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Serum S100B Protein Levels in Patients with Panic Disorder: Effect of Treatment with Selective Serotonine Reuptake Inhibitors

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Objective Altered serum S100B protein levels have been shown in several psychiatric disorders. Our aim was to investigate whether plasma S100B is different in patients with panic disorder (PD) when compared with controls. Our second aim was to investigate whether treatment with SSRIs have an effect on S100B levels in patients with PD.

Methods The sample included 32 patients diagnosed with PD (21 women, 11 men) per DSM-IV criteria and 21 healthy controls (11 women, 10 men). S100B levels were measured with BioVendor Human S100B ELISA (Enzyme Linked Immunosorbent Assay) kit.

Results 14 patients were not on drug treatment (43.8%) while 18 patients were taking various SSRIs. Median S100B value was 151.7 pg/mL (minimum-maximum: 120.4−164.7 pg/mL) in the control group, 147.4 pg/mL (minimum-maximum: 138.8−154.1 pg/mL) in the drug free group and 153.0 pg/mL (minimum-maximum: 137.9−164.7 pg/mL) in the treatment group. Kruskal-Wallis analysis showed a significant diffrerence among the three groups (z=9.9, df=2, p=0.007). Follow up Mann-Whitney-U tests indicated that while the control and the patients with treatment were not significantly different (z=-0.05, p=0.96), there were significant differences between the control group and untreated patients (z=-2.6, p=0.009) and treated and untreated patients (z=-3.0, p=0.003).

Conclusion Our results suggested that, serum S100B protein level might be decreased in untreated PD patients and that patients who were treated with SSRIs had similar S100B level to healthy controls. **Psychiatry Investig 2015;12(2):260-262**

Key Words S100B protein, Panic disorder, Selective serotonine reuptake inhibitors.

INTRODUCTION

Panic disorder (PD) is one of the most common psychiatric disorders in general population and neuroanatomical regions associated with PD include brain stem (noradrenergic neurons located at locus seruleus and serotonergic neurons located at median raphe nucleus), limbic system and prefrontal cortex.[1-3] Particularly, serotonergic system is implicated both in pathophysiology and treatment of PD. It has been suggested that highly sensitive serotonine receptors might have a possible role in PD pathophysiology.[2]

S100B protein, a member of S100 protein family, is a homodimeric acidic protein, has 21 kDA molecular weight and consists of 2 beta units.[4] S100B is expressed primarily by astrocytes and has autocrine and paracrine effects on glial and neuronal cells.[5] Astroglial 5HT1a activation release S100B.[6] Fluoxetine may also be able to stimulate S100B expression by a mechanism which is not clear, but appearently serotonin-independent.[7] Chronic exposure to fluoxetine, particularly during sensitive developmental periods, may lead to increased, long-lasting S100B immuno-reactivity in rat brains.[8]

S100B is found to be increased in peripheral blood and cerebrospinal fluid in patients with major depression, particularly during acute episodes of mood disorder.[9-14] In a neuropathological study, S100B immuno-positive astrocytes were decreased in density in patients with major depression or bipolar disorder.[15] Selective serotonin reuptake inhibitor use reverse reduced astrocytic S100B immunoreactivity in rats.[7,16,17] It has

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been suggested that increased serum S100B might be associated with positive response to fluoxetine in patients with MDD.[18] Increased S100B concentration in MDD might indicate better response to treatment and might be a biomarker for plasticity.[14,19]

Evidence that panic disorder (PD) is associated with serotonin comes from treatment studies which show that SSRIs are effective in decreasing PD[20] and from studies indicating that serotonin is relevant in anxiety by acting on prefrontal cortex and periaqueductal gray matter.[21] Following the preceeding discussion on the interactions between S100B protein and serotonin, our aim was to investigate whether plasma S100B is different in patients with PD when compared with controls. Our second aim was to investigate whether treatment withh SSRIs have an effect on S100B levels in patients with PD.

METHODS

The sample included 32 patients diagnosed with PD (21 women, 11 men) per DSM-IV criteria by using a semi-structured clinical interview, Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), and 21 healthy controls (11 women, 10 men). All patients were consecutive admissions to outpatient psychiatry clinic during June−December 2011. All patients and controls were 18−65 years of age and at least primary school graduates. Exclusion criteria were having a comorbid psychiatric disorder or general medical condition which can interfere with the diagnostic process.

