Original Article
https://doi.org/10.9758/cpn.2019.17.1.74
Clinical Psychopharmacology and Neuroscience 2019;17(1):74-79
pISSN 1738-1088 / eISSN 2093-4327

Changes in Pre- and Post-Electroconvulsive Therapy Serum Myostatin Levels in Patients with Treatment Resistant Depression

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Objective: Myostatin is a growth factor which is investigated regarding musculoskeletal system. Albeit its effect on muscle mass is known, it is considered likely having other unknown effects as well, particularly on central nervous system. With this study, it is aimed to find out that what type of effect electroconvulsive therapy (ECT) does on myostatin in patients with treatment resistant depression.
Methods: Twenty-nine patients with treatment resistant major depression and thirty healthy volunteers were included in the study. Pre- and post-ECT levels of myostatine were compared; also this results were compared to healthy controls.
Results: For 29 patients with treatment-resistant major depression, the pre-treatment mean myostatin level was 0.95±0.32 ng/ml and post-therapy myostatin level was 11.05±6.97 ng/ml. As a result of this study, it is found that ECT affects serum myostatin levels to a significant degree (t=4.17, $p<0.05$). It is also found that there was a significant relation between serum myostatin levels and depression scores (r=0.392, $p<0.05$).
Conclusion: With the present study and similar ones, it can be understood that how ECT achieves its effectiveness biologically.

KEY WORDS: Electroconvulsive therapy; Depression; Myostatine.

INTRODUCTION

Myostatin, also known as growth and differentiation factor-8 (GDF-8), a member of the transforming growth factor-β superfamily and regulated probably by microRNAs, plays an important role in the control of musculo-skeletal development as a negative regulator of muscle growth via Smads and non-Smad signal pathways.[1-4] In addition to its muscle growth inhibition, myostatin has recently been demonstrated to function in protein, fat and glucose metabolisms.[5] Blocking myostatin expression results in increased insulin sensitivity associated with increased adiponectin secretion from adipose tissue.[6]

There are some findings showing that myostatin has a potential role in neurotransmission, particularly in dopamine regulation,[7] but findings about this relationship are indirect. However, there is no data regarding myostatin in evaluation of efficacy of treatments such as antidepressants or electroconvulsive therapy (ECT) in psychiatric diseases, particularly in depression, so far. On the other hand, there are studies regarding depression and antidepressant effectiveness of adiponectin in the adipose tissue, induced by myostatin. In a study of Guo *et al.*[8] it was demonstrated that there was a relation between adiponectin and stress, anxiety and depression tendency. At the same time, there are data showing that adiponectin has antidepressant effectiveness.[9]

Myostatin is a molecule, mostly thought to be associated with chronic heart failure and musculo-skeletal system. It was shown that myostatin level increased in patients with chronic heart failure and it has changed in parallel with the exercise.[10,11] It was found that its level was changed depending on the type of exercise in normal healthy individuals.[12,13] As the molecule is directly thought to be associated with musculo-skeletal system, it has been subject to studies related to muscular activities.[14] However, in an application such as ECT, in which muscular activ-

Received: July 11, 2017 / **Revised:** August 10, 2017
Accepted: September 5, 2017
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ities continue and muscle contractions present despite use of muscle relaxants, it is not known how plasma level is affected.

It is known that ECT effects levels of brain-derived neurotrophic factor (BDNF), nerve growth factor, neuropeptide Y, somatostatine.[15-19] Despite of these findings, it is still unknown that "which molecule has main role in ECT's effect mechanism".[20]

In this study, we aimed to investigate the effectiveness of ECT on serum myostatin levels in patients with treatment resistant major depression. Moreover, we also aimed to investigate the relation between plasma myostatin levels and response to ECT.

METHODS

Participants

In this study, the patients with treatment resistant major depression, who received ECT in inpatient settings in Department of Psychiatry, Gülhane Military School of Medicine between 2015 and 2016, are evaluated. Thirty patients with treatment resistant major depression (12 males and 18 females) and a control group of 30 healthy people (12 meals and 18 females) are included in the study. Patients were evaluated according to the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) and twelve patients with comorbid psychiatric diseases were excluded from the study.

One female patient is excluded from the study as side effect secondary to ECT developed. Treatment resistance is defined as no response to at least three antidepressant therapies with appropriate dose and duration according to stage III definiton of Thase and Rush.[21] The drugs likely to affect seizure threshold (antidepressants or antipsychotics) were not given to patients during ECT. Benzodiazepine for sedation purpose was given in cases of requirement.

Patients and controls groups underwent a medical history taking and a physical assessment. They were screened for acute infectious diseases by measuring body temperature, erythrocyte sedimentation rate, C-reactive protein and urinary culture. Exclusion criteria were any additional axis I or axis II DSM-IV diagnosis, current pregnancy, acute or chronic infections within the last month, autoimmune, allergic, neoplastic, or endocrine diseases (thyroid and other endocrine dysfunctions) or other acute physical disorders, including surgery or cardiac or cerebral infarction within the last 3 months. Patients, who took any drug including nonsteroidal anti-inflammatory drugs or oral contraceptives in the last 6 weeks, were also excluded. Healthy volunteers were also interviewed and in addition to the above exclusion criteria, those with no lifetime or current diagnosis of any psychiatric disorders were included in the control group.

