ORIGINAL ARTICLE

Serum S100B levels in patients with depression

Parul Arora, Rajesh Sagar[1], Manju Mehta[1], Pooja Pallavi, Subhadra Sharma, Asok Kumar Mukhopadhyay
Departments of Laboratory Medicine and [1]Psychiatry, All India Institute of Medical Sciences, New Delhi, India

ABSTRACT

Background: The biochemical basis of depression has been related to blood–brain barrier (BBB) allowing/restricting a number of components to enter the brain milieu from the peripheral plasma milieu. S100B has been associated with BBB damage and is used as a marker of its integrity. Several studies have reported that depressive patients have increased levels of S100B in serum and cerebrospinal fluid.
Materials and Methods: Forty-two confirmed cases of depression, 13–25 years of ages were recruited from the Department of Psychiatry, All India Institute of Medical Sciences during the period from January 2013 to June 2014 along with 42 healthy controls of comparable age and sex. Psychometric evaluation of the patients and controls was done to assess the severity of depression using Beck's Depression Inventory-II and Hamilton Depression Rating Scale. Medical assessment and laboratory investigations were done. Serum S100B levels were measured using Sandwich ELISA. The results obtained were statistically analyzed.
Results: Levels of serum S100B were significantly elevated in patients with major depression as compared to controls. Significantly higher levels of S100B were seen only in females as compared to their healthy counterparts. Serum S100B was higher in depressed participants with the recurrent disorder than those with single episode. No correlation of levels of this marker was seen with clinical severity of the patients. It was found that with increased duration of illness for which the patient was being treated with antidepressants, the patients had higher levels of S100B.
Conclusions: Serum S100B can be used as a biomarker of depression.

Key words: Blood-brain barrier, depression, S100B

INTRODUCTION

Depression can be described as a state of low mood or loss of interest in one's daily activities.

Depression is a complex, heterogeneous disorder.[1] Many pathological mechanisms have been described for depression. Decrease in the levels of the neurotransmitter serotonin in the brain is the basis of serotonin hypothesis of depression.[2] Neurotropin hypothesis involves the disruption of neuroplasticity that is a fundamental mechanism of neuronal growth and adaptation, which involves the neurotrophic factors having multiple functions at different stages of development and at different locations in and around the nervous system.[3] Furthermore, depression is considered to be low-grade chronic neuroinflammation. There is the interaction of cytokines that are the mediators of inflammation with the brain through the blood-brain barrier. Thus, the impairment of psychoneuroimmune axis and altered levels of cytokines form the inflammatory basis

Address for correspondence: Dr. Asok Kumar Mukhopadhyay, Department of Laboratory Medicine, All India Institute of Medical Sciences, New Delhi - 110 029, India.
E-mail: mukhoak1953@gmail.com

Access this article online	
Website: www.indianjpsychiatry.org	Quick Response Code
DOI: 10.4103/psychiatry.IndianJPsychiatry_391_16	

How to cite this article: Arora P, Sagar R, Mehta M, Pallavi P, Sharma S, Mukhopadhyay AK. Serum S100B levels in patients with depression. Indian J Psychiatry 2019;61:70-6.

of depression.[4] Whether these mediators are the cause or the effect of depression is not known.

Involvement of these several neurotransmitters, multiple neuroimmunological and neurohormonal pathways have been the basis of various experimental studies to find reliable blood-derived biomarkers to identify, diagnose, or subclassify the patients of depression and study the treatment response in them.

Many studies on depression are in accordance with the biochemical basis of depression that has been related to the state of blood-brain barrier (BBB) allowing/restricting a number of components to enter the brain milieu from the peripheral plasma milieu.

The BBB is primarily composed of endothelial cells (ECs), astrocyte end-feet, and pericytes sharing a common basement membrane. The microvascular EC linked by tight junctions form a diffusion barrier allowing selective molecular communication between the plasma and the brain or central nervous system (CNS). Furthermore, some proteins are found exclusively or almost exclusively in the cerebrospinal fluid (CSF). Due to any disruption in BBB integrity, these proteins leak in both directions. S100B which is a calcium (Ca^2+)-binding protein has been associated with BBB damage and is used as a marker of the integrity of BBB. The directionality of S100B transfer across the BBB is from brain toward systemic milieu, unlike serum albumin, glial fibrillary acid protein, and neuron-specific enolase which are transferred from peripheral blood to the brain.

