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Original Article

The Accuracy of the S100B Protein Biomarker in the Prognosis of Patients with Acute Spinal Cord Injury

Kaveh Haddadi[1] Saeed Abediankenari[2] Saeed Ehteshami[3] Abbas Alipour[4] Hassan Shayan Majd[5] Hamed Jafarpour[5] Leila Asadian[6]

[1] Department of Neurosurgery, Orthopedic Research Center, Mazandaran University of Medical Science, Sari, Iran
[2] Immunogenetics Research Center, Mazandaran University of Medical Sciences, Sari, Iran
[3] Department of neurosurgery, Orthopedic Research Center, Mazandaran University of Medical Science, Sari, Iran
[4] Thalassemia Research Center, Mazandaran University of Medical Science, Sari, Iran
[5] Department of Neurosurgery, Student Research Committee, Faculty of Medicine, Mazandaran University of Medical Science, Sari, Iran
[6] Department of Emergency Medicine, Student Research Committee, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran

Address for correspondence Saeed Ehteshami, MD, Orthopedic Research Center, Mazandaran University of Medical Science, Sari +98 11 3354 3238, Iran (e-mail: paper87@yahoo.com).

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Abstract

Introduction The role of some biomarkers such as S100 beta (S100B) has been somewhat known in determining the severity of primary acute spinal cord injury (SCI), and today, it has been the basis of various relevant studies. Therefore, this study estimates the S100B level in serum and cerebrospinal fluid (CSF) in patients with spinal injuries.

Methods This was a descriptive-analytic study. In this study, 31 patients with acute SCI referred to Sari Imam Khomeini Hospital, Iran, were recruited. Patients were divided into two groups of complete and incomplete SCI according to the American Spinal Injury Association (ASIA). The S100B concentrations in serum and CSF levels were compared between the two groups.

Result There was only significant positive correlation between S100B CSF concentration and complete SCI based on the ASIA criterion, meaning that in cases of complete SCI the S100B CSF concentration was significantly increased correlation coefficient (CC) ($cc = 0.529$ and $p = 0.002$). Based on the results of serum S100B protein concentration, 14.70 ng/dL with a sensitivity of 66.7% and specificity of 55% was determined as cutoff for complete SCI. Also, about the CSF S100B protein level variable, concentration of 342.18 ng/dL with 100% sensitivity and 64% specificity was determined as cutoff for complete injury.

Conclusion The results of this unique study have shown that S100B were useful markers for predicting the prognosis of patients with acute SCI and cutoff points determined for serum and especially CSF concentrations can differentiate complete and incomplete SCI.

Keywords
- cerebrospinal fluid
- S100 beta protein
- spinal cord injury

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Introduction

In many of the acute conditions that occur for some patients, such as traumas (accidents, conflicts, and falling downs, etc.) and some diseases of the central nervous system (CNS), we see acute injury to the spinal cord.[1] Acute spinal cord injury (SCI) will cause problems for the patient and alter the lifestyle of the patients and will create many constraints for the family and the health system of the country, including problems with high costs.[2] There have been various reports of acute SCI, but what the World Health Organization has reported is 40 to 80 cases per million populations.[3] Studies in the United States have shown that approximately 14,000 people suffer from acute SCI each year.[4] There have been few studies in Iran and no exact statistics are available, but in one of them in the city of Kashan over 4 years of those with vertebral injuries, 17.3% had SCI.[5] The manifestations and severity of SCI vary greatly by type, severity, and location of injury, as well as individual factors.[6] Diagnosis of acute injury in the early stages and timely treatment can reduce the severity of the injury and partly improve the patient's outcome. For this purpose, specialized physicians use clinical examinations and imaging, the most important of which is magnetic resonance imaging. However, different biomarkers have been investigated to determine the prognosis of these patients, one being the S100 beta (S100B) protein.[7] The S100B protein is produced by astrocytes in the developing and mature nervous system.[1,6] At first, it was described as a neuron-specific protein, but ensuing characterization indicated that S100B is concentrated mainly in the glial cells of the CNS.[8,9] It can be identified either from arterial or venous blood and is stable for several hours after sampling.[10,11] The role of some biomarkers such as S100B, has been somewhat known in determining the severity of primary SCI, and today, it has been the basis of various relevant studies.[8] S100B is a calcium-bound dimmer protein that is in the astrocyte and Schwann in the central and peripheral nervous system and is involved in the extracellular and intracellular regulation of cellular calcium metabolism. These proteins are named because dissolve in 100% ammonium sulfate saturated solution.[11] These proteins prevent the death of neuronal cells and have neuroprotective effects by buffering calcium ions in the nervous system.[10,11] It also has a role in creating the plasticity of the spinal cord after injury and stimulates neuronal growth after SCI.[4] In addition, elevation in S100B levels has been reported in cerebrospinal fluid (CSF) and serum in various neurological abnormality, for example, hemorrhage and cerebral infarction.[12]

