30% for a 60 year old). The duration of seizures as measured by electroencephalography was kept above 25 s. If no seizure activity resulted, the stimulus was increased 1.5-fold at the next session. Stimulus electrode placement was bilateral on the front-temporal scalp. During ECT, motor convulsions, electroencephalography, induced tachycardia, and electromyography were monitored. ECT was performed twice a week, and each patient received a total of 4–10 sessions. Clinical manifestations were evaluated after four, six, eight, or ten sessions of ECT using the MADRS. ECT was completed on the basis of the clinical judgment of the treating psychiatrist.

BDNF immunoassay

Blood samples (5 mL) were collected between 8:00 and 9:00 a.m. They were kept at room temperature for 1 hour by centrifugation for 20 min at 2,000×*g* at room temperature. Serum was then separated and stored at −80°C until analysis. Enzyme-linked immunoassay was performed using the BDNF Emax Immuno Assay System Kit (Promega, Madison, WI, U.S.A.) according to the instructions from the manufacturer. Flat-bottom 96-well plates were coated with anti-BDNF monoclonal antibody and incubated at 4°C for 18 h. The plates were then incubated in a block and sample buffer at room temperature for 1 h. Samples and BDNF standard (from 7.5 to 500 pg/ml) were added in triplicate to the plates, which were then incubated for 2 h with shaking at room temperature. Following that, plates were incubated with anti-human BDNF polyclonal antibody for 2 h at room temperature. Anti-immunogloblin Y horseradish peroxidase conjugate was then added to each well and plates were incubated for 1 h with shaking at room temperature. Plates were incubated in peroxidase substrate and tetramethylbenzidine solution to produce a color reaction. The reaction was stopped after 10 min with 1 N HCl, and absorbance was measured at 450 nm.

Data collection

Longitudinal blood sampling (BDNF) and concomitant MADRS evaluations were performed at T0, T1 and T2. Responders were defined as those patients in whom MADRS score decreased by ≥50%, and non-responders were defined as those in whom scores decreased by <50%. Data were collected on various demographic and illness variables, such as sex, age, number of previous depressive episodes, duration of current episode, presence or absence of psychotic symptoms, age at onset of mental illness, medication history, and medication during the course of ECT.

Statistical analysis

The clinical characteristics of all patients, responders, and non-responders were analyzed by chi-square test or the unpaired *t*-test where appropriate. Since serum BDNF levels did not show a normal distribution, non-parametric tests were used. The Mann-Whitney *U*-test was used to compare serum BDNF levels between responders and non-responders at T0, T1, and T2. Comparisons within each group were analyzed using the methods of Friedman. Spearman correlation coefficient analysis was used to evaluate bivariate correlations. Values of $p < 0.05$ were regarded as significant.

All statistical analyses were performed using SPSS 18.0J for Windows software (IBM, Tokyo, Japan).

Results

Patient characteristics are shown in **Table 1**. The 30 patients included 21 women and 9 men (mean (±standard deviation) age, 66.5±11.2 years). Twenty-two patients were classified as responders, and the re-

Table 1. Clinical Characteristics of All Patients, Responders, and Non-responders

	All patients (N=30)	Responders (n=22)	Non-responders (n=8)	Analysis
Sex (male/female)	9/21	7/15	2/6	χ^2=0.13 p=0.719
Age (years)	66.5±11.2	65.5±12.2	69.1±7.9	t=-0.77 p=0.449
Number of previous depressive episodes	3.3±2.4	3.6±2.3	3.1±3.0	t=0.19 p=0.851
Duration of current episode (months)	6.4±11.4	5.8±10.9	8.3±13.0	t=-0.52 p=0.606
MADRS score	40.7±8.7	41.5±8.5	38.6±9.6	t=0.78 p=0.442
MMSE score	26.5±3.2	26.9±3.3	25.5±2.8	t=1.09 p=0.287
Psychotic symptoms (%)	50%	54.50%	37.50%	χ^2=0.68 p=0409
Number of ECT	6.8±2.3	6.3±2.0	8.1±2.5	t=0.17 p=0.09
Age at onset of mental illness (years)	57.8±16.6	56.9±18.1	60.3±12.5	t=-0.48 p=0.635

Data are expressed as mean ±SD

Analysis was performed using the χ^2 test, unpaired t test, and Mann-Whitney U test to compare responders and nonresponders.

