SERUM S100B LEVELS IN PATIENTS WITH MAJOR DEPRESSION AND PANIC DISORDER

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ABSTRACT

Objective: *S100B, which is a member of S100 proteins, is the major neurotropic factor of serotonergic neurons, and it has such duties as synaptic plasticity, new neuron formation and axon germination. The micromolar concentrations of extracellular S100B induce apoptosis and neurodegeneration, whereas nanomolar concentrations make neurit grow and maintain the survival of the neuron during the growth. The aim of this study was to examine the probable relationship between S100B levels in the patients with major depression and panic disorder and the diagnosis and treatment of the diseases.*

Material and Method: *34 patients recently-diagnosed with major depression, 33 patients recently-diagnosed with panic disorders and 33 the healthy control group demographically similar to each other were included. Our patient groups were chosen from the ones whose Beck Depression and Beck Anxiety inventories are >16, while the control group was chosen from the ones whose Beck Depression and Beck Anxiety inventories are <13. Serum S100B (Electrochemiluminescence Immunoassay, Roche Elecsy 2010) and calcium (Colorimetric Endpoint Methot, Roche Modular) ranges of the patient groups were measured in pre-treatment and post-treatment with a month-selective serotonin reuptake inhibitors (SSRI).*

Results: *When we compare cases among the groups, S100B mean levels of the major depression group (0.056±0.025 µg/L) (0.052 [0.02-0.16]) and the panic disorder group (0.064±0.045 µg/L) (0.0545 [0.03-0.28]) are higher than S100B level of the control group (0.046±0.020 µg/L) (0.044 [0.024-0.097]) ($p<0.05$). Before and after the treatment, any significant changes in S100B levels both of the major depression and the panic disorder groups were not found ($p=0.173$; $p=0.777$; respectively)*

Conclusion: *S100B levels are significantly higher in the patients with major depression and panic disorder than the control group. Therefore, S100B levels can be biological markers for mood disorders (depression, anxiety).*

Keywords: *S100B, calcium levels, major depression, panic disorder.* **Nobel Med 2018; 14(3): 39-44**

MAJOR DEPRESYON VE PANİK BOZUKLUKTA SERUM S100B SEVİYELERİ

ÖZET

Amaç: S100 proteinlerinin bir üyesi olan S100B, serotonerjik nöronların major nörotrofik faktörüdür, erişkin beyninde sinaptik plastisite, yeni nöron oluşumu ve akson filizlenmesi gibi görevleri vardır. Ekstrasellüler S100B'nin mikromolar konsantrasyonları apoptosis ve nörodejenerasyonu indüklerken nanomolar konsantrasyonları, nörit büyümesini ve nöronun gelişimi süresince hayatta kalmasını sağlar. Bu çalışmanın amacı, major depresyon ve panik bozukluğu olan hastalarda S100B seviyelerinin, hastalığın tanısı ve tedavisi ile ilgili muhtemel ilişkisini araştırmaktır.

Materyal ve Metot: Bu çalışmaya yeni tanı almış 34 major depresyonlu hasta, 33 panik bozukluğu olan hasta ve demografik özellikleri benzer 33 sağlıklı kontrol grubu dahil edildi. Hasta gruplarımız Beck Depresyon ve Beck Anksiyete ölçekleri >16 olanlardan, kontrol grubu ise Beck Depresyon ve Beck Anksiyete ölçekleri <13 olanlardan seçilmişti. Hasta grubunda tedavi öncesi ve bir aylık Selektif Seratonun Gerialım İnhibitörü (SSRI) ile tedavi sonrası serum S100B (Elektrokemilüminesans Immunoassay, Roche Elecsy, 2010) ve Kalsiyum (Kolorimetrik Endpoint Yöntem, Roche Modular) seviyelerine bakıldı.

Bulgular: Olgularımızı grup içi karşılaştırdığımız zaman major depresyon grubunun S100B değeri; (0,056±0,025 µg/L) (0,052 [0,02-0,16]) ve panik bozukluk grubunun serum S100B değeri; (0,064±0,045 µg/L) (0,0545 [0,03-0,28]), kontrol grubunun S100B değerine göre (0,046±0,020 µg/L) (0,044 [0,024-0,097]) daha yüksektir (p<0,05). Tedavi öncesi ve tedavi sonrası hem major depresyonda hem panik bozukluk grubunda S100B seviyelerinde anlamlı değişiklik görülmemiştir (sırasıyla, p=0,173; p=0,777).