S100B is produced by the astrocytes or can spill from injured astrocytic cells and enter the extracellular space or bloodstream. It is also a neurotrophic factor involved in neuroplasticity[5] which is disrupted in depression along with the decrease in levels of growth factors.[6] Elevated S100B levels in serum or CSF can be correlated with the presence of neuropathological conditions, including neurodegenerative diseases or traumatic head injury. Effects of S100B depend on its concentration.[7] When secreted in small amounts, in nanomolar concentrations, it activates growth or differentiation of neurons and astrocytes.[8] However, in very high amount, in micromolar concentrations, it causes apoptosis of cells and can be neurotoxic.[9,10] Normal serum S100B levels can reliably exclude major CNS pathology. It has a potential clinical role in the therapeutic decision-making process. It is however not clear yet, whether stress and BBB damage cause inflammation that leads to depression or it is the disease itself causing BBB damage and stress. A cause-effect relationship is yet to be determined. Several studies have reported that depressive patients have increased levels of S100B in the serum and CSF.[8,11-14] High levels of serum S100B have been related to a favorable therapeutic response.[11] These high levels correspond to neuron growth and synaptogenesis in depressive patients. The role of S100B in neuroplastic mechanisms in neuronal pathways has also been studied in conditions other than depression such as Alzheimer's disease,[15] schizophrenia,[8,12,16] and mania.[17]

This study was undertaken to look into the serum levels of S100B in participants of age 13–25 years with major depression as compared to healthy controls of comparable age and gender and also to analyze the correlation of the levels with clinical severity of depression assessed by psychometric evaluation scores.

MATERIALS AND METHODS

In this case–control study, the potential relationship of BBB damage and depression has been studied by comparing serum S100B levels in subjects diagnosed with major depression to healthy controls of comparable age and gender.

Subjects

Cases

Forty-two confirmed cases of depressed participants, 13–25 years of age were recruited from the child-guidance-clinic and walk-in-clinic of the Department of Psychiatry, All India Institute of Medical Sciences (AIIMS) during the period from January 2013 to June 2014 after approval by the Ethics Committee of AIIMS. Written informed consent was taken from participant/parent/guardian/legally acceptable representative of the patient before they were included in the study.

The 13–25-year-old depressed participants diagnosed with major depression by Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria for depression based on the Structured Clinical Interview for DSM Disorders-nonpatient version (SCID-I/NP)[18,19] were included in the study. Exclusion criteria for the depressed participants were (1) comorbid medical illness, detailed clinical history, and routine clinical hematology and chemistry investigations were carried out to exclude the same; (2) present or history of psychotic disorders, mental retardation, posttraumatic stress disorder, eating disorder, and substance abuse within the last 12 months; (3) history of medication with antibiotics, steroids, and immune modulators; (4) febrile illness (temperature >99°F) within 4 weeks before blood collection; and (5) in females, a positive urine pregnancy test. We have excluded pregnant females because S100B is a potential peripheral biomarker in hypertensive disorders of pregnancy.[20,21]

5 (males)/42 patients and 4 (males)/42 controls were smokers and few were occasional alcoholics taking an average of two drinks (60 ml) per week. None of our patients was a substance abuser. Family history of depression was present in 12/42 patients with major depression.

Controls

A comparable group of 42 healthy volunteers of 13–25 years age from community, including school-going children and young adults were recruited as controls. These healthy controls were chosen from participants of comparable age, gender, and socioeconomic status (assessed by Modified Kuppuswamy's socioeconomic scale[22]). They had no past or present DSM-IV Axis I disorder, as determined by the SCID-I/NP. Consent was taken from participant/parent/guardian/legally acceptable representatives of the healthy controls. Each of them was assessed using a clinical interview and General Health Questionnaire-12.[23] Control participants were assessed using psychometric evaluation scores same as on depressed participants. Participants with any personal or family history of psychiatric illness, diagnosed autoimmune disease, or with a history of any substance abuse were excluded from the study. All healthy controls were free of any acute/chronic physical illness within the 4 weeks before the study. The controls thus recruited for the study showed normal laboratory findings in blood hematological and chemistry, renal, and liver function tests. Females with positive urine pregnancy test were excluded from the study.

Psychometric evaluation

Psychometric evaluation of the patients and the controls was done. Based on the interview, the psychiatrist rated the severity of depression on the Beck's Depression Inventory (BDI-II)[24] and Hamilton Depression Rating Scale (HAM-D).[25] For the adolescents, stressful life event scale (SLES)[26] was also used to assess the stressful events causing disturbance and anxiety to the patient. A local language (Hindi) version of the psychometric evaluation scales was used wherever applicable.