Socio-demographic (age, gender, level of education, and marital status) and clinical conditions of the subjects were examined by using a data query form. Major depressive episode was diagnosed using the DSM-5. The severity of depression was evaluated with the 21-item Beck Depression Inventory (BDI). The validity and reliability studies of the Turkish version of the form were conducted by Hisli.[22]

The study was approved by Gülhane Military Medical Academy, Ethical Statement of Clinical Researches (50687469-1491-42-15/SEK.1677). Written informed consent form was obtained from each participant.

Application and Sample Collection

The patients with treatment resistant major depression, for whom ECT was planned, were screened according to SCID-I for additional diagnoses. Necessary psychometric assessments, biochemical examinations and consultations were done by the treatment team. The BDI scale was applied twice; before and after the ECT application to patients who met the criteria to be included in the study without any contraindication to ECT, and venous blood samples were drawn to measure the myostatin levels. In the control group, venous blood samples were drawn only once to measure the myostatin levels.

ECT Application

ECT was carried out by a team of an anesthesiologist, a psychiatrist, a psychiatric nurse and anesthesia technicians at the ECT unit of the Department of Psychiatry. Subsequent to a fasting period (8-12 hours) and after the standard anesthesia monitoring, patient-specific doses of propofol (0.75-1 mg/kg) for anesthesia induction and the muscle relaxant succinylcholine (1 mg/kg) were administered intravenously to all patients by an anesthesiologist.

Bilateral ECT was administered. The number of ECT applications in our study was between 8 and 15 for a frequency of thrice a week, and this number could be in-

creased or decreased by the patient's clinical response. Electrical stimulus was provided by a Mecta Spectrum 5000Q ECT (Portland, OR, USA) device. In the ECT application, the formation of 25 seconds of long-term convulsions was targeted by administering square wave-type pulses of 550 to 800 mA (frequency, 30-70 Hz). The seizure threshold was terminated at the first treatment. Stimuli were given with increasing intensity until a generalized seizure was induced. All patients were oxygenated by positive pressure ventilation via mask until resumption of spontaneous respiration.

Serum Myostatin Levels

Peripheral venous blood samples were collected in serum tubes from all participants at 6:00 to 9:00 am. All samples were allowed to clot before centrifuged at 1,000×*g* for 15 minutes and were stored at −80°C until analysis. Serum concentrations of myostatin (GDF-8) were determined in duplicate with commercially available enzyme-linked immunosorbent assay (ELISA kits; Wuhan Eiaab Science Co. Ltd., Wuhan, China). The minimum detectable level of myostatin was 0.156 ng/ml. Intra- and interassay coefficients of variation were 6.9% and 9.7%, respectively.

Statistical Analyses

Kolmogorov-Smirnov test was used to check if the sample distribution was normal. Inter-group comparison of the demographic variables was done using an ANOVA for continuous variables and the chi-square test for categorical variables. Correlations between variables were assessed with the Pearson's correlation coefficient. Paired *t* test was used to investigate changes in myostatin levels before and after treatment. Data are presented as mean standard deviation. All tests were two-tailed with a significance level set at 0.05. The rate was set to α=0.05 and *p* values equal to or lower than this value were considered statistically significant. SPSS version 15.00 (SPSS Inc., Chicago, IL, USA) was used for data analysis.

RESULTS

Socio-demographic Characteristics

The study was concluded by 29 patients and 30 healthy volunteers. There was no difference between the two groups in terms of age, marital status, education and gender. The groups were also similar in terms of socio-demographic features (Table 1).

Clinical Scales and Changes with Treatment

Pre-ECT BDI scores were found to be 42.13±8.14; while post-ECT BDI scores were 15.89±6.89. The difference between the two measurements was found to be statistically significant (t=17.28, $p<0.05$).

Myostatin Measurements

For 29 patients with treatment-resistant major depression, the pre-treatment mean myostatin level was 0.95±0.32 ng/ml, while in the control group the mean myostatin level was 0.87±0.21 ng/ml. There was no statistically significant difference between pre-therapy myostatin levels of the patient group and the control group (t=1.28, p=0.229). However, post-therapy myostatin level of the patient group was measured to be 11.05±6.97 ng/ml. There was a statistically significant difference between post-therapy myostatin levels of the patient group and post-therapy myostatin levels of the control group (t=5.08; $p<0.05$). Accordingly, there was a statistically significant difference between in pre-therapy myostatin levels and post-therapy myostatin levels of the patient

Table 1. Socio-demographic and clinical characteristics of patient and control groups

Characteristic	Major depression (n=29)	Control (n=30)	t/χ^2	*p* value
Sex				
Male	12 (41.4)	12 (40.0)	0.564	0.453
Female	17 (58.6)	18 (60.0)		
Age (yr)	36.66±9.70	33.60±11.23	0.908	0.368
Education level (yr)	9.7±4.0	11.2±4.3	1.334	0.188
No. of electroconvulsive therapy	11.6±2.0 (8-15)			

Values are presented as number (%) or mean±standard deviation (range).
t, by Student's t test; χ^2, Pearson's chi-square test.