maining 8 patients were non-responders. No significant differences were found in age (t=−0.77, p=0.45), number of previous depressive episodes (t=0.19, p=0.85), duration of current episodes (t=−0.52, p=0.61), total MADRS score at T0 (t=0.78, p=0.44), MMSE score at T0 (t=1.09, p=0.29), psychotic symptoms (χ^2=0.68 p=0.41), number of ECT (t=0.17, p=0.09), or age at onset of mental illness (t=−0.48, p=0.66) between responders and non-responders. No significant difference in mean daily dose of antidepressant was identified between responders (imipramine-equivalents: 133.9±104.6 mg/day) and non-responders (143.6±64.3 mg/day; t=0.24, p=0.81). No significant difference in platelet count was seen between responders (246.2±54.7 $\times 10^3/\mu l$) and non-responders (240.3±65.8 $\times 10^3/\mu l$; t=0.25 p=0.80).

Changes in total MADRS score during the study period

Mean MADRS scores in all patients at T0, T1, and T2 were 40.7±8.7, 17.5±8.5, and 12.9±7.5, respectively. MADRS scores in all patients decreased from T0 to T2. Significant differences were evident between T0 and T1 (p<0.0001), between T0 and T2 (p<0.0001), and between T1 and T2 (p<0.0001).

In responders at T0, T1, and T2, mean MADRS scores were 41.5±8.5, 14.0±6.6, and 9.2±4.2, respectively. Again, significant differences were evident between T0 and T1 (p<0.0001), between T0 and T2 (p<0.0001), and between T1 and T2 (p<0.0001).

In non-responders at T0, T1, and T2, mean MADRS scores were 38.6±9.6, 27.1±5.3, and 23.3±3.8, respectively. Significant differences were seen between T0 and T1 (p<0.0001), between T0 and T2 (p=0.0001), and between T1 and T2 (p=0.018), whereas a decrease of total MADRS scores did not fulfill the definition of responders to ECT.

Changes in serum BDNF levels during the study period

Mean serum BDNF levels in all patients at T0, T1, and T2 were 16.37±13.26 ng/ml, 16.82±13.60 ng/ml, and 18.98±17.95 ng/ml, respectively. Serum BDNF levels in all patients showed no significant difference during the entire study period (Friedman test, χ^2=0.22, df=2, p=0.89; **Fig. 1a**). Serum BDNF levels also showed no significant difference between responders and non-responders at T0, T1, and T2 (Mann-Whitney U-test, T0: z=−1.27, p=0.219; T1: z=−0.33, p=0.765; T2: z=−0.05, p=0.982).

In responders, mean serum BDNF levels at T0, T1, and T2 were 14.73±12.53 ng/ml, 16.29±13.83