Laboratory method

Routine medical assessment and laboratory investigations (complete blood count, kidney and liver function tests, and urine examination) were done on all participants.

S100B measurement

Sandwich enzyme-linked immunosorbent assay was performed in the departmental research laboratory for quantitative determination of the serum levels of S100B according to the manufacturer's instructions. Quantitative measurement of serum S100B was performed in duplicate for each of the aliquots using ELISA kit manufactured by Cloud-Clone Corp. This sandwich ELISA is based on microtiter plate precoated with an antibody specific to S100B. Standards or samples were then added to the appropriate microtiter plate wells with a biotin-conjugated antibody specific to S100B followed by avidin conjugated to horseradish peroxidase with appropriate incubation periods and washing steps. Following this, 3,3',5,5'-tetramethylbenzidine substrate solution was added. Only those wells containing S100B, biotin-conjugated antibody, and enzyme-conjugated avidin exhibited a change in color. Enzyme-substrate reaction was terminated by the addition of sulfuric acid solution. The absorbance was read in duplicate using a Bio-Rad xMarkMicroplate reader (Bio-Rad Laboratories, Hercules, CA, USA) at 450 nm. The intraassay and interassay coefficients of variation for all analyses were <6%. The mean of the available duplicate sample values was used.

Statistical analysis

Statistical program STATA (Version 11.2, released 2009, StataCorp, College Station, Texas) was used for all statistical computations. For the group comparisons, parametric (two-tailed unpaired Student's *t*-test) and nonparametric (Wilcoxon Rank-sum test) statistics were used. The distribution of parameters was considered nonparametric when standard deviation exceeded half of the mean value. For categorical variables, differences between the groups were assessed using the Chi-square test. For intergroup comparisons, the Kruskal–Wallis one-way analysis of variance was used. The Bonferroni correction method was used for ascertaining the significance level for assessing *post hoc* comparisons (set at the level of $P \leq 0.016$). Correlations between serum S100B and the depression and anxiety scores were calculated. Pearson's correlation coefficient was used to assess the relationship. Two-tailed $P \leq 0.05$ was regarded as statistically significant.

RESULTS

The demographic and clinical characteristics of 42 cases and 42 controls were as given in Table 1. There was no significant difference in the age ($P = 0.186$), male/female ratio ($P = 0.330$), and body mass index ($P = 0.120$) between

Table 1: Demographic and clinical profile

	Depressed (*n*=42)	Healthy controls (*n*=42)	*P*
Demography			
Age* (years)	19.81±4.26	20.62±4.00	0.186
Male/female	25/17	23/19	0.330
BMI* (kg/m^2)	23.29±1.34	23.68±1.68	0.120
Lifestyle			
Years of education*	10.69±2.44	11.33±3.04	0.144
Last year's household income in lakhs	4.00 (2-12)	4.75 (1.75-15)	0.234
Number of smokers, *n* (%)	5/42 (11.90)	4/42 (9.52)	0.364
Average drinks per week	0-4 (*n*=19)	0-3 (*n*=17)	0.030
Psychometric evaluation scores			
BDI	28 (17-47)	2 (0-4)	<0.001
HAM-D	21 (10-31)	1 (0-4)	<0.001
SLES	6 (2-12)	2 (0-4)	<0.001

*Mean±SD or values are expressed as median (minimum-maximum). Wilcoxon rank-sum test was used to compare medians while Student's *t*-test was used to compare means in two groups. Chi-Square test was used to assess the gender-based distribution. *n* – Number of participants; BMI – Body mass index; BDI – Beck's Depression Inventory; HAM-D – Hamilton Depression Rating Scale; SLES – Stressful life event scale; SD – Standard deviation

the depressed participants and the healthy controls. Thus, the two groups were satisfactorily comparable.

Clinical profile and therapeutic history of patients

The mean duration of illness at the time of presentation for which they received the treatment was 15.95 ± 11.53 months. The mean duration of the current episode was 4.71 ± 1.63 months. Average number of episodes of major depression in the participants was 1.79 ± 0.72. All the 42 patients with major depression were on treatment with antidepressants. Of the total 42 depressed patients, 33 were prescribed selective serotonin reuptake inhibitors (SSRIs), eight were on treatment with tricyclic antidepressants (TCA), and one was on treatment with a combination of SSRI and TCA. None of the included patients suffered from any comorbid illness as the patients were recruited considering the inclusion and exclusion criteria. None of the patients was on any other medication such as steroids, antibiotics, or immune modulators for any other medical illness. Family history of depression was present in 12/42 patients with major depression.

