

# Brain-Derived Neurotrophic Factor and Electroconvulsive Therapy in a Schizophrenic Patient With Treatment-Resistant Paranoid-Hallucinatory Symptoms

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**Abstract:** It has been proposed that deficits in the production and the utilization of brain-derived neurotrophic factor (BDNF) may contribute to the pathogenesis of schizophrenia. At the same time, electroconvulsive shock, an experimental model of electroconvulsive therapy (ECT), has been shown to induce an increase of BDNF protein in brains of animal models. These findings suggest that one putative mechanism of action of ECT is the regulation of BDNF and/or related neurotrophins. In this case report, a 54-year-old man with severe treatment-resistant schizophrenic symptoms was treated with ECT. To evaluate the effect of ECT on BDNF serum levels, we collected a blood sample before each ECT session. During the course of ECT treatment, the paranoid and hallucinatory symptoms gradually improved, whereas BDNF levels increased over time. In addition, there was a general improvement of its positive and negative schizophrenic symptoms and depressive state.

In conclusion, this case report further validates the therapeutic efficacy of ECT in schizophrenic patients with inadequate or poor response to traditional treatments. Moreover, ECT therapeutic effect is associated with an increase in BDNF serum levels. Further studies are needed to characterize the relationship between BDNF and ECT in schizophrenic patients.

**Key Words:** ECT, BDNF, schizophrenia

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Electroconvulsive therapy (ECT) has been recognized to be an effective treatment for affective disorders, acute schizophrenia, catatonic symptoms, and neuroleptic malignant syndrome. Electroconvulsive therapy has efficacy in treatment-resistant cases, with a rate greater than 60%, and low incidence of adverse effects.<sup>1</sup> However, despite this, ECT mechanism of action is still elusive.

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family and is widely expressed in the central nervous system. Brain-derived neurotrophic factor plays a major role in survival and maintenance of dopaminergic neurons and synaptic plasticity.<sup>2</sup> In the recent years, it has been repeatedly proposed that deficits in the production or utilization of BDNF may contribute to the pathogenesis of schizophrenia.<sup>3</sup> This hypothesis has been supported by human data showing that schizo-

phrenic patients show lower levels of neurotrophins in plasma<sup>4</sup> as well as in the central nervous system<sup>5</sup> as compared with healthy controls. Supporting this hypothesis, preclinical studies have shown that electroconvulsive seizures produce a robust increase in BDNF mRNA<sup>6</sup> and protein<sup>7</sup> in different rat brain areas such as septum, cerebral cortex, striatum, and hippocampus.<sup>8–12</sup>

These findings suggest that a putative mechanism of action of ECT is the regulation of BDNF and/or related neurotrophins.<sup>12</sup> However, whether ECT could affect the levels of BDNF and the clinical outcome in schizophrenic patients is still an open question. In this study, we describe the case of a drug-resistant schizoaffective patient treated with a 6-session ECT whose BDNF levels were measured before every ECT session.

A 54-year-old, right-handed white man with severe treatment-resistant paranoid-hallucinatory symptoms was admitted to Villa Maria Pia, a private psychiatric facility located in Rome and accredited by the Italian National Health Service. The admission followed a progressive deterioration of his physical, neurological, and psychiatric state, including severe social withdrawal. The patient was adequately orientated and manifested an obvious slowness in thinking. His speech was difficult to follow and at times was incoherent, closely resembling the speech pattern characteristic of schizophrenic thought disorder. He was experiencing auditory hallucinations (including his own thoughts recorded and played over the public address system) and developed paranoid delusions against the hospital and staff. He reported feelings of being watched and filmed in his room. He presented delusions of reference about the television and thought that strangers knew his history. His mood was mildly depressed with short episodes of subjective tension and anxiety. The symptoms described fully met the criterion A for schizophrenia according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*.<sup>13</sup>

Patient psychiatric history started at age 24 years, during university studies. Before that, the patient did not show symptoms of psychiatric disturbances. During his 28-year psychiatric history, the patient was treated with either various antipsychotics, including risperidone (6 mg/d for 3 months), quetiapine (750 mg/d for 1.5 months), and paliperidone (6 mg/d for 2 months), or combined treatments of atypical and typical antipsychotics including haloperidol (4 mg/d for 3 months) and chlorpromazine (200 mg/d for 7 months). Antidepressant therapy (paroxetine 20 mg/d for 6 months and venlafaxine 225 mg/d for 2 months) was also added. However, these pharmacological treatments only induced partial remission of his symptoms and thus failed to significantly improve his condition.