Several studies have been performed to investigate the association between serum S100B protein level and the recovery and prognosis of patients with SCI, but the precise role of this biomarker in predicting outcome in these patients remains unclear.[13,14] The results of some systematic review and meta-analysis show that measuring the level of S100B protein in serum and CSF has diagnostic value in diagnosis of SCI in animal models. This biomarker increases during the initial 6 hours following injury and remains high until 24 hours after it. However, more than 24 hours after the injury, serum level of this protein returns to the level of animals without SCI.[15] Serum protein levels have also been studied in all studies, but we have simultaneously studied serum levels and CSF levels in human patients with pure SCI, which has been one of the advantages and benefits of this study. In this study, we also measured and quantified cutoffs for serum and CSF levels of S100B protein, which is another positive point of this study. It should also be noted that there has been no study in Iran on this issue and other studies conducted in other countries have been very limited. Therefore, this unique study estimates the S100B level in serum and CSF in patients with spinal injuries and aimed at estimating the accuracy of this biomarker in determining the prognosis of SCI in patients.

Material and Methods

This was a descriptive-analytic study. In this study, 31 patients with acute SCI referred to Imam Khomeini Hospital, Sari, Iran, in 2014 to 2015 were recruited. All methods were performed in accordance with the Mazandaran University of Medical Sciences guidelines and regulations. This project was implemented after approval by the Ethics Committee of Biomedical Researches of Mazandaran University of Medical Sciences and the registered ethic number is: IR.MAZUMS.REC.94.1511. Informed consent was obtained from each patient.

Patients Selection

The inclusion criteria of patients in the study were age of over 18 and admission within 24 hours. The site of injury included cervical, thoracic, and lumbar, and blunt injury of the spinal cord. The exclusion criteria were brain, orthopaedic, and abdominal lesions, infiltrative cerebrospinal injuries, pregnancy, patients with unstable vital signs requiring long admission in the intensive care unit, injury to the cauda equina, concurrent infections at the injured spinal cord or other areas, spinal cord shock, patients with cerebrospinal tumors, and dissatisfaction of patient or patient's companion.

Evaluation of Patients to Assess the Status of Spinal Cord Injury

The severity of SCI (both sensory and motor) was measured and recorded by the neurosurgeon within the first 24 hours of injury by referring to the classification of American Spinal Injury Association (ASIA), International Standards for Neurological Classification of Spinal Cord Injury. In this classification, the type of injury is categorized from A to E.[14] In this study, grade A patients are defined as complete injury and other grades (B, C, and D) except grade E were considered as incomplete SCI.

Laboratory Procedures

To measure S100B concentrations, blood samples were collected between 24 and 48 hours after injury as well as CSF samples through lumbar spinal puncture or during laminectomy during surgery. The samples were coagulated for

10 minutes at 25°C, centrifuged for 20 minutes (3,000 revolutions per minute), and stored at –80°C until the analysis of samples. The serum S100B protein concentration was measured by the electrochemiluminescence immunoassay kit and of the CSF specimen by the US SPEC FAX machine.