Psychometric evaluation scores: BDI scores, HAM-D scores, and SLES, as expected were found to be significantly higher in patients as compared to the control groups ($P < 0.001$; $P < 0.001$; $P < 0.001$, respectively).

The mean concentration of serum S100B was significantly higher ($P = 0.023$) in depressed participants 94.12 ± 56.08 pg/ml [median (range): 96.96 pg/ml (13.47–271.75 pg/ml)] as compared to the healthy controls 69.03 ± 55.23 pg/ml [median (range): 47.21 pg/ml (14.1–191.75 pg/ml)] as given in Table 2.

Serum S100B levels showed a significant difference between the patient and healthy controls only in the female group of participants. There was no significant difference in serum levels in the male participants [Table 3]. When this gender-wise comparison was done within the depressed participants, it was seen that there was no significant difference in serum S100B levels between the male and female depressed participants. Furthermore, no difference was found in psychometric evaluation scores (BDI and HAM-D) between the male depressed patients and female depressed patients [Table 4].

The levels of serum S100B in participants with single episode of depression were compared with those having recurrent depressive disorder and healthy controls using one-way ANOVA. The levels were significantly higher ($P < 0.001$) in those with recurrent depressive disorder (106.57 pg/ml [13.47–271.75 pg/ml]) than participants with first episode (48.96 pg/ml [16.81–144.43 pg/ml]). Furthermore, serum S100B levels were significantly higher ($P < 0.001$) in participants with recurrent depressive disorder (106.57 pg/ml [13.47–271.75 pg/ml]) than healthy controls (47.21 pg/ml [14.1–191.pg/ml]) as shown in Table 5.

Table 2: Serum S100B levels

	Depressed (*n*=42)	Healthy controls (*n*=42)	*P*
S100B (pg/ml)	96.96 (13.47-271.75)	47.21 (14.1-191.75)	0.023

Wilcoxon rank-sum test was used to compare medians of the two groups. Values are expressed as median (minimum-maximum). *n* – Number of participants

Table 3: Similar gender comparison of psychometric evaluation scores and serum S100B levels between the depressed and healthy controls

	Depressed	Healthy controls	P
BDI*			
Male	29.20±5.74	1.30±1.40	<0.001
Female	28.24±5.49	2.00±1.76	<0.001
HAM-D*			
Male	20.44±4.13	1.00±1.17	<0.001
Female	21.53±5.42	1.74±1.63	<0.001
S100B (pg/ml)			
Male	98.43 (16.81-271.75)	67.99 (18.83-188.54)	0.473
Female	93.29 (13.47-226.10)	26.25 (14.1-191.75)	0.024

*Mean±SD or values are expressed as median (minimum-maximum). Wilcoxon rank-sum test was used to compare medians while Student's *t*-test was used to compare means in two groups. Chi-Square test was used to assess the gender-based distribution. *n* – Number of participants; BDI – Beck's Depression Inventory; HAM-D – Hamilton Depression Rating Scale; SD – Standard deviation

Furthermore, no significant correlation was seen between the severity of depression as assessed by BDI in the patient group and the increase in levels of serum S100B [Table 6].

ANOVA/Kruskal–Wallis test was used to study the effect of treatment (t/t) with antidepressants for the duration of illness. Participants were divided as those whose total duration of illness and medication <6 months and those with more than 6 months. We found on the comparison that initially before 6 months, S100B was not significantly higher than healthy controls, however, as the duration increased serum levels of S100 B increased [Table 7].

DISCUSSION

Major findings of our study are as follows: (1) Levels of serum S100B were significantly elevated in the patients with major depression as compared to healthy controls. (2) Significantly higher levels of S100B were seen only in females as compared to their healthy control counterparts. There was no significant difference in the levels of serum S100B between the depressed males and females. (3) Serum S100B was higher in depressed participants with the recurrent disorder than those with single episode. (4) No correlation of the levels of this marker was seen with the clinical severity of the patients. All the depressive disorder patients had moderate-to-severe degree of depression on psychometric evaluation by BDI

Table 4: Gender wise comparison of psychometric evaluation scores and serum S100B levels within depressed participants

