Usefulness of S100B Protein in Neurological Disorders
Turker Yardan,1 Ali Kemal Erenler,2 Ahmet Baydin,3 Keramettin Aydin,4 Cengiz Cokluk5
Department of Emergency Medicine,1-3 Department of Neurosurgery,4,5 Ondokuz Mayis University School of Medicine, Samsun, Turkey.

Abstract
In recent years, there has been an increased interest in the clinical use of brain markers. The S100B is a calcium-binding peptide and is used as a parameter of glial activation and/or death in many disorders of the central nervous system (CNS). It plays important roles in normal CNS development and recovery after injury. Although S100B is mainly found in astroglial and Schwann cells, it also has extracerebral sources. S100B is a useful neurobiochemical marker of brain damage such as in circulatory arrest, stroke and traumatic brain injury. S100B is also associated with neurodegenerative diseases like Alzheimer's disease or other chronic neurological diseases. Moreover, S100B may have a potential in predicting the efficiency of treatment and prognosis. In this review, an updated overview of the role of S100B in human neurological disorders is presented.

Keywords: Neurological disorders, S100B protein, brain marker.

Introduction
Disorders of the central nervous system (CNS) can be assessed with the help of biochemical markers. Especially in recent years, there has been an increased interest in the clinical use of brain markers such as S100 proteins. S100B is a calcium-binding peptide produced mainly by astrocytes that exerts paracrine and autocrine effects on neurons and glia.1 An increased level of S100B is associated with pathological injury or clinical severity in a variety of disorders affecting the CNS. In this review, we aimed to present an updated overview of the literature on S100B with respect to human neurological disorders.

S100 Protein Family:
Calcium is an intracellular second messenger that has several regulatory roles in many functional events and processes like conduction and transmission of the nerve impulse, muscle contraction, cell motility, growth and differentiation, gene expression, apoptosis, and necrosis.2 As a result of cellular evolution, calcium-binding proteins are formed to regulate the level of cytosolic calcium and transduce calcium signals.3

The S100 protein family is the largest subgroup of the calcium-binding EF-hand (helix E-loop-helix F) protein group.4 These were first described by Moore in 1965, and the name "S100" was given because of their solubility in a 100% saturated solution with ammonium sulphate. An unfractionated mixture of S100A1 and S100B was the first identified member of this family.5 At present, at least 25 proteins have been identified as belonging to the S100 protein family.6 S100 proteins belong to the S100/calmodulin/parvalbumin/troponin C superfamily, with low molecular weight of about 9-13 kDa.5 Although they are usually thought to be calcium sensor proteins that modulate biological activities via calcium,7 it is understood that some S100 proteins bind to Zinc (Zn+2) and calcium. This binding is thought to suggest the possibility that their biological activity might be regulated by Zn+2 and calcium. Their important property is that they can only be found in vertebrates and, unlike other EF hand proteins such as calmodulin and troponin C, S100 proteins form both homo- and heterodimer protein complexes.8

S100 protein contains a mixture of hetero- and
homodimers of two types of subunit (α, β) with different amino acid compositions. S100A is described as a heterodimer of αβ, while S100B is a homodimer of ββ. While S100α is found abundantly in neurons in muscles, kidney and other organs, S100β is localized in neural glial and Schwann cells. The protein previously known as S100α is now known as protein S100A1, and the former protein S100β is now named protein S100B.

**Structure and Functions of S100B Protein:**

S100B has a homodimeric structure and each beta monomer has a weight of approximately 10.5 kDa. Like other S100 proteins, binding of calcium to S100B induces a large conformational change that allows hydrophobic residues to expose and interact with other proteins in order to confer biological activity. S100B is located in the cytoplasm and nucleus of the astrocytes along with other members of the S100 family, and it regulates the cytoskeletal structure and cell proliferation. Although it has been shown that S100B is mainly found in astroglial and Schwann cells, it has also been found in adipocytes, chondrocytes, lymphocytes, bone marrow cells, and melanocytes. S100B is mainly eliminated by the kidney.