Sonuç: S100B seviyeleri, major depresyon ve panik bozukluğu olan hastalarda kontrol grubuna göre anlamlı derecede yüksektir. Bu yüzden S100B seviyeleri duygudurum bozukluklarının (depresyon, anksiyete) tanısında, izlenmesinde biyolojik marker olabilir.

Anahtar kelimeler: S100B, kalsiyum seviyeleri, major depresyon, panik bozukluk. **Nobel Med 2018; 14(3): 39-44**

INTRODUCTION

Depression is a public health problem that is endemic worldwide and contributes greatly to the loss of labor force and disability. The risk of having a depressive episode over the span of one's life is generally accepted as being between 18% and 20%. According to the studies done in the USA in 2015, nearly 17 million adults aged over 18 years old, that is, approximately 7% of all American adults, had a major depression attack at least once in their lives. And the epidemiological studies in our country are limited and their results are quite variable. The rates change between at least 4.8% and at most 48%.[1-4] Anxiety disorders (generalized anxiety disorder, panic disorder, social anxiety disorder) are the most prevalent psychiatric disorders. Panic disorder with or without agoraphobia is the next most common type with a prevalence of 6.0%. Women are 1.5 to two times more likely than men to receive a diagnosis of anxiety disorder.[5]

Anxiety and depression (mood disorders) can occur either separately or together. Several postmortem and neurobiological screening studies have indicated that atrophy and the loss of neurons in the prefrontal cortex and hippocampus occur in patients with anxiety and depression. Recent studies have shown that the brains of depressed patients' have structural changes in the mood-related regions and a decrease in glial cells and neurons. There are many studies claiming that depression and mood disorders occur as a result of a decrease in the self repair and renewal capabilities of neurons or glial cells. It has been suggested that depression occurs because of damage in the hippocampal neurons and that some antidepressants inhibit this damage, accelerating new neuron formation and enhancing neuroplasticity. Neuroplasticity is very important for the vital functions of neurons, and therefore its impairment may be the cause of some disorders. At present, theories regarding impairment and/or insufficiency of neuroplasticity playing a role in various psychiatric and medical disorders are gaining attention.[6-10]

The S100B protein family has been studied for 30 years. The first member of this family to be described was S100B, and it was defined as the mixture of S100A1. The monomer of S100B is found in the central nervous system, particularly in the cytoplasm of astrocytes. S100B can form homodimers or heterodimers with S100A1. It regulates cell shape, energy metabolism, contraction, cell-to-cell communication, intracellular signal transduction, and cell growth and can

be actively released by astrocytes. The effects of extracellular S100B depend on its concentration. S100B has neurotrophic and neuroprotective effects at physiologic nanomolar concentrations. However, higher (micromolar) concentrations of S100B are neurotoxic and expressed in astrocytic death.[11,12]

This study aims to show that S100B plays a role in reducing neuroplasticity and causing calcium imbalance, both of which are thought to play a role in the pathogenesis of major depression and panic disorder. We tested to see whether S100B could be a biologic marker in major depression and panic disorder and whether serum levels of S100B and calcium change before treatment and after 4 weeks of treatment.

MATERIAL AND METHOD

Biomedical Researches Ethics Committee's approval was received for this study from Şişli Etfal Training and Research Hospital (SETRH) with decision (29/06/2010 date and 106 issue number). All participants were informed about the study and the informed consent forms were signed. The study was conducted in SETRH. Major depressive disorder and panic disorder patients were recruited.

In this prospective study, we included 34 patients (8 males, 26 females) who were diagnosed with their first episode of major depressive disorder and 33 patients (10 males, 23 females) who were diagnosed with panic disorder for the first time based on criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and 33 Healty Control group (10 males, 23 females). All of the patients were treated with selective serotonin reuptake inhibitors antidepressan (paroxetine, sertraline, citalopram, fluoxetine, escitalopram, and fluvoxamine) at the Sisli Etfal Training and Research Hospital.

Patients with mental retardation, neurological disorder, diabetes, hypertension, asthma, acute infection, endocrine, renal and hepatic diseases and other psycotic disorders, substance users, using antidepressants or who were <17 years or >65 years were excluded.

After an examination and a follow-up in the psychiatry clinic, patients were included in the study with their permission. We applied the Beck Depression and Anxiety inventories in accordance with the DSM-IV criteria on the patients with major depression and panic disorder. Those whose Beck Depression and Beck Anxiety score was >16, were included in the study. The control group consisted of subjects whose Beck Anxiety and Depression score were <13.