	Depressed			Healthy controls		
	Male (*n*=25)	Female (*n*=17)	*P*	Male (*n*=23)	Female (*n*=19)	*P*
BDI*	29.20±5.74	28.24±5.49	0.708	1.30±1.40	2.00±1.76	0.152
HAM-D*	20.44±4.13	21.53±5.42	0.388	1.00±1.17	1.74±1.63	0.164
S100B (pg/ml)	98.43 (16.81-271.75)	93.29 (13.47-226.10)	0.768	67.99 (18.83-188.54)	26.25 (14.1-191.75)	0.026

*Mean±SD or values are expressed as median (minimum–maximum). Wilcoxon rank-sum test was used to compare medians while student's *t*-test was used to compare means in two groups. Chi-Square test was used to assess the gender-based distribution. *n* – Number of participants; BDI – Beck's Depression Inventory; HAM-D – Hamilton Depression Rating Scale; SD – Standard deviation

Table 5: Serum S100B levels in depressed participants with single episode, recurrent episodes of depression, and healthy controls

	Single episode (*n*=15)	Recurrent episodes (*n*=27)	Healthy controls (*n*=42)
S100B (pg/ml)	48.96 (16.81-144.43)	106.57 (13.47-271.75)	47.21 (14.1-191.75)

Values are expressed as median (minimum-maximum). *n* – Number of participants

Table 6: Correlations of clinical severity of depression with serum S100B levels

BDI and S100B	Depressed			Healthy controls		
	Female (*n*=17)	Male (*n*=25)	Overall	Female (*n*=19)	Male (*n*=23)	Overall
Correlation	−0.158	0.119	0.022	−0.512	0.259	−0.172
P	0.545	0.570	0.888	0.25	0.233	0.277

Pearson's correlation coefficient was used to assess the relationship. *n* – Number of participants; BDI – Beck's Depression Inventory

and HAM-D at the time of evaluation. (5) It was found that serum S100B levels were higher in those depressed subjects who were treated for more than 6 months than those who were not.

BBB can be considered to be a gateway to psychiatric illness such as depression, and S100B is a recognized marker of BBB damage.[27] It is also a neurotrophic factor that is involved in neuroplasticity. S100B has been studied as a biomarker in the various neuropsychiatric disorders such as depression, Alzheimer's disease, anxiety disorders, schizophrenia, and other affective disorders.[27-29] S100B is released by astrocytes. S100B mostly found in astroglial cells and Schwann cells, is also present in adipocytes, chondrocytes, melanocytes, bone marrow cells, and lymphocytes. Increased levels of serum, plasma, and CSF S100B have been studied in patients of major depression. It has been seen that an increase in the levels of S100B is not related to other markers such as glial fibrillary acidic protein, myelin basic protein, and neuron-specific enolase which are the other structural markers. It indicates that S100B is released from the astrocytes and not its leakage from the damaged cells.[30]

The serum levels of S100B in our patients 96.96 pg/ml (13.47–271.75 pg/ml) were significantly higher than that of the healthy controls 47.21 pg/ml (14.1–191.75 pg/ml) ($P = 0.023$). Since the levels are increased only in small quantity in comparison to controls, it implies this to be a part of physiological process and a part of normal neuroplastic process. Several studies concur with our result and have reported that depressive patients have increased levels of S100B in the serum[8,11-13,31,32] and CSF.[33] Rothermundt *et al*. 2001a, b[8,12] reported that the serum S100B levels in melancholic-depressive patients were higher than those in normal controls. They suggested that since S100B is a marker for neuroplasticity, high level of serum S100B might correspond to neuron growth and synaptogenesis during the process of synaptic remodeling in depressive patients. Effects of S100B depend on its concentration.[7] The increase in S100B level signifies a breach in the integrity of the BBB; however, it is not a result of damage. When secreted in small nanomolar concentrations, it signifies the activation of growth and differentiation of neurons and astrocytes.[5,34] However, higher amounts of S100B in micromolar concentrations cause apoptosis of cells and can be neurotoxic.[9,10] This micromolar increase of S100B in CSF and plasma is seen after traumatic brain injury, subarachnoid hemorrhage, and ischemic or toxic brain injury.[35-37] It has been seen that increased levels of S100B can be correlated to lesions or changes seen on CT scan and can help in early detection of patients at risk of developing secondary increase in intracranial pressure or fatal outcomes.[38] In this study, when similar gender depressed and healthy controls were compared, it was found that significantly higher levels of S100B were present in females as compared to their healthy control counterparts. There was no significant difference in the levels of serum S100B between the depressed males and females. On the other hand, a significant difference in the serum S100B levels of the male and female healthy controls was observed. Yang *et al*. 2008[32] found that S100B levels in female depressed patients were higher than those of male depressed participants. Arolt *et al*. 2003[11] did not find any gender differences in serum S100B levels. Hetzel *et al*. 2005[39] did not consider the effect of gender on levels of serum S100B in depression. Thus, no conclusive result can be made regarding the gender differences.However, the reasons for the gender differences if present may be because of differences in education, stress, role of family, or differences in cognitive ability.