The effects of S100B depend on its concentrations. At nanomolar concentrations, S100B in vitro stimulates neurite outgrowth in cerebral cortex neurons and enhances survival of neurons in various systems during development. S100B in vitro has a neurotrophic activity for neuronal cells during the neuronal maturation and glial cell proliferation. S100B decreases cell death and the loss of mitochondrial function resulting from glucose deprivation. With its neurotrophic and gliotrophic actions, S100B probably plays important roles in normal CNS development and recovery after injury. In contrast to the stated effects of nanomolar levels of S100B, micromolar levels of extracellular S100B may have deleterious effects. At these concentrations, extracellular S100B in vitro stimulates the expression of proinflammatory cytokines and induces apoptosis. S100B exerts its neurotoxic effects in vitro by inducing apoptosis in neurons. Recent observations show that micromolar concentrations of S100B produce apoptotic death by interacting with the Receptor for Advanced Glycation End Products (RAGE), causing elevation in reactive oxygen species, cytochrome C release and activation of the caspase cascade. S100B might contribute to neuropathological changes in the course of neurodegeneration and/or brain inflammatory diseases by the activation of microglia as well. When a metabolic injury occurs, such as the deprivation of oxygen, serum and glucose, the early process during the glial response is the secretion of S100B. The high concentrations of S100B cause neuronal death through nitric oxide release from astrocytes. S100B has been shown to help to identify the subgroup of patients suffering from traumatic brain injury (TBI). The studies were able to demonstrate the relation between S100B in the acute stage of head trauma. In severe head trauma, S100B clearly provides a reliable marker for the evaluation of severity.

**Measurement of S100B Protein:**

S100B can be measured by several methods, such as immunoradiometric assay (IRM), immunoluminometric assay (LIA), mass spectroscopy, western blot, enzyme linked immunosorbent assay (ELISA), electrochemiluminescence, and quantitative polymerase chain reaction (PCR). All these available methods differ with regard to specificity, sensitivity, sample application, and, of course, economic costs. Contrasting results are sometimes enthusiastically discussed while ignoring or underestimating methodological differences.

**S100B as a Marker in Neurologic Disorders:**

As such a biomarker, S100B is primarily produced by astrocytes in the CNS and represents astrocytic activation. An immunohistochemical study indicated that astrocytes are the predominant S100B-positive cells in gray matter, and oligodendrocytes are the predominant S100B-positive cells in white matter. Intra- or extracellular S100B mRNA and protein levels have been used as a parameter of astrocyte activation and/or death in several situations of brain injury. Elevation in serum or CSF S100B concentrations is associated with a variety of disorders affecting the CNS. Although in many instances its release may be an effect of the condition rather than the cause, it is nonetheless strongly implicated that S100B can be considered a strong candidate as a marker of CNS injury.

In recent years, many researchers have performed S100B measurements in patients suffering from traumatic brain injury (TBI). The studies were able to demonstrate the relation between S100B in the acute stage of head trauma. In severe head trauma, S100B clearly provides a reliable marker for the evaluation of severity. It is also known that S100 parameters are related to intracranial pressure and cranial computed tomography (CT) findings. With a cut-off limit of 0.10-microg/L, it is reported that the measurement of serum S100B has been shown to help to identify the subgroup of
patients with head trauma-relevant lesions on CT scan, with a sensitivity of 99% and a specificity of 30%. Adding the measurement of S-100B concentration to the clinical decision rules for a cranial CT scan in patients with minor head injury could allow a 30% reduction in scans.21 Korfias et al22 concluded that serum S-100B protein reflects injury severity and improves prediction of outcome after severe TBI. S-100B may also have a role in assessing the efficacy of treatment after severe TBI. However, in a recently published study, it was reported that although serum S100B levels 24 hours after injury are significantly correlated with outcome after severe TBI, S100B does not have the prognostic performance needed to guide therapy.23 It was suggested that S100B is a sensitive biomarker for early prediction of the development of increased intracranial pressure and mortality after acute brain injury. It was concluded that monitoring of S100B levels could contribute to early detection of patients at risk of secondary increase in intracranial pressure and subsequent fatal outcome, and that this would allow earlier targeting of required treatment strategies in selected patients.15 Besides other functions, S100B may have a potential therapeutic role in TBI. Kleindienst et al24 investigated whether an intraventricular infusion of S100B enhances neurogenesis within the hippocampus after experimental TBI in rats. They found significantly enhanced neural cell proliferation in the dentate gyri after the treatment. Evaluation of the potential therapeutic role of S100B in TBI as well as in other CNS disorders is needed.

