**ARAŞTIRMA YAZILARI** **ORIGINAL ARTICLE**

# AKUT SEREBRAL İSKEMİLİ HASTALARDA S 100 B SERUM PROTEİN KONSANTRASYONLARI

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## ÖZET

**Amaç :** Bu çalışmanın amacı, akut serebral iskemi tanısı alan hastaların serum S100 B seviyelerinin kronik iskemik lezyonları olan hastalarınki ile karşılaştırmaktır.
**Gereç ve Yöntem :** Çalışma grubu olarak alınan 20 akut serebral iskemili hasta, beyin görüntülemelerinde kronik iskemik gliyotik lezyonları olan 20 kontrol grubu hastası ile karşılaştırıldı. Akut serebral iskemili hastalardan inmenin 2,24,48,72. saatlerinde, kontrol grubundan da serebral iskemi tanısı konulduktan sonra S 100 B için kan alındı. S100 B'nın bazal değeri 0,12 µg/L olarak kabul edildi.
**Bulgular:** Akut serebral iskemili hastaların S100 B değerlerindeki yükseklik istatistiksel olarak anlamlı bulundu. Akut serebral iskemisi ve serebral ödemi olan hastaların 24,48 ve 72. saatlerdeki S100 B değerleri 2. saate göre daha yüksek bulundu. Serebral ödemi olan hastaların ortalama S100 B düzeyleri, olmayanlara göre daha yüksekti. En yüksek değer serebral ödem ve çift olan hastada idi.
**Sonuç:** S100 B protein seviyesinde yükselme santral sinir sistemindeki herhangi bir hasarın göstergesi olabilir. Daha ileri çalışmalarla, proteinin bazal seviyesinin, akut inme sonrası protein seviyesindeki artış ile zamansal korelasyonun netleştirilmesi bu protein değerini akut inme tanısı ve progresyon takibi açısından kullanışlı kılacaktır.
**Anahtar Sözcükler:** S100B, akut serebral iskemi, kronik serebral iskemi

## S100 B SERUM PROTEIN CONCENTRATIONS IN ACUTE CEREBRAL ISCHAEMIA

## SUMMARY

**Background:** The aim of this study was to compare the serum S100 B values of acute cerebral ischaemia patients with patients with chronic ischaemic lesions.
**Materials and Methods:** Twenty consecutive patients with acute cerebral ischaemia were included the study group and were compared with 20 consecutive patients who had chronic ischaemic gliotic lesions on cerebral images.
Sera for S100 B levels were collected from the study group on 2, 24, 48 and 72 hours after stroke onset and from the control group after the diagnosis of old cerebral ischaemia. The base value of S100 B was accepted as 0.12 µg/L.
**Results:** Statistically significant elevation in S100 B values was found in acute cerebral ischaemia patients. The S100 B values of patiens with acute cerebral ischemia and oedema in 24th, 48 th and 72 nd hours were higher than the values in 2 nd hour. Mean S100 B values in cerebral oedema patients were higher. The highest level was in patients with cerebral oedema and shift.
**Conclusions:** Evaluated levels of the protein indicate any cell damage in the central nervous system. With further studies, clearing the basic value of the protein and time related changes after acute stroke would make it a useful marker for the diagnosis and follow-up the progression of acute stroke.
**Key words:** S100B, acute cerebral ischaemia, chronic cerebral ischaemia

## MATERIALS AND METHODS

Twenty consecutive patients with acute CI (8 men and 12 women; mean age: 70.3 ± 11.05; 49.00 to 86.00 years) who admitted to our neurology clinic within 2 hours were included the study group. A neurologist diagnosed acute stroke and coma, according to the neurological examination and history. The diagnosis of CI was detected by 1.5 tesla magnetic resonance imaging (MRI) using perfusion and diffusion imagines.

The study group was compared with 20 consecutive patients consisting the control group (10 men and 10 women; mean age: 67.5 ± 9.2; 45.00 to 80.00 years). The control group had chronic ischaemic gliotic lesions on Computed Tomography (by spiral-computed tomography; Siemens-Somatom Balance) or MRI.

Patients with cerebral hemorrhage, with a history of a previous stroke, head injury or central nervous system infarction within the last 3 months were not included in the study group. Also, three

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patients were dropped out from the study because of early death and excluded from statistical analysis.

S-100 B serum levels (venous blood samples) were collected from the study group on 2,24,48 and 72nd hours after stroke onset and from the control group after the diagnosis of chronic ischaemic gliotic lesions. Sera were separated by a biochemist, after centrifugation at 5000 rpm for 5 minutes, stored at –20oC and thawed before analysis. S100B levels were measured by immunoluminometric assay (Liaison Brahms PCT, Byk-Sangtec Diagnostica, Ditezenbach, Germany) and sample for quality control was included in each assay. The inter-assay and intra-assay coefficients of variation for the lowest mean value (0.28 µg/L) were 10.1% and 5.5%, respectively. The PCT levels in healthy individuals, as determined with this assay, were < 0.12 µg/L. Serum levels above this value accepted as elevated and below this level as decreased.