Table 7: Effect of treatment with antidepressants for the duration of illness on the mean S100B levels in the depressed participants as compared to the healthy controls analysis of variance/Kruskal-Wallis test used for the comparison

	Median (range)			*P*			
	≤6 months m(*n*=13) (A)	>6 months (*n*=29) (B)	Healthy controls (*n*=42) (C)	Overall	A versus B	A versus C	B versus C
S100B (pg/ml)	30.34 (13.47-144.43)	102.12 (48.96-271.75)	47.21 (14.1-191.75)	<0.001	<0.001	0.513	0.001

Values are expressed as median (minimum–maximum). *n* – Number of participants

It was seen that serum S100B was higher in depressed participants with the recurrent disorder (106.57 pg/ml [13.47–271.75 pg/ml]) than those with first episode (48.96 pg/ml [16.81–144.43 pg/ml]). Yang *et al*. 2008[32] found that S100B levels in participants with the first episode were significantly lower than those with recurrent depression. Since S100B is a marker of neuroplasticity, in patients with recurrent depression, repeated damage, and regeneration of the neurons as a compensatory response could be the cause for increased S100B levels in the participants with recurrent depression. However, Arolt *et al*. 2003[11] did not find any significant difference between the patients with first episode versus those with recurrent depression. This indicates that increased number of depressive episodes might have an effect on the levels of S100B in serum.

No correlation of the levels of this marker was found with the clinical severity of the patients using the Pearson's correlation coefficient. All the patients had moderate-to-severe degree of depression on psychometric evaluation by BDI and HAM-D at the time of evaluation. Similar to our findings, Arolt *et al*. 2003[11] as well as Yang *et al*. 2008[32] also did not find any correlation between S100B levels and severity of depressive and anxiety symptoms, or the duration of illness and current episode. However, S100B measured in sera from patients diagnosed with major depression[8] showed a positive correlation of the severity of depression with S100B levels.

Another interesting feature in our study is that with increased duration of illness for which the patient was being treated the patients had higher levels of S100B. We did not have any treatment naïve patients. However, to study the effect of medication on serum S100B, we divided the patients into those having total duration of illness <6 months and more than 6 months. It was seen that serum levels of S100B were higher in those who were on treatment for more than 6 months when compared to the healthy controls ($P = 0.001$). As the duration of illness for which the patient was being treated increased, serum S100B level increased suggesting the role of antidepressants in neuroplasticity. This was indicated by significantly higher S100B levels in those depressed subjects who were on treatment for more than 6 months than those who were treated for less than 6 months ($P < 0.001$). The findings were similar to a study showed that after 4 weeks of treatment with antidepressants, the levels of S100B further increased as compared to the baseline levels and the responders had significantly higher levels than nonresponders.[11] Another study by Jang *et al*. 2008[40] showed that the patients with higher baseline serum S100B levels responded better to the therapy suggesting that the baseline serum S100B level is associated with enhancement of the growth and differentiation of neurons, which results in a favorable therapeutic response to antidepressants. Furthermore, the patients with high baseline serum S100B levels clinically improved within 6 weeks of treatment with antidepressants; however, the increases in their serum S100B levels during 6 weeks of antidepressant treatment were minimal. Furthermore, the patients who had low levels of serum S100B at baseline did not show clinical improvement within 6 weeks of treatment with antidepressants but had higher serum S100B levels after 6 weeks of antidepressant treatment.[40] Thus, S100B may be a prerequisite for neuroplastic changes that are required to improve depression. This indicates the importance of S100B in neurogenesis as a compensatory response to any disruption in neuroplasticity that is related to antidepressant response. Antidepressants exert their effects by increasing neurogenesis and modulating the signaling pathways involved in neuroplasticity. Therefore, the levels of neuroplasticity in depressive patients can affect their response to antidepressants.

The strength of our study was the homogenous group of participants included in the study. There are no studies in the literature that have looked into this BBB damage marker S100B particularly for the adolescent and young adult patients of 13–25 years age with major depression in Indian population attending tertiary care hospital.

