Research Article

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The Relationship of Serum S100B Levels with Infarction Size and Clinical Outcome in Acute Ischemic Stroke Patients

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ABSTRACT

Introduction: S100B protein, which helps nerve development and differentiation, is produced by astrocytes and can be detected in peripheral circulation after brain damage. In this study, we aimed to investigate the relationship between the serum S100B protein level and the infarction volume and clinical outcome and also the early prognostic role of serum S100B protein in patients with ischemic stroke.

Method: Fifty patients admitted in the first 24-hour period of acute ischemic stroke were evaluated prospectively, and the findings were compared to those of the controls (n=26). S100B levels of the patients and neurological findings on days 1, 3, and 5 and their functional outcomes on the discharge day and at the first month were recorded by the same examiner.

Results: S100B levels were not affected by sex, age, or concomitant systemic diseases. The maximum levels of S100B were recorded on the 3rd day, and there was a correlation between infarct size and S100B levels. No correlation between the severity of stroke and S100B level was found. There was a poor correlation between the functional outcomes of the patients at the 1st month and S100B levels and on the 3rd day.

Conclusion: The detection of high S100B levels in peripheral circulation after acute ischemic stroke and the correlations of S100B levels with infarct size (good) and disability (poor) imply that S100B protein may be used as a peripheral marker in acute ischemic stroke patients. *(Archives of Neuropsychiatry 2014; 51: 395-400)*

Key words: Brain, cerebrovascular disorders, biological markers, prognosis

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Introduction

Stroke is one of the leading causes of death in developed countries and ranks first among diseases causing disability (1,2). The incidence of stroke increases with age, and 80% of them are due to ischemia (3).

Among the family of non-ubiquitous Ca^{2+}-modulated proteins, S100B is mainly produced by astrocytes. S100B plays an important role in nerve growth, differentiation, and reparation of nerves (4,5,6,7). While it originates a protective effect at physiologic levels, after excretion from the cell, elevated extracellular concentrations lead to cell damage, which can be involved in the pathophysiology of neurodegenerative processes (6,8). During brain damage, S100B spreads easily to the cerebrospinal fluid (CSF) and also to the blood (5,6). Increased S100B levels secondary to trauma and various ischemic conditions were reported in several studies (9,10,11). Recently, biochemical markers have gained importance in the identification of brain injury.

In this study, S100B levels were assessed in patients with ischemic stroke, and the relationship with the infarct size, localization, stroke severity, and clinical outcomes were evaluated.

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Method

In this study, 50 acute ischemic stroke patients, admitted within the first 24 hours of the stroke onset, were evaluated in a period of 6 months (May 2011-October 2011). Control subjects consisted of 26 healthy age- and sex-matched groups. Patients who were admitted 24 hours after stroke onset; suffering from stroke secondary to trauma, tumor, infection; diagnosed with brain tumor or systemic malignancy, transient ischemic attacks, epidural, subdural or subarachnoid hemorrhage; and patients with a history of head trauma or acute myocardial infarction within the last 3 months were excluded from the study.

The patients' age, sex, comorbid risk factors, radiological findings, and neurological examinations on the 1st, 3rd and 5th days of the stroke onset were recorded. Neurological examinations on the 1st, 3rd, and 5th days of stroke onset were recorded by NIHSS (National Institute of Health Stroke Scale). NIHSS score was classified as 0-1: normal, 2-7: mild, 8-14: moderate, 15 and higher: severe (12,13).

In the 1st, 3rd, and 5th days following stroke onset, 5 ml blood sampling was performed from the antecubital vein into flat vacutainers with gel separator tubes. After a rest at room temperature for about 20 minutes in order to obtain complete coagulation, serum was separated after 10 minutes of centrifugation at 4000 rpm. The serum samples were stored in Eppendorf tubes at -80°C until assessment. The results were recorded in pg/ml after analyzing the samples according to the protocol of the kit by using the sandwich enzyme immunoassay method and the Human S100B ELISA kit (S100B; BioVendor Research and Diagnostic Products, Brno, Chezch Republic)

Stroke subtypes were grouped as TACI (total anterior circulation infarct), PACI (partial anterior circulation infarct), POCI (posterior circulation infarct), and LACI (lacunar infarct) according to the classification of OCSP (Oxfordshire Community Stroke Project) (14).