After exacerbation of his psychotic symptoms (approximately 15 months ago), the patient was admitted to our clinic and was treated with both typical (haloperidol 6 mg/d for 3 months) and atypical (quetiapine 600 mg/d for 1.5 months, olanzapine 10 mg/d for 15 days, risperidone 6 mg/d, and chlorpromazine 300 mg/d up to the start of ECT procedure) antipsychotics.

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The patient was also treated with benzodiazepines (clonazepam 2 mg/d for 2 months and lorazepam 5 mg/d up to the start of ECT procedure). Nevertheless, even these new pharmacological treatments failed to improve his condition. Treatment-resistance status was determined according to the criteria of Kane and colleagues,<sup>14</sup> and recommendations to initiate ECT were accepted by the patient and his wife.

## MATERIALS AND METHODS

After written informed consent, the local ethical committee approved this study. Before the ECT sessions, neither did the patient show hematologic or hematochemical abnormalities, nor the magnetic resonance imaging scan showed signs of brain damage. The electrocardiogram, electroencephalogram, and blood parameters were normal. To evaluate the effect of ECT on BDNF serum levels, we collected a blood sample before each ECT session.

The day preceding ECT procedure, treatment with lorazepam was suspended. Electroconvulsive therapy procedure started with a premedication, which included thiopental (3.0 mg/kg intravenously administered) and succinylcholine (0.7 mg/kg intravenously administered). Oxygen was administered before and after treatment. Electroconvulsive therapy was performed between 7:00 and 9:00 A.M., using a Thymatron intravenous device with standard settings<sup>15</sup> with a bipolar brief-pulse square wave. The patient was treated with bilateral ECT. Two stimulus electrodes were placed over the left and right frontotemporal scalp. Electroconvulsive therapy treatment conditions have been set up as follow: charge delivered max, 504 millicoulomb (mC); current, 0.9 A; frequency, 10 to 70 Hz; pulse width, 0.50 milliseconds; duration max, 8 seconds. During ECT, an electroencephalogram and electromyogram were also obtained. Treatment was given 3 times a week. At the end of the sixth ECT session, the average duration of the epileptic seizures was  $32.2 \pm 5.9$  seconds, and the average charge delivered was  $353.5 \pm 11.4$  mC. The stimulus test was estimated during the first ECT session and defined as the minimum charge (90 mC) for inducing a 15-second seizure. Seizure threshold in the first ECT session, using a standard titration protocol,<sup>16</sup> was determined by an ascending method of limits procedure administering a series of progressively longer pulse trains at 20-second intervals until a seizure was induced. Subsequent treatments were given at 1.5 times the seizure threshold. At the time of ECT, the patient was under risperidone (4 mg/d), sertraline (100 mg/d), and biperiden (6 mg/d) treatments. These therapies also continued during the ECT course.

Psychopathological state was rated with the Brief Psychiatric Rating Scale,<sup>17</sup> the Positive and Negative Symptoms Scale (PANSS),<sup>18</sup> and the Hamilton Depression Rating Scale.<sup>19</sup> For the BDNF assay, 5 mL of blood was taken 30 minutes before each ECT session into an anticoagulant-free vacuum tube. The blood was centrifuged until 20 minutes after the venipuncture at 2000g for 5 minutes, and serum was kept frozen at  $-80^{\circ}\text{C}$  until assayed. Brain-derived neurotrophic factor serum levels were measured with sandwich enzyme-linked immunosorbent assay, using a commercial kit according to the manufacturer's instructions (cat. N° DY248; R&D Systems, Minneapolis, Minn).