Major limitation of our study was that we being the highest tertiary level hospital, all the patients were on treatment with antidepressants for variable duration of time. Thus, a baseline level of these markers before medication could not be obtained for comparison. Other limitation of our study was relatively small sample size. Furthermore, we were not able to completely rule out the dietary differences between the two groups. However, evaluating the use of nonprescribed drugs or alternative medicines and diet should be carried out in future studies. It will also be useful in future studies to measure S100B levels throughout the treatment of the patients to see the neurotropic response of the patients to stress and severity of depression. These studies will be helpful in establishing serum S100B as a marker of severity as well as of response to treatment in patients with severe depression.

CONCLUSION

Serum S100 B could be examined further as a candidate of potential biomarker in moderate to severe depression specially when the depression is recurrent and more than six month duration.

Acknowledgment

The authors are grateful to all participants who participated in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Nestler EJ, Barrot M, DiLeone RJ, Eisch AJ, Gold SJ, Monteggia LM, *et al.* Neurobiology of depression. Neuron 2002;34:13-25.
2. Albert PR, Benkelfat C. The neurobiology of depression – Revisiting the serotonin hypothesis. II. Genetic, epigenetic and clinical studies. Philos Trans R Soc Lond B Biol Sci 2013;368:20120535.
3. Duman RS, Li N. A neurotrophic hypothesis of depression: Role of synaptogenesis in the actions of NMDA receptor antagonists. Philos Trans R Soc Lond B Biol Sci 2012;367:2475-84.
4. Felger JC, Lotrich FE. Inflammatory cytokines in depression: Neurobiological mechanisms and therapeutic implications. Neuroscience 2013;246:199-229.
5. Rothermundt M, Peters M, Prehn JH, Arolt V. S100B in brain damage and neurodegeneration. Microsc Res Tech 2003;60:614-32.
6. Karege F, Perret G, Bondolfi G, Schwald M, Bertschy G, Aubry JM, *et al.* Decreased serum brain-derived neurotrophic factor levels in major depressed patients. Psychiatry Res 2002;109:143-8.
7. Schäfer BW, Heizmann CW. The S100 family of EF-hand calcium-binding proteins: Functions and pathology. Trends Biochem Sci 1996;21:134-40.
8. Rothermundt M, Arolt V, Wiesmann M, Missler U, Peters M, Rudolf S, *et al.* S-100B is increased in melancholic but not in non-melancholic major depression. J Affect Disord 2001;66:89-93.
9. Missler U, Wiesmann M, Friedrich C, Kaps M. S-100 protein and neuron-specific enolase concentrations in blood as indicators of infarction volume and prognosis in acute ischemic stroke. Stroke 1997;28:1956-60.
10. Rothoerl RD, Woertgen C, Brawanski A. S-100 serum levels and outcome after severe head injury. Acta Neurochir Suppl 2000;76:97-100.
11. Arolt V, Peters M, Erfurth A, Wiesmann M, Missler U, Rudolf S, *et al.* S100B and response to treatment in major depression: A pilot study. Eur Neuropsychopharmacol 2003;13:235-9.
12. Rothermundt M, Missler U, Arolt V, Peters M, Leadbeater J, Wiesmann M, *et al.* Increased S100B blood levels in unmedicated and treated schizophrenic patients are correlated with negative symptomatology. Mol Psychiatry 2001b; 6:445-9.
13. Schroeter ML, Abdul-Khaliq H, Diefenbacher A, Blasig IE. S100B is increased in mood disorders and may be reduced by antidepressive treatment. Neuroreport 2002;13:1675-8.
14. Schroeter ML, Abdul-Khaliq H, Krebs M, Diefenbacher A, Blasig IE. Serum markers support disease-specific glial pathology in major depression. J Affect Disord 2008;111:271-80.
15. Griffin WS, Stanley LC, Ling C, White L, MacLeod V, Perrot LJ, *et al.* Brain interleukin 1 and S-100 immunoreactivity are elevated in down syndrome and Alzheimer disease. Proc Natl Acad Sci U S A 1989;86:7611-5.
16. Aleksovska K, Leoncini E, Bonassi S, Cesario A, Boccia S, Frustaci A, *et al.* Systematic review and meta-analysis of circulating S100B blood levels in schizophrenia. PLoS One 2014;9:e106342.