Statistical Analysis

Normality distribution of data was evaluated using the Kolmogorov–Smirnov test. All quantitative data including age, serum, and CSF level of the protein S100B have non-normal distribution. Therefore, nonparametric tests were used during the study to analyze them. Also, in this study, the relationship between quantitative variables based on chi-square test was investigated. The mean of S100B concentrations in serum and CSF levels were compared between the two groups by Man–Whitney test. Correlations between variables of type of injury were evaluated by the ASIA criterion, and S100B CSF concentration and serum S100B concentration were done based on Spearman's test. The cutoff point was determined for the concentration of serum protein and CSF protein based on the receiver operating characteristic (ROC) curve test. All analyses were performed with SPSS version 24.

Results

Thirty-one patients with SCI enrolled in the study. According to the ASIA, 9 patients (29%) had complete and 22 patients (71%) had incomplete SCI. The mean ± standard deviation age in the complete group was 35.55 ± 16.56 years and in the incomplete group was 39.86 ± 12.69 years, and there was no significant difference between the two groups ($p = 0.439$). In the incomplete group, 17 cases (77.3%) were male and the incomplete group 5 cases (22.7%) were male which was not statistically significant ($p = 0.457$).

As shown in ►**Table 1**, the mean of S100B concentration in serum and CSF in the complete group was higher than in the incomplete group. This difference was significant only in the serum ($p = 0.002$).

Correlation analysis between variables showed that there was an only significant positive correlation between CSF and the complete group based on the ASIA criterion, meaning that in cases of complete SCI the S100B CSF concentration was significantly increased (cc = 0.529, $p = 0.002$). On the other hand, this evaluation showed that there was no significant correlation between the concentration of CSF and serum of S100B (cc = 0.070, $p = 0.709$).

The cutoff point for complete injury was measured for the serum level of S100B protein. Based on the results of S100B protein concentration, 14.70 ng/dL with sensitivity of 66.7% and specificity of 55% was determined as the cutoff for complete SCI. According to the ROC diagram, the area below the diagram is 0.586. Also, about the CSF level variable, concentration of 342.18 ng/dL with 100% sensitivity and 64% specificity was determined as the cutoff for complete SCI. According to the ROC diagram, the area below the diagram is 0.823 (►**Fig. 1**).

Discussion

This study aimed to investigate the role of S100B protein in the diagnosis and prognosis of patients with acute SCI. As mentioned in previous sections, numerous biomarkers have been evaluated for this purpose, and so far none have been proven to be accurate in predicting injury. One of these biomarkers was the S100B protein, whose role has not been elucidated, but in this study, we sought to determine the role of this biomarker. Our results showed the mean of S100B concentration in serum and CSF in the complete injury group was higher than in the incomplete injury group, also serum S100B protein concentration of 14.70 ng/dL with a sensitivity of 66.7% and specificity of 55% was determined as the cutoff for complete SCI. Also, about the CSF S100B protein level variable, concentration of 342.18 ng/dL with 100% sensitivity and 64% specificity was determined as the cutoff for complete injury.

As can be seen, the specificity and sensitivity of the serum level and CSF protein level can be compared. On the other hand, it was found that evaluation of CSF level in patients with SCI has high value for determining the prognosis of patients and this is the same limitation and flaw in the study that has existed in other studies and is well illustrated in our study. We will review other studies in this regard; in a systematic review in 2019 the role of this biomarker has been evaluated based on other studies. The results of this study also showed that CSF protein level has high value and will remain elevated up to 12 hours after injury, but their serum levels will decrease gradually, which confirms the results of our study.[15] It should be noted, however, that only 7 studies were evaluated in this study, and the type of systematic review study has less value than ours. Lee et al measured the serum S100B level in 32 patients aged over 18 years and in the healthy subjects then determined the cutoff point at

Table 1 Comparison of the mean S100B concentration levels in serum and CSF between two groups

Group		Number	Mean ± SD (ng/dL)	*p*-Value
Serum	Incomplete injury	22	16.96 ± 7.19	0.985
	Complete injury	9	17.01 ± 4.73	
CSF	Incomplete injury	22	209.76 ± 167.99	0.002
	Complete injury	9	405.78 ± 14.31	

Abbreviation: CSF, cerebrospinal fluid.
Note: Man–Whitney test.