Magnetic resonance imaging (MRI) was performed by a 1.5-Tesla field-strength (MAGNETOM Avanto; Siemens Healthcare, Erlangen, Germany) device. Infarct volume was calculated by slice thickness of 5 mm in the axial plane and gap between cross-sections of 1.5 mm in diffusion-weighted sequences. Patients were divided into two disability groups according to the modified Rankin scores (mRS) performed during hospital discharge and at the first month of the event: normal-mild and moderate-to-severe (15). The control group consisted of 26 sex- and age-matched individuals, taking in consideration the exclusion criteria. Serum S100B levels were measured intentionally only once.

Study was approved by the ethics committee of Bakirkoy Dr. Sadi Konuk Training and Research Hospital on 12/19/2011 with protocol number 2011/120.

Statistical Analysis

The Number Cruncher Statistical System (NCSS) 2007 Statistical Software (Utah, USA) package program was used. For the evaluation of data, descriptive statistical methods (mean, standard deviation), Friedman test for repeated measurements of multiple groups, Kruskal-Wallis test for comparison of multiple groups, Mann-Whitney U-test for comparison of two groups, Spearman correlation test for correlation, and Fisher's exact chi-square test for comparison of qualitative data were used.

Results

Fifty patients, 24 men (48%) and 26 women (52%), with ages between 40 and 98 years (68±13 years), were enrolled in the study. Patients were divided into groups according to the localization and size of the lesions: 2 cases of TACI (4%), 21 cases of PACI (42%), 27 cases of POCI (54%).

Four patients died during their admission (2 POCI, 1 TACI, 1 PACI), and S100B measurements of these patients could not be completed. One patient died because of acute coronary syndrome within the first month and was excluded from the first-month disability examination. Serial measurements of S100B of 11 patients could not be completed due to various reasons (4 exitus patients, early discharge of 7 patients who were lost to follow-up).

There was no statistical difference between the S100B levels of male and female patients on the 1st, 3rd, and 5th days. Eighty-two percent of hypertension (HT), 56% of diabetes mellitus (DM), 36% of coronary artery disease (CAD), and 34% of hyperlipidemia (HL) cases were detected in ischemic stroke patients, and S100B levels were not affected by these common systemic risk factors (Table 1).

Alteration of S100B levels did not show any significant differences between the 1st to 3rd days and the 1st to 5th days (p=.113 and p=.548). S100B values of the 3rd day were significantly higher than S100B values of the 5th day (p=.017). The S100B levels of stroke patients were respectively as follows: the 1st day [median (min-max)=112.5 (51-2815)], the 3rd day [median (min-max)=123 (53-2913)], and the 5th day [median (min-max)=105 (50-2544)] pg/ml (Fr=7.74, p=.021). There was no statistical difference between the mild and moderate-severe groups of percentage variations of the 3rd and 5th day S100B levels according to the 1st day (Table 2).

Also, no statistically significant difference was found in S100B levels of the 1st, 3rd, and 5th days between anterior system (TACI and PACI) and posterior system (POCI) strokes (Table 3).

Serum S100B levels on the 3rd and 5th days, especially on the 3rd day, were well correlated with infarct volume (p=.0001 and p=.0001), and there was a weak correlation between the first-month mRS score and S100B levels of the 3rd day (p=.03) (Table 4). There was no significant relationship between the concurrent NIHS scores and S100B levels (day 1, day 3, day 5) (p=.440, p=.736, p=.440).

All S100B level measurements showed significantly higher values than the control group (1st day, 3rd day, 5th day) (p=.0001, p=.0001, p=.002).

Table 1. The relationship between stroke patient's gender and risc factors to S100B

	S100B(pg/ml)		
	1st day	3rd day	5th day
Female(n=26)	165.5±156.9	204±237.4	197.5±276.9
Male (n=24)	265.6±506.6	384.5±696	324±508.8
P	.872	.991	.869
HT (+) (n=41)	219.7±242.9	410.4±670.3	386.2±610.8
HT (-) (n=9)	492.8±887.5	333.1±315.3	283.3±305.9
P	.087	.739	.631
DM (+) (n=28)	190.2±257.4	303.7±391.5	292.9±412.3
DM (-) (n=22)	368.9±578.5	525.4±832.6	443.6±686.8
P	.150	.233	.404
HL (+) (n=17)	364.4±705.6	546.8±797	509.9±605
HL (-) (n=33)	219.7±177.6	314.4±488.5	280.2±516.8
P	.268	.226	.219
CAD (+) (n=18)	169.8±156.4	489.6±779.1	546.8±801.6
CAD (-) (n=32)	324.5±524.3	344.9±514.9	259.2±325.6
P	.230	.453	.121

