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The role of S100B protein as a potential marker in affective disorder

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Summary

Introduction. Both recurrent depressive disorders and affective bipolar disorders are characterized by the changes in glial tissue. S100B protein is a calcium-binding molecule, mainly secreted by glial cells, which, depending on its concentration, has a trophic or toxic effect on neuronal cells. In the recent years, due to the postulated glial hypothesis of affective disorders and the ideas concerning brain neuroplasticity, there has been a growing interest in S100B protein and its role in affective disorders.

Aim and method. The aim of this study was to review the available subject literature from the recent years. This article presents a review of studies from the last years based on the literature available in PubMed/MEDLINE database.

Conclusions. In the previous studies conducted in patients with mood disorders it has been shown that the increased S100B protein serum level occurs both in patients with depression and with mania compared to the patients from control group. The studies were mainly conducted on adult population; there are no studies on children and adolescents with bipolar affective disorder so far. The majority of studies indicated the more important association between the increased S100B protein levels and the occurrence of a depressive episode as well as the regulation of S100B protein level during the effective pharmacological treatment, which can be a potential marker of the efficacy of treatment.

Key words: bipolar affective disorder, S100B protein, glial hypothesis

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Introduction

S100B protein of molecular weight 10 kDa is a calcium-binding molecule of acidic S100 protein family. S100B protein is localized in cytoplasm of ependymal cells of the choroid plexus – astro – and oligodendrocytes which actively secrete it [1]. This protein takes part in the regulation of metabolism of central nervous system cells, their proliferation and intracellular signal transmission [2]. S100B protein level in serum and cerebrospinal fluid is considered as an indicator of glial cells activation [3], so the determination of S100B blood serum concentration in neurology serves as one of the biochemical markers used in the assessment of the extent and course of ischemic stroke [4]. During recent years, a growing interest in this protein with regard to mental illnesses is associated with its properties in the central nervous system (CNS). In humans the gene encoding S100B protein is located on 21q22.3 chromosome [5]. This region is also considered to play an important role in bipolar affective disorder [6, 7]. What is interesting, the influence of S100B protein on brain tissue differs depending on its concentration in the CNS. In nanomolar concentrations it stimulates the growth and differentiation of neurons and astrocytes, reducing the stress-induced damages, whereas in micromolar concentrations it has a negative effect, stimulating neuronal apoptosis, production of proinflammatory factors and release of TNF-alpha (tumor necrosis factor alpha) by microglial cells [8, 9]. In the in vivo studies Schroeter et al. confirmed the hypothesis assuming the participation of pathological processes occurring in glial cells in the affective disorders [10]. In this study researchers assessed the concentration of the neuron specific enolase (NSE) and serum S100B protein levels in 10 patients with depression and 10 control subjects. They demonstrated statistically significantly higher concentrations of S100B serum level compared with control group, while the levels of NSE does not differ significantly between groups. The authors also conducted a quantitative meta-analysis of all published studies on S100B involving patients with mood disorders (n = 193). Among the group, 86 patients had a diagnosis of depressive episode, 63 persons manic episode, and 44 persons at the time of the survey were in euthymic mood. The meta-analysis also included 132 healthy controls. The results showed elevated levels of serum S100B in patients with affective disorder (either depression or mania), compared to the control group. They also observed that S100B serum concentration decreases during antidepressive treatment.

Glial disorders in bipolar affective disorder

According to the reports from recent years, affective disorders, including recurrent depressive disorders and bipolar affective disorders, are characterized by pathological changes in glial tissue [11]. Glial cells are necessary for the proper functioning of synapses. They also support the work of the neurons. They are divided into two classes: macroglia and microglia. Macroglia include astrocytes, oligodendrocytes