Since S100B has been shown to be increased in the blood and CSF after TBI in humans, many studies have focused on S100B under various cerebral ischaemic conditions.1 Single S100B values, obtained 48 and 72 hours after stroke onset, predict the functional outcome and infarct volume in nonlacunar middle cerebral artery infarction.25 Typically, S100B reaches its peak levels during the first 3-4 days in acute ischaemic stroke.26 In 2007, Ishibashi et al[26] found greater serum S100B levels in patients with right hemisphere stroke than in those with left hemisphere infarct. They also concluded that elevation in S100B was related more to the corresponding hemispheric impairment. Moreover, the effectiveness of a recanalizing intervention can be closely monitored by serum S100B level. After early canalization by intravenous administration of tissue plasminogen activator (t-PA), significant reduction in serum S100B levels was determined in patients with stroke.27 Similar to its use in stroke, many researchers are interested in determining S100B as a marker of hypoxic brain dysfunction or damage in different clinical problems. It was found that levels of S100B were correlated with the bypass time in cardiac surgery.28 Rosen et al29 reported that increased S100B was related to coma depth, time of anoxia and abnormal brain stem reflexes and poor outcome after cardiac arrest.

Migraine is a common disorder characterized by severe headache attacks and related symptoms. Although the pathophysiology of migraine is not completely understood yet, migraine is thought to be a neurovascular disorder.30 In 2005, Papandreou et al31 showed that serum concentrations of S100B were higher in children suffering from migraine than in those with tension-type headache or healthy control persons. They suggested that S100B may contribute to migraine pathology by participation in a glial activation cycle leading to neuroinflammation and dysfunction. They also concluded that serum S100B determination may be a useful biochemical marker for migraine in acute recurrent headache in childhood. Recently, it was shown that the serum concentrations of S100B are elevated during a migraine attack and are further increased after a pain-free period of 2-4 days.30 Based upon current data, further studies are necessary to evaluate the role of S100B as well as its relevance as a possible diagnostic parameter in migraine.

Determination of S100B level may be useful in the management of patients with subarachnoid haemorrhage (SAH). S100B serum concentrations correlate well with initial SAH severity evaluated either clinically (World Federation of Neurological Surgeons grading scale)12 or by CT (Fisher score)13 in patients with SAH.34 Moreover, S100B levels in blood and CSF are good predictors of outcome in SAH patients.35,36 Initial and mean daily values above 0.4 µg/L significantly predict a poor outcome.34 S100B is also diagnostic for secondary complications of SAH such as intracranial hypertension and cerebral infarction but not for vasospasm.36 Serum and CSF concentrations of S100B could discriminate patients with good and bad outcome, but CSF measurements do not provide a higher accuracy than serum samples. Thus, when favouring S100B analysis, sampling serum values is sufficient for outcome prognosis and the detection of secondary complications.36