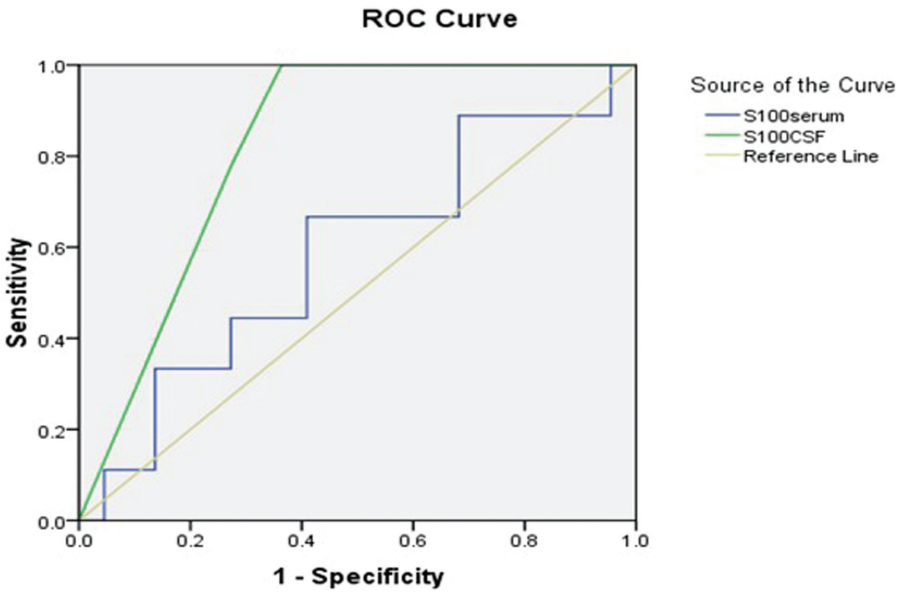

Fig. 1 Cutoff point for complete injury based on variable levels of S100B protein in cerebrospinal fluid (CSF) and serum.

0.12 ng/L, and showed that in the patients with SCI, the serum level of this biomarker is more than the cutoff point.[14] In another study, the results showed that there was a significant correlation between serum levels of S100B and SCI, but in this study, only serum levels of this protein were assessed and only mean serum levels were reported in patients. The mean serum level of S100B in patients with vertebral fractures and SCI was 1.18 µg/L, which is similar to our study, but the unit of report in two studies is different.[9] As can be seen, studies determining the cutoff point are very limited and many limit themselves to measuring serum levels. On the other hand, serum and CSF levels in these patients need to be measured in future studies at a specific interval time after vertebral injury.

So, S100B biomarker may offer a valuable measure of the magnitude of primary injury to the spinal cord after acute trauma, and it is in this setting that S100B rising in acute spinal cord may play a significant role in the research programs for new and effective neuroprotective treatments.

One of the limitations of our study was the lack of follow-up of this protein level over time and it is suggested that further studies be focused on this issue in order to clarify the duration and half-life of these biomarkers.

Conclusion

The results of this unique study have shown that S100B were useful markers for predicting the prognosis of patients with acute SCI and the cutoff points determined for serum and specially CSF concentrations can differentiate complete and incomplete SCI.

What Is Known

Many biomarkers have been studied in neurodegenerative disorders, but they have not yet been found to be effective in identifying and treating acute spinal cord injury (SCI). The role of some biomarkers such as S100 beta (S100B) has been somewhat known in determining the severity of primary SCI.

What Is New

The results of this unique study have shown that S100B is a useful marker for predicting the prognosis of patients with acute spinal cord injury (SCI) and the cutoff points determined especially for cerebrospinal fluid concentrations can differentiate complete and incomplete spinal cord injury.

Conflict of Interest

None declared.

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