and Schwann cells. Microglia is a component of the immune system and plays a key role in the neuroinfections, its function is, inter alia, the removal of tissue breakdown products, necrotic foci. Numerous studies have shown that in the frontal cortex area in patients with depression or bipolar disorder the number of glial cells is reduced compared to persons without mood disorders [12–14]. These deficits in glial cells may be the result of altered gliogenesis related to the factors that weaken the proliferation of glial cells. Among the factors which may affect glial proliferation are e.g., stress-related hormones, neurotransmitters such as glutamate. Glial cells through the role they play in the metabolism of neurons and control of neurotransmitters release, in the situation of substantial disruption of their functions (e.g., reduction of their number, or changes in morphology), may become a factor which induces symptoms of depression. The presence of a genetic predisposition and presence of specific environmental factors (e.g., stress) can lead to pathology of the glial cells, and consequently to disturbances in the functioning of neurons as the disease progresses [15]. The glial hypothesis was confirmed in post mortem histopathological examinations, which showed a decreased density of glial cells in prefrontal brain regions of patients with mood disorders [16, 17]. These changes mainly involved astrocytes and oligodendrocytes. The studies on animal models revealed the primary character of the changes in glial tissue [18]. What is more, it was demonstrated that antidepressant drugs prevent a reduction of astroglial cells and the further studies have shown that the changes occurring in brain cells during affective disorders are dynamic [19]. In a study of Polyakova et al. researchers estimated potential brain plasticity factors, neuroglia and neurons functioning, by assessing the levels of: brain-derived neurotrophic factor (BDNF), S100B and neuron specific enolase (NSE). The study involved 27 people diagnosed with a minor depression and 82 people from the control group. S100B protein serum levels were statistically significantly increased in a male group with depressive symptoms compared to men from control group. There were no significant differences between the groups in BDNF and NSE serum levels. Researches did not find a correlation between serum S100B levels and age in patients with depression. Instead, S100B correlated positively with age in healthy controls [20]. The reduction of density and number of glial cells takes place in the early period of depressive disorders, while the changes in neurons appear along with the progress of the illness. Significant differences in the course of changes in brain cells were shown depending on the age of patients with depressive disorders [21]. The reduction of glial cells is mainly observed in the younger groups of patients, whereas neural changes are found in the older patients, with average age over 60 years, what can indicate the age-dependent differences in the pathogenesis of depressive disorders. An in vivo studies meta-analysis of S100B protein blood serum level in 174 patients with affective disorders and 102 people from control group revealed the important differences between the younger and older groups of patients suffering from affective disorders [22]. In the older patients S100B protein level was significantly higher compared to the group of younger patients and it was demonstrated that in both groups its levels

were significantly higher in comparison with control group. No effect of the disease duration or the age of the illness onset on S100B protein serum levels was found. It is worth noting that changes in S100B level associated with physiological ageing processes were taken into account when comparing the study group with the control group. In the discussion the authors of the study emphasized the need for conducting further research on S100B serum level in patients of all ages in order to determine the cause of the differences described above.

S100B as a marker of affective disorders

S100B protein, as a molecule actively secreted by oligodendrocytes and astrocytes, was considered as a useful biomarker of the changes in glial tissue, easy to assess in human blood serum. A meta-analysis by Schroeter et al. from 2013 showed increased level of S100B protein in blood serum and cerebrospinal fluid of both patients with depressive disorders and of patients with bipolar affective disorder, as compared to control groups. The differences were particularly pronounced in case of acute depressive and manic episodes [2]. A further evidence of the participation of S100B protein in the pathogenesis of affective disorders was provided by the meta-analysis by Schroeter et al. (2014) on *S100B* gene expression, which confirmed an increased expression of this gene in the hippocampi of patients with bipolar affective disorders [23]. In the study by Roche et al. it was postulated that some gene variants of S100B protein can predispose to the occurrence of a subtype of bipolar affective disorder with psychotic symptoms [24]. In another study, Yang et al. examined *S100B* gene polymorphism in patients suffering from MDD (n = 150) compared to the control group (n = 150) in the Chinese population. The results did not show association between *S100B* gene polymorphism and depression. However, the authors observed differences in S100B genotypes between the first and subsequent episodes of depression [25].

Of course, it should be stressed that the increased level of S100B protein is specific not only for affective disorders. In the meta-analysis of 19 studies, taking into account 420 patients with schizophrenia, 173 patients with affective disorders and 577 people from control group, it was demonstrated that S100B level is significantly elevated both in patients with schizophrenia and affective disorders [26]. However, S100B serum level did not allow for the recognition of this protein as a marker to differentiate between schizophrenia and affective disorders. On the other hand, it enabled the differentiation between depressive and bipolar affective disorders, because S100B level in people with depressive episodes was significantly higher compared to people with manic episode. The results of studies by Schroeter et al. confirmed the hypothesis of glial tissue pathology in depressive disorders, because in serum of patients the increased level of S100B protein was demonstrated concurrent with normal level of neuron specific enolase (NSE) [2, 10]. It seems that in case of depressive disorders an increase in S100B level is a result of secretion of this protein by glial

cells, not the effect of structural lesion of brain tissue. However, there is still an open question whether the increase in S100B serum level is also a result of the damage of blood-brain barrier, which is mainly composed of astrocytes [27, 28]. In a recent study, Schmidt et al. evaluated the serum levels of NSE and S100B in cerebrospinal fluid in patients with depression (n = 31) compared to the control group (n = 32) using electrochemiluminescence immunoassays method (ECLIA). The results showed differences between the groups in terms of increased NSE serum levels in patients with depression compared to the control group, while there were no such differences in the S100B serum levels [29].