Blood samples were collected from all patients after an 8-10 hour fast between the hours 8:00–10:00 in the morning. Serum S100B levels in the samples were measured according to the following methods (Roche Elecsy 2010, Roche Diagnostics, Germany).[13] Venous blood samples were collected and placed in separator gel tubes to measure serum calcium and S100B levels. Samples were centrifuged at 3600 relative centrifugal force for 10 minute. The serum samples for S100B were placed in Eppendorf tubes and stored at -80°C. According to the manufacturer's protocols, the fully automated test required 18 minute to run and required a probe volume of at least 20 mg/L. The lower detection limit was 0.005 mg/L, and concentrations of up to 39 mg/L could be measured without dilution. The venous blood that was collected to measure serum calcium levels was studied in a biochemistry analyser (Roche Hitachi, Roche Diagnostics, Germany) the same day.[13] The intra and inter-assay coefficients of variation (cv) were 1.8 to 2.4% for S100B and 1.0 to 2.5% for calcium.

Statistical analysis of our results was conducted using SPSS 21 (SPSS Inc., Chicago, IL, USA) version 21.0. To determine whether data was normally distributed, we employed the Kolmogorov-Smirnov test. For both descriptive statistical methods and comparison of quantitative data, we used the Mann-Whitney U test. To make within-group comparisons of parameters, we used the Wilcoxon test.

To compare qualitative data, we used the chi-square test. To analyze the relationships among parameters, we used the Spearman correlation test. The results were analyzed using a $p \leq 0.05$ significance level and 95% confidence intervals.

RESULTS

The study included 100 subjects, 72 female and 28 male, with ages ranging between 17 and 65 years. The subjects were broken down into three groups based on their diagnosis: Major Depression (n=34), Panic Disorder (n=33), and control (n=33). There were no statistically significant differences between the groups for average age, sex ($p>0.05$). The inter-group comparison of the subjects revealed that the pre-treatment mean levels of S100B in the major depression group (0.056±0.025 µg/L) (0.052 [0.02-0.16]) and panic disorders group (0.064±0.045 µg/L) (0.0545 [0.03-0.28]), were higher than those in the control group (0.046±0.020 µg/L) (0.044 [0.024-0.097]) (Figure 1).

When the S100B levels of the control group were compared to the pre- and post-treatment S100B levels

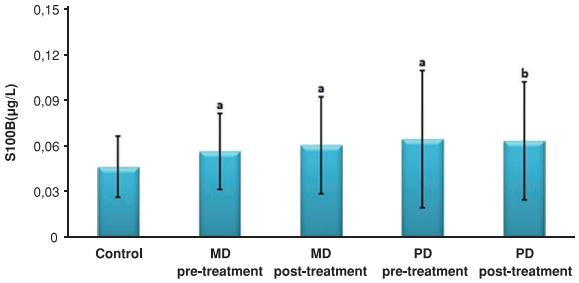

Figure 1. Comparison of pre- and post-treatment S100B levels of the subjects to those of the control group
MD: Major Depression, PD: Panic Disorder,
[a]$p \leq 0.05$ When compared to the control group
[b]$p \leq 0.01$ When compared to the control group

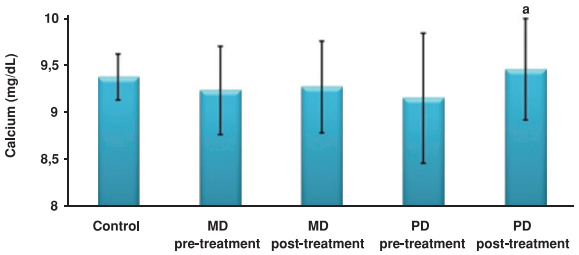

Figure 2. Comparison of pre- and post-treatment Calcium levels of the subjects to those of the control group
MD: Major Depression, PD: Panic Disorder,
[a]$p \leq 0.05$ When compared to the PD pre-treatment group

of subjects with major depressive and panic disorder, statistically significant differences were found (MD pre-treatment; $p \leq 0.05$, MD post-treatment; $p \leq 0.05$, PD pre-treatment; $p \leq 0.05$, PD post-treatment; $p \leq 0.01$, respectively) (Table, Figure 1).

No statistically significant differences in the S100B levels were found both in the major depression and panic disorder groups pre- and post-treatment (p=0.173; p=0.777) (Figure 1). No significant differences were found between pre- and post-treatment calcium levels in the major depression group (9.22±0.46 mg/dl; 9.26±0.48 mg/dl) (p=0.677). In the panic disorder group, there was a statistically significant increase in the calcium levels post-treatment as compared to the pre-treatment levels (9.15±0.68 mg/dl; 9.44±0.54 mg/dl) (p=0.038) (Table, Figure 2).