HT: hypertension, DM: diabetes mellitus, CAD: coronary artery disease, HL:hyperlipidemia, (+): Present, (-): absent, p>0.05 not significant

Table 2. S100B percentage change rates

S100B	1st day - 3rd day Change median (min-max)	1st day - 5th day Change median (min-max)
Mild	n=28	n=18
	-.02 (-.89 - 17.32)	.03 (-.90 - 13.67)
Medium-Severe	n=32	n=7
	.39 (-.63 - 9.92)	-.27 (-.60 - 36.41)
p	0260	.900

p>.05 not significant

Conclusion

Recently, many research studies were conducted in order to identify the post-stroke damage rate and to estimate its effect on the disease prognosis (16). Neurological examination or repeated neuroimaging might not be sufficient when cooperation with the patient cannot be established or if the patient is in a coma state. In these circumstances, the presence of a marker that can be monitored in serum would provide a convenience. One of the neurobiochemicals recently researched is S100B, a complicated neuroglia interaction-modulating protein (17,18,19). The correlation between lesion size and serum levels of this protein and also the relationship of it with the early clinical and/or functional outcome in acute post-stroke patients were reported in several studies.

In a study conducted by Beer et al. (20), serum S100B protein concentrations of 57 acute ischemic stroke patients, admitted to the hospital within 96 hours, showed a correlation to the grade of systemic inflammation regardless of the ischemic lesion size. Abraha et al. compared 68 ischemic stroke patients to 51 controls and found that the serum S100B levels of the patients were higher than that of the controls due to the size of infarction in TACI and lower in lacunar infarcts. In the same study, functional outcomes of the patients were evaluated by Barthel scale and mRS at the third month, and it was reported that the outcomes were compatible with S100B levels in acute phase (16). Missler et al. have reached similar conclusions in their study including 44 ischemic stroke patients (21). In our study, the highest serum S100B levels, especially on the third day, correlated well with the infarct volume, and this result led us to think that serum S100B levels show the width of brain injury and can be used as a peripheral marker.

In many studies, it is reported that the time needed to reach maximum levels of S100B protein, which also has increased levels after traumatic brain injury and hypoxic conditions, is longer in infarction, and it reaches its maximum level 2-3 days later in acute ischemic stroke (10,18,22,23,24,25,26). Weglews et al. showed in their study including 53 patients with ischemic and 14 with hemorrhagic stroke that in serial measurements, serum S100B concentrations reached the highest levels during the third day in ischemic stroke patients but on the first day in hemorrhagic stroke patients (27). In our study, consistent with the literature, there were significant differences of S100B levels on the third and fifth days, reaching the highest levels on the 3rd day. However, when comparing the percentage variation of the third and fifth days of S100B values to that of the first day, no significant difference was found between the mild and moderate-severe groups. Unlike other studies, we detected approximately the same high S100B levels during the first and the third day, and we assume that late (end of the first day) admission time of the patients to the hospital or not precisely specifying the time might result in progression of inflammation in the necrosis area. The measurements of the highest S100B levels on the third day might be related to the edema effect occurring 2-3 days after ischemic infarct, with a large number of astrocytes undergoing necrosis and progression of inflammation, triggering the deterioration in the blood-brain barrier.

In the Middelheim Multidisciplinary Stroke Study, it was reported that cerebrospinal fluid S100B protein levels of 89 strokes patients (68 ischemic strokes, 21 transient ischemic attacks) obtained at admission (average 8 hours) and 35 healthy volunteers were in association with infarct volume, stroke severity (NIHSS), and the outcome (3-month mRS) (28). Kenangil et al. showed that S100B values of 26 acute stroke patients, assessed on the 1st, 3rd, and 7th days, reached maximum levels in patients with infarcts larger than 2/3 of the middle cerebral artery territory on the 3rd day, and they indicated these findings as poor outcome and disability (25).