Other factors, such as sex and the number of previous depressive episodes, also can influence the level of S100B protein in serum of patients with depressive disorders. In a study of Yang et al. patients with depression (n = 54) showed higher serum S100B levels than control group (n = 35); higher values were observed in women compared to men. A positive relationship between higher concentrations of S100B in the blood and the completed episodes of depression and family burden was also observed. The authors stressed, however, that in the absence of more research on the subject the relationship between higher levels of S100B and recurrent episodes of depression cannot be definitely confirmed [30]. In the study by Dietrich et al., S100B protein serum level in patients with depressive disorders in remission was assessed and the amplitudes of N2 and P3 components of Event-Related Potentials were analyzed [31]. A group of patients with elevated S100B serum level presented normal amplitude of event-related potentials, whereas a group with normal S100B level showed decreased amplitude of N2 and P3 potentials. That situation might indicate the impairment of the processes connected with focusing attention in the group of patients with normal level of S100B protein. The authors of the study pointed out the need to continue the research in order to determine the influence of increased S100B level on restoring normal cognitive processes in patients with depressive disorders. The studies by Zhang et al., carried out in patients with recurrent depression, revealed the relation between S100B blood level and memory processes. The authors postulated a neuroprotective effect of moderately elevated S100B serum level in affective disorders [32]. However, a major limitation of the above-mentioned study was a small number of patients. An analysis of the interaction between the overexpression of S100B protein and chronic psychosocial stress occurring during adolescence and its further influence on emotions, behavior and neurogenesis in adults also seem to be interesting. In the work by Buschert et al., from 2013, it is suggested that the elevated level of S100B protein can increase the susceptibility to environmental stimuli in young people during adolescence, what can be further associated with the occurrence of specific behavioral phenotypes and neuronal changes in adulthood. These can lead to a greater risk of the occurrence of mental disorders in the presence of negative environmental stimuli and also affect the positive outcome of treatment in favorable environment [33].

Pharmacotherapy and S100B serum level

The S100B protein is indicated as a potential predictor of antidepressant treatment response in patients with depression. Ambree et al. conducted a study to assess the relationship between the serum S100B levels and antidepressant response in patients with melancholic type of depression (n = 40). Patients were treated with venlafaxine or imipramine, control visits were carried out in baseline and after 7 weeks and 6 months of treatment. Patients who have been found to have higher serum S100B levels showed significantly better antidepressant response both in 7 weeks and 6 month of treatment. Low concentrations of S100B were associated with lack of response to treatment with venlafaxine and imipramine [34]. Such correlation may indicate the usefulness of the assessment of S100B protein level as a potential marker of the efficacy of treatment. However, the authors drew attention to the limitations of the study associated with the lack of identical protocols concerning antidepressant treatment and the possible influence of rescue medications. In the other study, the authors compared S100B protein level in 59 patients with depressive disorders before and after the implementation of 6-week pharmacotherapy with antidepressant drugs and demonstrated that the baseline S100B serum level has the influence on the effects of treatment [35]. Patients who better responded to treatment had initially higher S100B serum level than patients who were less responsive to the medications. This may suggest a positive impact of the elevated serum level of S100B protein on the plasticity processes in the CNS, what may result in more effective pharmacotherapy. The authors of the cited studies emphasized the need for conducting further research on larger groups of patients, with simultaneous standardization of pharmacotherapy protocol, which would allow the assessment of the influence of specific drugs on S100B protein serum level and allow determining its participation in depressive disorders at the molecular level [35, 36].

Recapitulation

The previous studies have shown the presence of elevated S100B protein serum level in patients with mood disorders (both depression and mania), as compared to control group. The works that have been carried out so far emphasized a stronger relationship between the occurrence of episodes of depression than mania and antidepressant treatment appears to have a regulatory effect on the level of S100B protein. There is no evidence that such a relationship exists in case of treatment of manic episodes. Depending on the concentration, S100B protein can stimulate the growth and differentiation of neurons and astrocytes reducing the stress-induced damages or, on the contrary, can stimulate neuronal apoptosis. Due to the fact that mood disorders are associated with glial pathology, conducting the research taking into account the role of S100B protein as a potential marker of mood disorders appears to be justified. In the future works it should be determined whether it reflects

compensatory mechanisms, or rather expresses a different degree of influence of glial pathology on the formation of affective disorders among the group of younger and older patients.

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