Table. Demographical and biochemistrical data of the groups

	Control n=33	MD Pre-treatment n=34	MD Post-treatment n=34	PD Pre-treatment n=33	PD Post-treatment n=33
Age	34.2±12.01	36.2±10.3	-	35±12.02	-
Sex	23/10	26/8	-	23/10	-
S100B µg/L	0.046±0.020	0.056±0.025[a]	0.061±0.032[a]	0.064±0.045[a]	0.063 ± 0.039[b]
Median(Min-Max)	0.044 (0.024-0.097)	0.052 (0.029-0.154)	0.054 (0.024-0.158)	0.057 (0.026-0.278)	0.050 (0.032-0.250)
Calcium mg/dL	9.36±0.25	9.22±0.46	9.26±0.48	9.15±0.67	9.44±0.53[c]
Median (Min-Max)	9.4 (8.6-9.7)	9.3 (8.3-10.1)	9.4 (8.0-10.2)	9.3 (8.2-11.2)	9.5 (8.0-10.9)

MD: Major Depression, **PD:** Panic Disorder
[a]$p \leq 0.05$ When compared to the control group
[b]$p \leq 0.01$ When compared to the control group
[c]$p \leq 0.05$, When compared to the PD pre-treatment group

DISCUSSION

The biological markers used to make decisions about the diagnosis, treatment, and prognosis in depression and anxiety remain very limited. Therefore, new etiological models are being developed to understand the pathophysiology of depression and anxiety. Several studies have investigated the possible roles of other neurotransmitter systems, aside from the monoaminergic system, on depression etiology. Therefore, going forward, the focus of the study should not be restricted to only neurotransmitter changes but rather include other pathologies in the brain.[14,15]

In a previous study, researchers found that S100B could be detected in astroglial and oligodendroglial cells but not in microglial cells.[16] In addition, histopathological changes were detected in oligodentrocytes and astrocytes in paients with mood disorders.[17] In the same study, they reported a statistically significant difference in the S100B levels between the subjects and the control group. Thus, they claim that the S100B protein can be used as a glial marker protein for mood disorders. Because histopathological changes in astrocytes and/or oligodendrocytes cause an increase in S100B secretion and cause this protein, which has a concentration-based effect, increasing S100B levels in plasma, some cellular damage is caused in the brain. Moreover, this condition prevents neuroplasticity, which can be formed by antidepressants.

Panic disorder is associated with depression and other anxiety disorders.[18] There are studies indicating that the deficiency of calcium increases the suspectibility to anxiety and may even has a role in pathogenesis of panic disorder.[19] This study indicates that the post-treatment calcium levels of the patients with panic disorder increase significantly in comparison to the pre-treatment calcium levels. Moreover, it reveals that the S100B levels of the patients with panic disorder is significantly higher than the ones of the control group. These results indicate that the treatment through SSRIs may increase the calcium levels of the patients with panic disorder, leading to an increase in the resistance to anxiety. That S100B levels shows no changes in the pre-treatement and post-treatment

can be associated with the indeficiency of treatment duration (4 weeks). We consider that it will be better to examine the changes in S100B levels through long-lasting treatments.

It has been thought that S100B, which is a neurotrophic factor, may have a role in pathophysiology of mood disorders. S100B serotonergic neurons are major neurotropic factors and have such duties in an adult's brain as synaptic plasticity, new neuron formation and axon germination. By binding to 5HT1A receptor of the serotonin, astroglial cells start S100B secretion. Neuroplasticity help many significant functions maintain and its deficiency can lead to some diseases. As monoamine hypothesis is not capable of explaining the etiology of depression and its treatment, new models and new pathophysiological mechanisms for mood disorders should be considered.[20-24]

CONCLUSION

When the S100B levels of the control group were compared to the pre- and post-treatment S100B levels of subjects with major depressive and panic disorder, statistically significant differences were found. Moreover, the post-treatment calcium levels of the patients with panic disorders changed significantly. Therefore, S100B levels can be biological markers for mood disorders. Calcium levels can also be significant in monitorising in respond to the treatment of the patients with panic disorders. We consider that more extensive works in this area are needed in order to fully understand the relationship between neuroplasticity and S100B.

*The authors declare that there are no conflicts of interest.

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