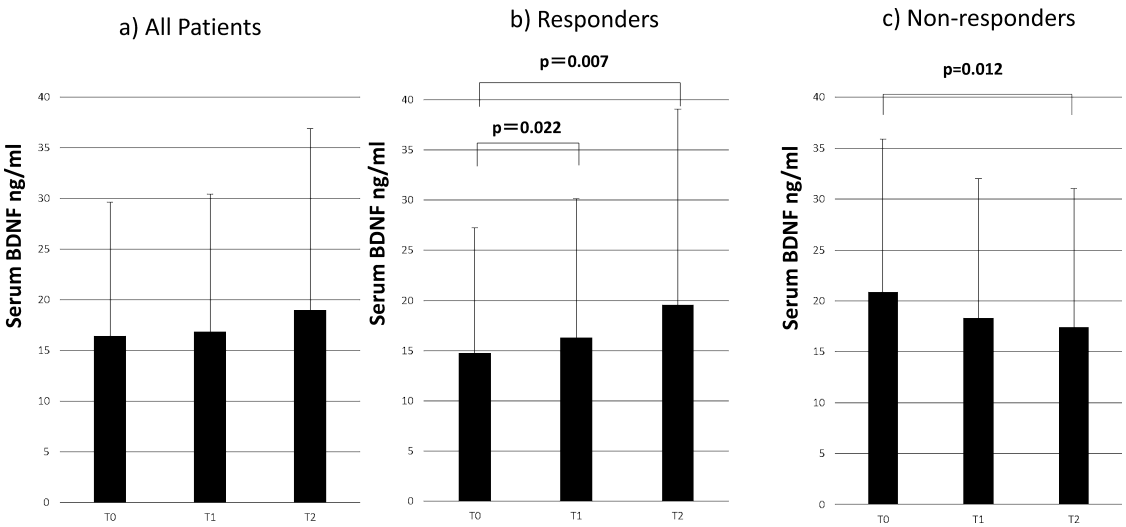

Fig. 1. Longitudinal changes in serum BDNF values in responders and non-responders during the study period. Serum BDNF levels of: **a**) all patients; **b**) responders; **c**) non-responders. T0, baseline, the day before ECT; T1, the day after the last ECT session; T2, 1 month after last ECT session.
p values from paired Wilcoxon signed-rank test.

ng/ml, and 19.56±19.53 ng/ml, respectively. Serum BDNF levels in responders differed significantly (Friedman test χ^2=6.14, df=2, p=0.04; **Fig. 1b**). Significant differences were identified between T0 and T1 (Mann-Whitney U-test, z=−2.29, p=0.022) and between T0 and T2 (z=−2.69, p=0.007). Serum BDNF levels in responders showed a progressive and significant increase from T0 to T2.

In non-responders, serum BDNF levels at T0, T1, and T2 were 20.86±15.03 ng/ml, 18.30±13.74 ng/ml, and 17.39±13.65 ng/ml, respectively. Serum levels of BDNF in non-responders differed significantly (Friedman test, χ^2=10.75, df=2, p=0.005; **Fig. 1c**). A significant difference was seen between T0 and T2 (Mann-Whitney U-test, z=−2.52, p=0.012).

Correlation between change in serum BDNF level and total MADRS score

No significant correlation between change in total MADRS score in all patients and change in serum BDNF level was apparent when comparing T0-T1 (r=0.302, p=0.105) or T0-T2 (r=0.309, p=0.097) using the Spearman correlation coefficient.

In responders, no significant correlation between change in total MADRS score and change in serum BDNF level was seen when comparing T0-T1 (r=0.044, p=0.816) or T0-T2 (r=0.376, p=0.085).

In non-responders, no significant correlation between change in total MADRS score and change in serum BDNF level was identified when comparing T0-T1 (r=0.108, p=0.798) or T0-T2 (r=0.238, p=0.570).

Discussion

In this study, the most striking finding was that serum BDNF levels after ECT increased progressively in responders for 1 month after ECT, while non-responders showed results in the opposite direction. Furthermore, no significant association was found between changes in serum BDNF level and total MADRS score following ECT.

The present results seem to indicate that changes in serum BDNF level after ECT are closely associated with responder status. These results are associated with previous work by Okamoto et al.[9] and Piccinni et al.[12], in that significant increases in BDNF levels were found in responders, but not in non-responders. The present results are in line with the notion that increased BDNF levels represent a biological, state-dependent marker of response following ECT, as suggested by Piccinni et al[12]. As we found no significant association between changes in BDNF levels and those in total MADRS scores in all patients (including responders and non-responders), increased serum BDNF levels following ECT might relate to the state of the patient as represented by response or non-response, rather than changes in depression rating scale scores. Increased BDNF levels

after ECT seem likely to be highly associated with the differences in pathophysiology between responder and non-responders.

Regarding so-called state-dependent or state-related changes in peripheral BDNF levels after ECT in treatment-resistant depressive patients, interactions between neuro-hormonal changes and changes in the neuro-plastic effects of BDNF would be involved, as suggested in a previous study[12]. Possible interactions include the following. First, hypothalamus-pituitary-adrenocortical (HPA) abnormalities have been considered to be highly involved in the pathophysiology of depression[23]. Second, resolution of HPA dysregulation (e.g., resolution of elevated corticosteroid activity) has been identified among depressive patients who respond to ECT, but not to antidepressants[24]. Third, corticosteroid hormones have been found to down-regulate BDNF mRNA and protein expression in depressive patients[25]. Taken together, resolution of elevated corticosteroid activity might occur after ECT in responders, but not in non-responders. Such attenuated corticosteroid activity would alleviate the down-regulating effects on BDNF activity, resulting in increased serum levels of BDNF in responders, as observed in the present study. Conversely, the down-regulating effects of corticosteroid activity on BDNF activity in non-responders might not cease and may last during and even after ECT, resulting in decreased levels of serum BDNF in non-responders. With regard to mechanism of antidepressive effect of ECT, enhancement of dopaminergic and serotonergic neurotransmission as well as resolution of HPA dysregulation has been thought to play important roles[26),27]. Considering the results of the present study, alternation of dopaminergic and serotonergic neurotransmission following ECT might induce an antidepressant effect to some extent in both responders and non-responders, while in non-responders their depressive symptoms may insufficiently ameliorate, presumably due to lack of elevation in serum BDNF levels, resulting in the patients being non-responders. Since we did not measure levels of corticosteroid hormones, dopamine, and serotonin, or BDNF activity in the CNS, such speculations must remain to be clarified in the future.