S100B measurement

After written informed costent was acquired, venous blood samples were drawn from all patients and controls after 8 to 10 hours of fasting, between 8:00 a.m. and 10:00 a.m. Blood samples were centrifuged for 10 minutes at 3000 rotation/minute. Serum samples were separated and stored at -80 degrees Celcius. S100B levels were measured with BioVendor Human S100B ELISA (Enzyme Linked Immunosorbent Assay) kit.

Data analysis

Statistical Package for Social Science (SPSS) 15.00 for Windows software was used for data analysis. In order to compare patient and control groups, we used Mann-Whitney U test. To compare patients with treatment, patients without treatment and controls, we used Kruskal-Wallis test, followed by Mann-Whitney-U tests. Chi-square test was used to compare the distribution of categorical variables. $p<0.05$ was reported as statistically significant.

RESULTS

Of the 32 patients in the PD group, 25 had only PD and 7 (21.9%) had PD with agoraphobia. There were 21 women (65.6%) in the patient group and 11 women (52.4%) in the control group. There were no significant differences between the groups in terms of gender (χ^2=0.93, p=0.33), age (z=-0.76, p=0.45), education (χ^2=0.65, p=0.89), and family history (χ^2=0.20, p=0.77).

14 patients were not on drug treatment (43.8%) while 18 patients were taking various SSRIs.

Median S100B value was 151.7 pg/mL (minimum−maximum: 120.4−164.7 pg/mL) in the control group, while median S100B value was 150.5 pg/mL (minimum−maximum: 137.9−164.7 pg/mL) in the patient group. There were no significant differences between the two group. When treatment was taken into account, median S100B was 147.4 pg/mL (minimum−maximum: 138.8−154.1 pg/mL) in the drug free group and 153.0 pg/mL (minimum−maximum: 137.9−164.7 pg/mL) in the treatment group. Kruskal-Wallis analysis showed a significant difference among the three groups (z=9.9, df=2, p=0.007). Follow up Mann-Whitney U tests indicated that while the control and the patients with treatment were not significantly different (z=-0.05, p=0.96), there were significant differences between the control group and untreated patients (z=-2.6, p=0.009) and treated and untreated patients (z=-3.0, p=0.003).

DISCUSSION

Several studies to date have indicated that S100B protein, a glial marker, is increased in subjects with mood disorders, particularly during acute mood episodes.[9-14] It has also been suggested that serotonin system is associated with S100B and that SSRIs effect S100B levels, although the exact mechanism is not clear, yet.[7,16-18] Based on the studies indicating role of serotonin in PD,[20,21] we sought to investigate whether serum S100B protein level is different from healthy controls in this group. Our results showed that, there were no significant differences between the whole patient group, which included patients both with and without treatment, and the healthy control group. On the other hand, significant differences emerged when medication status was taken into account. While serum S100B levels of treated patients with PD and healthy controls were very similar, S100B levels of both groups were significantly higher than the untreated PD group. These results suggest that, PD itself might be associated with decreased S100B levels, and SSRI treatment might lead to an improvement. In rats, it has been shown that chronic unpredictable stres led to decreased levels of S100B in CSF and hippocampus, which was reversed by administration of fluoxetine.[17] Although increased S100B levels

in various conditions, including schizophrenia and neurodegenerative disorders, have been reported,[13] to date the association between anxiety disorders and S100B levels has not been throughly investigated. Therefore, it is difficult to compare our results with previous studies. However, most of the studies reported increased serum S100B levels in various conditions,which was interpreted as glial alteration,[12] so it is not easy to comment on lower levels in patients with PD. On the other hand, when previous studies investigating the change of S100B levels with SSRIs were reviewed, results suggested that SSRI's increase S100B levels.[7,16-18] Our results were generally in line with these previous studies.

The present study had several limitations. First, the patient group included both treated and untreated patients and treated patients were incorporated to our study regardless with their remission status. Second, treatment effects were not investigated in a pre-treatment, post-treatment design, therefore, it is difficult to definitely state treatment effects. Third, in recent studies, it has been suggested that body mass index may be an important confounder for serum S100B levels, and we did not control that variable. Fourth, we did not have a continuous measure for disease severity, and therefore could not evaluate whether there is an association between PD severity and S100B levels. Last, as an inherent limitation of cross-sectional studies, it was not possible to comment on causality. Nevertheless, our results suggested that, serum S100B protein level might be decreased in untreated PD patients and that patients who were treated with SSRIs had similar S100B level to healthy controls.

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