Alzheimer’s disease (AD) is a common neurodegenerative disease characterized by a progressive dementia. The typical neuropathological features in AD are amyloid plaques and intraneuronal neurofibrillary tangles. In patients with AD and frontotemporal lobe dementia, S100B protein levels are significantly increased.37,38 There is an apparent interaction between ß-amyloid and expression of S100B. It was shown that ß-amyloid stimulates the synthesis of both S100B mRNA and S100B protein in astrocyte cultures.39 In addition, there is accumulating epidemiological and cellular evidence of the importance of inflammation in AD. Extracellular S100B might participate in brain inflammation by activating astrocytes, microglia and neurons.13 The inflammation might be another factor affecting expression of S100B in AD. S100B has pathological relevance for the degeneration of the CNS in AD.40 Even though current data clearly need to be reproduced and
In Parkinson's disease (PD), which is a common neurodegenerative disease characterized by progressive loss of dopaminergic neurons, glial cells may participate in the pathophysiology of the disease. Since the temporal pattern of neuronal death in PD patients is unknown, it is difficult to evaluate the quantitative loss of neurons during the progression of the disease. An immunological study in mice reported that the expression of S100 proteins increased in astrocytes after neurotoxin exposure known to cause Parkinsonism in humans. A statistically significant increase in the immune responses to S100B was found, which suggests that it may reflect neurodegenerative brain damage occurring in PD. Schaf et al. reported there was no significant difference in the level of S100B between PD patients and controls, but found a correlation with the Hoehn and Yahr stage, leading to the suggestion that S100B may have a potential role as a marker of the degree of severity of this disease. They also stated that PD patients had lower levels of S100B in the beginning of the disease and individuals with reduced levels of S100B could be more susceptible to PD. These findings suggest that S100B may have a potential role in either the underlying mechanism of PD development or in the assessment of this disease.

In multiple sclerosis (MS), nervous tissue is damaged as a result of two distinct mechanisms. The subacute event is the focal inflammatory demyelination that leads to circumscribed tissue destruction in the CNS and presents clinically as an acute event. On the other hand, axonal degeneration is thought to be the most important mechanism underlying chronic progression in MS. Therefore, early changes in neuronal markers in body fluids might be expected in MS. Misler et al. reported increased S100B plasma level during acute exacerbation of the disease. Recently, it was reported that serum and CSF S100B were not related to MS. It was also suggested that S100B and other axonal markers were not suitable as biomarkers of MS activity in the early stage of this disease.

Amyotrophic lateral sclerosis (ALS) is one of the neurodegenerative diseases characterized by progressive motor neuron loss and astrogliosis. As an exception in patients with ALS, the serum concentrations of S100B are decreased. Süssmuth et al. reported that CSF S100B exerted a disease-related decrease in ALS patients. Similarly, Otto et al. reported that S-100B levels in the serum of ALS patients show a progressive reduction over the disease course. They concluded that a single measurement of S100 beta is not useful for the diagnosis of ALS, but that repetitive measurements can help to assess the progression of the disease. The suggested decrease in S100B concentrations over time may reflect the ongoing consumption and/or downregulation of S100B in the course of the disease.

Recent psychiatric researches have collected more knowledge implicating that neurodegeneration might be a pathogenetic factor in the development of major psychiatric disorders. In this context, some researchers have been interested in the role of S100B in psychiatric disorders. Schmitt et al. reported increased serum S100B levels in elderly, chronic schizophrenic patients as a possible marker of a long-term chronic course of the disease. Recently, it was suggested that serum S100B levels in chronic schizophrenia patients under antipsychotic medication may be increased, and a dysfunction of astrocytes and/or oligodendrocytes may play a role in the pathogenesis of schizophrenia. Several studies have reported that depressive patients have increased serum S100B levels. S100B may represent a biomarker for mood disorders, particularly major depression, and their treatment.

In the literature, there are studies supporting that S100B might be a useful marker in foetal distress and hypoxic ischaemic encephalopathy (HIE) and in predicting death due to perinatal asphyxia. Serum S100B level was significantly increased in newborns with HIE associated with acute brain damage. The S100B level should be measured immediately after birth within 24 hours as a biochemical screening marker of foetal distress and also as a marker of HIE in newborns with birth asphyxia. Recently, Gazzolo et al. showed a significant correlation between S100B concentrations and the occurrence of neonatal death. They reported at a cut-off >1.0 microg/L S100B had a sensitivity/specificity of 100% for predicting neonatal death.