Using the same three measurement times applied during the study period, Piccinni et al.[12] and Bocchio-Chiavetto et al.[7] reported that BDNF levels increased progressively following ECT, and the changes in BDNF levels following ECT have been suggested to be time-related[12]. Peripheral BDNF levels might take relatively longer to increase compared to the rapid effects of ECT[19]. The present results seems to be in the same direction as those from previous studies, and time-related changes in BDNF levels after ECT might be more robustly verified using the relatively longer measurement period of 1 month. Because BDNF affects cell growth and survival and is expressed in the CNS[3], the effects of BDNF on neuroplasticity after ECT would extend for some duration in depressive patients. A previous study also reported a progressive elevation of serum BDNF levels for 1 month following ECT, and it has been suggested that a progressive elevation of serum BDNF levels might represent the consequence of the adaptive process in depressed patients, such as a change of neuro-hormonal and psychoimmune systems, and alterations of platelets function[7]. There might be a possibility that such adaptive processes relate to progressive increase of serum BDNF levels following ECT. Accordingly, our results may suggest that changes at the peripheral BDNF level following ECT would involve both time- and state-related changes in treatment-resistant depressive patients. If this were the case, the results of a previous meta-analysis[19] may be partly accounted for, since that meta-analysis analyzed data from the perspective of changes in total MADRS scores or total HAM-D scores with the relatively short measurement periods, as mentioned before. Also, the relatively short timing of BDNF measurement might have affected the results of the study by Fernandes et al.[11], in which no significant association was found between serum BDNF levels and remission or response using measurements at 1 day after the last ECT session. The methodology used in this study (i.e., analyzing the data in responders and non-responders separately with a relatively longer period of measurement) may have been useful to clarify the association between serum BDNF levels and clinical response to ECT in refractory-depressed patients. More controlled studies with a larger number of subjects would be needed.

As some studies have reported that peripheral BDNF levels increase following antidepressant treatment in depressive patients[4),19),28], concomitant use of antidepressants before and throughout the study period would presumably have affected the results in our study. The regimen of concomitant antidepressant use was not changed before or throughout the study period, and no significant difference in daily administered dose of antidepressants (imipramine equivalent dose) was identified between responders and non-res-

ponders. Concomitant use of antidepressants thus seems less likely to have affected serum BDNF levels in the subjects of this study.

Circulating BDNF has been considered to reflect central neurotrophic activity, since BDNF can cross the blood-brain barrier via an active transport system[29]. An association between serum and cortical BDNF levels has been also reported[30]. The serum BDNF concentration measured in this study seems to reflect central BDNF activity in patients treated with ECT.

Differences in age, weight, and sex have been reported to affect peripheral BDNF levels[31]. One possibility is that individual conditions or gender differences affected both serum BDNF activity and response rate to ECT. Although we found no significant differences in age, weight, or gender between responders and non-responders in this study, these factors should be taken into account cautiously.

The limitation of this study may be the relatively small sample size. This small size means that we cannot generalize our present findings to a larger population. The present study found no significant difference in serum BDNF levels between responders and non-responders at T0, T1, and T2. One possibility is that the sample size of the present study affected the results. The results of this study must be interpreted with caution. In conclusion, the present results showed that serum BDNF levels after ECT increased progressively in responders, but not in non-responders, using a relatively longer measurement period. Our results provide important information to understand the exact role of BDNF in the antidepressive effects of ECT.

Conflicts of interest

Oga Sasaki and Noboru Yamaguchi have received research grants from MSD (Tokyo, Japan). The remaining authors have no financial or other relationships relevant to the subject of this article to declare.

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