## RESULTS

After 6 ECT sessions, the paranoid and hallucinatory symptoms gradually improved. "Voices" no longer gave commands, and the fear of being filmed lessened in intensity. In addition, he was able to take care of himself, read books, listen to music, play ping-pong, and go out with his wife. As neurological (reduction of antipsychotic-induced extrapyramidal symptoms) and psychiatric symptoms improved, the patient was discharged from the clinic.

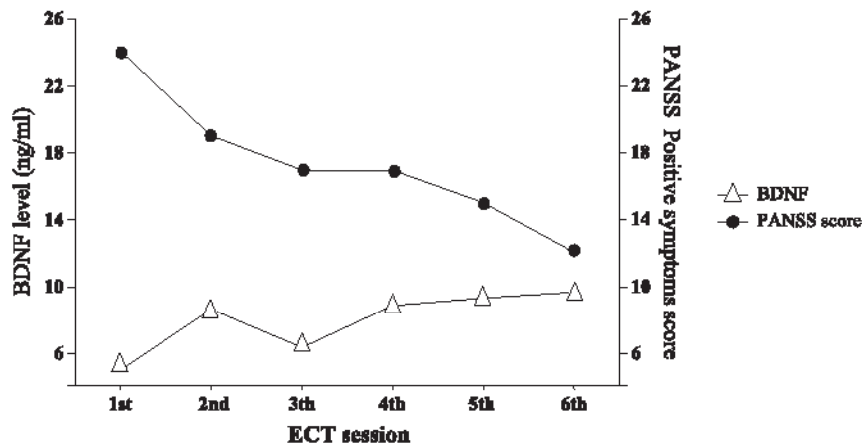
At the end of ECT sessions, there was a decrease in the total score of the Brief Psychiatric Rating Scale (from 48 to 36 points;  $P < 0.05$ ). A significant reduction was also found in PANSS total score (from 111 to 65;  $P < 0.05$ ) and PANSS positive (from 24 to 12;  $P < 0.05$ ) (Fig. 1) and negative (from 32 to 20;  $P < 0.05$ ), and general psychopathology (from 55 to 31;  $P < 0.05$ ) subscores. Hamilton Depression Rating Scale also decreased (from 20 to 11;  $P < 0.05$ ).

As shown in Figure 1, BDNF levels gradually increased over time, an effect associated with the number of ECT sessions.

## DISCUSSION

In the present case report, the effect of a course of ECT in a subject with schizophrenia symptoms on clinical outcomes was associated with determination of BDNF serum levels. The most important finding was that, together with the improvement of psychotic symptoms, we observed a progressive increase in BDNF levels during the course of ECT treatment (Fig. 1).

Several studies have shown that ECT is an effective treatment for other psychiatric disorders, such as refractory depression.<sup>20-28</sup> However, whereas some studies documented an increase in BDNF serum levels associated with therapeutic action of ECT,<sup>20-25</sup> other studies reported no changes in BDNF



**FIGURE 1.** Brain-derived neurotrophic factor levels and PANSS positive symptoms score before each ECT session. Brain-derived neurotrophic factor values are expressed in ng/mL.

after ECT treatment.<sup>26–28</sup> These differences suggest that the mechanism of action of ECT deserves more investigations and, at the same time, that a better definition of the category of patients who may benefit from ECT treatment is required, as also suggested by studies on BDNF gene polymorphism.<sup>28</sup>

Because of complex impact on brain functionality, there are multiple theories associated with the mechanisms of action of the ECT in schizophrenia. One plausible hypothesis is that increased levels of BDNF may provide beneficial effects on schizophrenia by enhancing dopamine synthesis and turnover.<sup>29</sup> This idea is supported by data showing that BDNF is involved in the maintenance of midbrain dopaminergic neurons<sup>30</sup> and in the regulation of synaptic plasticity.<sup>31</sup> The correlation between improved psychopathological state and increased serum BDNF levels after 6 ECT sessions further supports this notion.

In conclusion, this case report confirms that ECT may represent an effective therapeutic option in patients with inadequate or poor response to traditional antipsychotic treatment. Moreover, its therapeutic efficacy is associated with increased BDNF peripheral levels. Further studies are needed to better define the relationship between BDNF and ECT in schizophrenic patients.

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