Elting et al. compared the relationship of S100B protein levels with clinical findings in 21 ischemic stroke, 18 transient

Table 3. Distribution of S100B levels by days in stroke subgroups

S100B		Anterior system (n=23)	Posterior system (n=27)	MW	p
1st day	mean±SD	224.6±287.7	306.6±530.1		
	median (min-max)	99 (61-257)	131 (68-398)	286.5	.640
3rd day	mean±SD	311.2±420.8	465.88±741.6		
	median (min-max)	119 (9.5-374)	151 (79-517)	251	.800
5th day	mean±SD	286.6±409.1	42105±646.92	156	.380
	median (min-max)	105 (70-441)	61.5 (51.8-116.3)		
	Fr	7.18	1.91		
	p	0.028	0.385		

SD: Standard deviation, p>0.05 not significant, MW: Mann-Whitney U-test,
Fr: Friedman test

Table 4. Time difference of S100B between infarct volume at discharging of hospital and first month mRS

S100B (pg/ml)			Infarct volume mm³ (13.940±20.629)	mRS DH	mRS 1st month
			p	p	P
1st day	mean±SD median	268.8±433.6	.4	.202	.093
	(min-max)	112.5 (51-2815)			
3rd day	mean±SD median	395.3±614.9	.0001	.841	.03
	(min-max)	123 (53-2913)			
5th day	mean±SD median	362.4±553.5	.0001	.095	.059
	(min-max)	105 (50-2544)			

mRS: modified Rankin Scale, DH: Discharging of Hospital

ischemic attack, and 10 traumatic brain injury patients to that of 28 healthy controls. A correlation between the highest S100B levels measured on the 3rd day and NIHS scores of the 1st and 10th days was found. In trauma patients, the highest S100B levels were detected during the first day, and a correlation was distinguished with the Glasgow coma scales during admission and at the 6-month follow-up (26).

In the study conducted by Buttner et al., serum S100B protein levels were measured at 12 hours, 24 hours, and 2, 3, 4, 5, 7, and 10 days in 26 patients with anterior circulation infarction, and clinical state and post-stroke 4-week functional impairment were scored with the mRS, and the results were compared to 26 healthy controls. The highest levels of S100B were measured on the 2nd and 3rd days after the onset of symptoms in patients with larger infarctions and higher neurological deficits during admission, but no association was found between these higher values and prognosis (24). In two separate studies, Wunderlich et al. detected a strong correlation between neurological conditions and serum S100B concentrations in ischemic stroke patients and stated that it has a high predictive value in estimating early prognosis (23,29). In the Fassbender et al. study, it was expressed that S100 protein levels were correlated with infarct size in ischemic stroke, and furthermore, its concentrations measured on the 10th, 24th, and 72nd hours were well correlated to the patient's neurologic status (30).

In our study, a correlation between infarct size and the increase of S100B levels was observed but not between the stroke severity (by NIHSS) and levels of S100B. Consequently, we concluded that stroke severity or the clinical situation is related not only to the amount of neurons undergoing necrosis but also to the critical localizations of necrosis, as well. Foerch et al. measured S100B levels of 39 patients with MCA infarcts who reached the hospital within the first 6 hours at the 48th and 72nd hours and found a relationship with the functional outcome at 6 months and also with infarct volume. They concluded that S100B values measured at the 48th and 72nd hours in nonlacunar MCA infarcts are the most important predictive measurements to estimate the functional outcome and infarct volume (31).

Hermann et al. evaluated 32 patients with anterior circulation ischemia and found that S100B serum concentrations were associated with the size of brain lesions, neurologic status, and early functional outcome of the patients. A continuous rise of

S100B until the 4th day was detected in all patients. During the 2nd and 3rd day, S100B levels reached their peak levels. In patients with lacunar infarcts, S100B did not pass the limit value of 0.12 mg/L; in those with PACI, a minimal increase was detected; and in TACI, S100B values reached 18 times the peak values. In conclusion, S100B secretion showed a good correlation with the size of the infarction. They reported that measurement of serum S100B after acute ischemia could be useful in therapeutic interventions and monitoring (19).

In our study, the detection of a weak correlation between the functional status at the first month and the highest S100B levels on the 3rd day led us to think of S100B as a nonsufficient prognostic marker. Another finding was that gender factor and concomitant systemic diseases, such as DM, HT, and HL, in ischemic stroke patients have no effect on S100B levels. This finding may imply that S100B can specifically show the brain damage.

As a conclusion, high S100B protein levels in the peripheral circulation after ischemic stroke were detected and well correlation with the size of infarction, but a weak correlation with disabilities was found. Even if S100B protein might not be as sufficient in the prediction of the prognosis in head trauma, it could be used as a marker showing brain damage in peripheral blood during ischemic stroke.

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