Different forms of cancer exhibit dramatic changes in the expression of S100 proteins. With regard to neoplastic conditions, elevated S100B levels have been detected in brain...
tumours such as astrocytomas, where S100B seems to inhibit the function of the tumour suppressor gene p53 in a calcium-dependent manner, thereby contributing to cancer progression. It was suggested that serum S100B detection has a clinically valuable independent prognostic value in patients with melanoma. In addition, S100B serum levels are used for the early detection of recurrence or metastases.

It is known that CNS is a commonly affected area in the poisonings. In recent years, several toxicologists have investigated the role of S100B in clinical practice. Braver et al. reported that carbon monoxide (CO) poisoning is associated with elevated S100B levels. Similarly, we found that increased S100B levels were associated with loss of consciousness in acute CO poisoning. Recently, Cakir et al. found a negative correlation between S100B and Glasgow Coma Scale and a positive correlation between S100B and carboxyhaemoglobin levels, on admission, in patients with CO poisoning. These findings indicate that S100B has the potential to be useful in the assessment of hypoxic brain damage and in the management of CO poisoning. Increased S100B levels are also associated with depressed levels of consciousness and respiratory insufficiency in patients with benzodiazepine overdose. S100B might be used as a biochemical marker of benzodiazepine overdose.

**Conclusion**

S100B is released in to the circulation as a response to various neurological disorders. Current data suggest that S100B is a strong candidate to become a diagnostic and prognostic parameter for various neurological disorders. In addition, the potential therapeutic role of S100B in CNS disorders needs to be clarified. Further research should focus on gaining evidence for the use of S100B in well-known clinical problems as well as in as yet unknown areas of neuroscience.

**References**

universal subarachnoid hemorrhage scale: report of a committee of the World
Federation of Neurosurgical Societies. J Neurol Neurosurg Psychiatry 1988; 51:
1457.
33. Fisher CM, Kistler JP, Davis JM. Relation of cerebral vasospasm to
subarachnoid hemorrhage visualized by computerized tomographic scanning.
Prognosis value of plasma S100B protein levels after subarachnoid aneurysmal
S100B as an additional prognostic marker in subarachnoid aneurysmal
and S100B from serum and cerebrospinal fluid in patients with spontaneous
37. Green AJ, Harvey RJ, Thompson EJ, Rossor MN. Increased S100beta in the
cerebrospinal fluid of patients with frontotemporal dementia. Neurosci Lett
1997; 235: 5-8.
38. Fox NC, Freeborough PA. Brain atrophy progression measured from registered
Imaging 1997; 7: 1069-75.
39. Peña LA, Brecher CW, Marshak DR. Beta-Amyloid regulates gene expression
Cerebrospinal fluid S100B correlates with brain atrophy in Alzheimer's disease. J
41. Green AJ, Harvey RJ, Thompson EJ, Rossor MN. Increased S100beta in the
cerebrospinal fluid of patients with frontotemporal dementia. Neurosci Lett
1997; 235: 5-8.
42. Nooijen PT, Schoonderwaldt HC, Wevers RA, Hommes OR, Lamers KJ.
Cerebrospinal fluid S100B correlates with brain atrophy in Alzheimer's disease.
Biological markers for axonal degradation in CSF and blood of patients with
44. Süssmuth SD, Tumani H, Ecker D, Ludolph AC. Amyotrophic lateral sclerosis:
disease stage related changes of tau protein and S100 beta in cerebrospinal fluid
45. Otto M, Bahn E, Welting J, Bozkoff I, Bueche W. Decrease of S100 beta
carrier in serum of patients with amyotrophic lateral sclerosis. Neurosci Lett
1998; 240: 171-3.
serum S100B in elderly, chronic schizophrenic patients: negative correlation
serum S100B levels in chronic schizophrenic patients on long-term clozapine or
48. Schroeter ML, Abdul-Khalig H, Krebs M, Diefenbacher A, Blasig IE. Serum
markers support disease-specific gial pathology in major depression. J Affect
Diagnostic accuracy of S100B urinary testing at birth in full-term asphyxiated
50. Ambrozic J, Bunc M, Osredkar J, Brvar M. S100B protein in benzodiazepine

Vol. 61, No. 3, March 2011