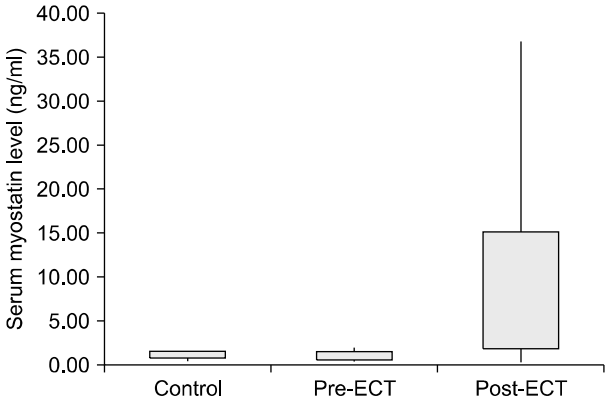

Fig. 1. Healty control group, serum myostatin levels of pre- and post-ECT patients.
ECT, post-electroconvulsive therapy.

group (t=4.17; $p<0.05$) (Fig. 1).

Relationship between BDI Scores and Myostatin and ECT

No statistically significant relation was found between myostatin levels and BDI scores. However, statistically significant and positive correlation was found between myostatin level and change in BDI scores (r=0.392, $p<0.05$). There was no significant difference between numbers of ECT and myostatin levels.

DISCUSSION

In our study, pre-ECT myostatin levels were same between patients and control group, but post-ECT levels were different between these groups. Patients post-ECT miyostatin levels were significantly higher than pre-ECT. This was the first important finding of our study. The second important result is finding a significant relation between myostatin levels and depression scores.

Our study is the first one to evaluate the relation between ECT and myostatin levels. We believe that shedding light on this subject may contribute to understanding the effect mechanism of ECT. The most widely used method to observe ictal motor activity during ECT is to prevent muscle relaxant to pass through a limb of the patient (generally by placing a cuff around the right or left arm).[23] This condition may be a reason for the elevation of myostatin level.

Results of the studies, performed on the subject of musculo-skeletal system and myostatin level, are contradictory. It was demonstrated that the elevated myostatin levels in patients with chronic heart diseases decreased after exercise training.[11] A previous animal study reported that stretching and electrical stimulation to muscle, which mimic exercise training, decreased myostatin levels.[14] In our study, elevation of myostatin level in the opposite way may be a result of the muscular activities during ECT being very different from the regular exercise. Because exercise training has shown inconsistent effects on myostatin expression in healthy volunteers, depending on the muscle type and the form of exercise.[12,13]

It seems very strange to us that albeit there is a relation between myostatin levels and depression scores, there is no relation between numbers of ECT and myostatin levels. Yet, there is no study on effect of myostatin on mood. Myostatin is thought to increase the adiponectin synthesis in adipose tissue.[24] However, adiponectin is a protein on which studies are carried out regarding depression. AdipoR1 and AdipoR2 are adiponectin receptors in central nervous system, and they play a role in mood regulation, being effective in various parts of the brain including hippocampus.[25,26] In animal model studies, adiponectin demonstrated antidepressant-like effect.[9,26] Yet, there is no sufficient data regarding the nature of the relation between depression and myostatin. However, as said above, there is a close interaction between adiponectin and myostatin. Myostatin may indirectly affect the depressive mood through adiponectin. As result of animal model studies and growth factor studies such as BDNF and vascular endothelial growth factor, ECT is thought to increase hippocampal neurogenesis.[27-29] Hippocampal neurogenesis with anti-depressant effects has been related to adiponectin secretion.[30] ECT is thought to be related to hippocampal growth and antidepressant effects and adiponectin is also thought to be a potential biological determinant.[31] We are of the opinion that myostatin has an effective role in all those effects, and it can contribute to shedding light on these steps.

Direct relation between the change in myostatin levels and the change BDI scales, which is a determinant of ECT response, and no relation between pre-ECT myostatin and BDI scores in this study, give rise to thought that myostatin change can be used as a determinant of response to ECT, such as adiponectin.

This study contains some limitations. First, it could be performed on a larger group of patients. Second, myo-

statin levels could be compared between patients with treatment resistant depression and other patients with depression. Within sametime other biomarkers could be determined which effects levels of myostatin. Patients' myostatin levels could be measured several times during therapy, and it could be found out that each ECT session yielded what kind of results. We believe that particularly the studies in which adiponectin levels will be measured together with myostatin levels will be the most valuable in the future.

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