17. Machado-Vieira R, Lara DR, Portela LV, Gonçalves CA, Soares JC, Kapczinski F, *et al.* Elevated serum S100B protein in drug-free bipolar patients during first manic episode: A pilot study. Eur Neuropsychopharmacol 2002;12:269-72.
18. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. (DSM-IV). 4th ed. Washington, DC: American Psychiatric Association; 1994.
19. First MB, Spitzer RL, Miriam G, Williams Janet BW. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Non-Patient Edition. (SCID-I/NP). New York: Biometrics Research, New York State Psychiatric Institute; November, 2002.
20. Wikström AK, Ekegren L, Karlsson M, Wikström J, Bergenheim M, Åkerud H, *et al.* Plasma levels of S100B during pregnancy in women developing pre-eclampsia. Pregnancy Hypertens 2012;2:398-402.
21. Bergman L, Akhter T, Wikström AK, Wikström J, Naessen T, Åkerud H, *et al.* Plasma levels of S100B in preeclampsia and association with possible central nervous system effects. Am J Hypertens 2014;27:1105-11.
22. Kumar N, Shekhar C, Kumar P, Kundu AS. Kuppuswamy's socioeconomic status scale-updating for 2007. Indian J Pediatr 2007;74:1131-2.
23. Goldberg DP, Williams P. A User's Guide to the General Health Questionnaire. Windsor UK: NFER Nelson; 1988.
24. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561-71.
25. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56-62.
26. Mehta M, Pande P. Stress in School Children. Proceedings of the 5th Biennial Conference IACAMH. Bangalore: NIMHANS; 2001. p. 158-63.
27. Kapural M, Krizanac-Bengez Lj, Barnett G, Perl J, Masaryk T, Apollo D, *et al.* Serum S-100beta as a possible marker of blood-brain barrier disruption. Brain Res 2002;940:102-4.
28. Marchi N, Cavaglia M, Fazio V, Bhudia S, Hallene K, Janigro D, *et al.* Peripheral markers of blood-brain barrier damage. Clin Chim Acta 2004;342:1-2.
29. Rothermundt M, Ponath G, Arolt V. S100B in schizophrenic psychosis. Int Rev Neurobiol 2004;59:445-70.
30. Steiner J, Bielau H, Bernstein HG, Bogerts B, Wunderlich MT. Increased cerebrospinal fluid and serum levels of S100B in first-onset schizophrenia are not related to a degenerative release of glial fibrillar acidic protein, myelin basic protein and neurone-specific enolase from glia or neurones. J Neurol Neurosurg Psychiatry 2006;77:1284-7.
31. Dietrich DE, Hauser U, Peters M, Zhang Y, Wiesmann M, Hasselmann M, *et al.* Target evaluation processing and serum levels of nerve tissue protein S100B in patients with remitted major depression. Neurosci Lett 2004;354:69-73.
32. Yang K, Xie GR, Hu YQ, Mao FQ, Su LY. The effects of gender and numbers of depressive episodes on serum S100B levels in patients with major depression. J Neural Transm (Vienna) 2008;115:1687-94.
33. Grabe HJ, Ahrens N, Rose HJ, Kessler C, Freyberger HJ. Neurotrophic factor S100 beta in major depression. Neuropsychobiology 2001;44:88-90.
34. Donato R. S100: A multigenic family of calcium-modulated proteins of the EF-hand type with intracellular and extracellular functional roles. Int J Biochem Cell Biol 2001;33:637-68.
35. Bloomfield SM, McKinney J, Smith L, Brisman J. Reliability of S100B in predicting severity of central nervous system injury. Neurocrit Care 2007;6:121-38.
36. Kleindienst A, Ross Bullock M. A critical analysis of the role of the neurotrophic protein S100B in acute brain injury. J Neurotrauma 2006;23:1185-200.
37. Weiss N, Sanchez-Peña P, Roche S, Beaudeux JL, Colonne C, Coriat P, *et al.* Prognosis value of plasma S100B protein levels after subarachnoid aneurysmal hemorrhage. Anesthesiology 2006;104:658-66.
38. Petzold A, Green AJ, Keir G, Fairley S, Kitchen N, Smith M, *et al.* Role of serum S100B as an early predictor of high intracranial pressure and mortality in brain injury: A pilot study. Crit Care Med 2002;30:2705-10.
39. Hetzel G, Moeller O, Evers S, Erfurth A, Ponath G, Arolt V, *et al.* The astroglial protein S100B and visually evoked event-related potentials before and after antidepressant treatment. Psychopharmacology (Berl) 2005;178:161-6.
40. Jang BS, Kim H, Lim SW, Jang KW, Kim DK. Serum S100B levels and major depressive disorder: Its characteristics and role in antidepressant response. Psychiatry Investig 2008;5:193-8.