The statistical package SPSS for windows (release 10.0) were used for data analysis. Numerical values were reported as mean±SD or as a proportion of the sample size. Comparisons between the study and control groups were made with the $X^2$ test for categorical data's, Mann Whitney U test and Wilcoxon signed tests for continuous data. A p value< 0.05 was accepted as statistically significant.

**RESULTS:**

The demographic findings of patients are summarized in table 1.

The base value of S100 B was taken as 0.12 µg/L in our study. Elevated concentrations (≥ 0.12 µg/L) were found in 19 of 20 (95%) acute CI patients

but in 6 of 20 (30 %) patients of control group (with Mann Whitney U test; p=0,00; see table 1).

The levels of S-100 B protein in blood change over time after acute CI and the protein levels of the control group were observed in table 2.

In 12 of 20 (60 %) acute CI patients, elevation was observed on all 2,24,48 and 72nd hours. Fourteen of 20 (70 %) patients had elevated values at the 2nd hours, 17 of 20 patients (85 %) at the 24th hours, 16 of 20 patients (80 %) at the 48th hours and 15 of 20 (75 %) patients at the 72nd hours. Mean protein values according to the hours (for 2- 24-48 and 72 hours) was 0.23 ± 0.18 µg/L, 0.55 ± 0.64 µg/L, 0.81 ± 1.08 µg/L, 0.77±1.16 µg/L respectively.

Table 1: Demographic findings of the patients.

| Variable | Study Group (n=20) | Control group (n=20) | P |
|---|---|---|---|
| Age (mean ±SD) | 70.3±11.05 | 67.5±9.2 | 0.42 |
| Sex ( male/female) | 12/8 | 10/10 | 0.52 |
| Hypertention | 17 ( 85 %) | 18 (90%) | 1 |
| Diabetes Mellitus | 9 (45 %) | 10 ( 50 %) | 0.75 |
| Hyperlipidemia | 12 (60 %) | 13 ( 65 %) | 0.74 |
| Hemiparesia( Left/right) | 10 (50 %) | 2 ( 10%) | 0.014 |
| Hemiplegia (Left/right) | 4 (20%) | 0 | 0.10 |
| Monoparasia (Left/ right; arm/leg) | 2 (10 %) | 1 (5%) | 1 |
| S100B (µg/L) | 0.59±0.62 | 0.09±0.06 | 0.00 |
| S100B (≥ 0.12µg/L). | 19 (95%) | 6 (30%) | 0.00 |

Table 2: S100 B values and MRI findings of the study and control groups' patients.

| Patient | S100B values of the study group (n=20) (µg/L) | | | | S100 B values of the kontrol grup (n=20) | MRI Shift | Oedema |
|---|---|---|---|---|---|---|---|
| | 2 h | 24 h | 48 h | 72 h | | | |
| Patient 1 | 0.15 | 0.13 | 0.25 | 0.19 | 0.18 | - | - |
| Patient2 | 0.72 | 1.61 | 1.38 | 1.18 | 1.22 | - | + |
| Patient3 | 0.10 | 0.55 | 1.01 | 0.20 | 0.46 | - | - |
| Patient4 | 0.09 | 0.07 | 0.22 | 0.13 | 0.12 | - | - |
| Patient5 | 0.64 | 0.54 | 0.47 | 0.38 | 0.50 | - | + |
| Patient6 | 0.32 | 0.34 | 0.23 | 0.17 | 0.26 | - | - |
| Patient7 | 0.23 | 0.55 | 3.72 | 3.48 | 1.99 | - | + |
| Patient8 | 0.16 | 0.26 | 0.21 | 0.10 | 0.18 | - | + |
| Patient9 | 0.23 | 0.55 | 1.04 | 1.37 | 0.79 | - | - |
| Patient10 | 0.37 | 1.31 | 1.70 | 1.90 | 1.32 | - | + |
| Patient11 | 0.08 | 0.16 | 0.19 | 0.22 | 0.16 | - | + |
| Patient12 | 0.12 | 1.11 | 0.09 | 0.08 | 0.35 | - | + |
| Patient13 | 0.37 | 0.11 | 3.62 | 4.19 | 2.07 | + | + |
| Patient14 | 0.16 | 0.28 | 0.23 | 0.21 | 0.22 | - | + |
| Patient15 | 0.08 | 0.14 | 0.08 | 0.11 | 0.10 | - | - |
| Patient16 | 0.33 | 0.38 | 0.55 | 0.77 | 0.50 | - | + |
| Patient17 | 0.11 | 0.17 | 0.10 | 0.09 | 0.11 | - | - |
| Patient18 | 0.23 | 2.58 | 1.08 | 0.47 | 1.09 | - | + |
| Patient19 | 0.13 | 0.20 | 0.13 | 0.14 | 0.15 | - | - |
| Patient20 | 0.07 | 0.07 | 0.08 | 0.06 | 0.07 | - | - |
| Mean S100 B cording to times (µg/L) | 0.23 ± 0.18 | 0.55 ± 0.64 | 0.81 ± 1.08 | 0.77 ± 1.16 | | | |

The highest but not statistically significant elevations of mean S100B values (0.81±1.08 µg/L) were found at the 48 th hour. Meaningful elevation was found on 24-48 and 72nd hours when compared with 2nd hours (with Wilcoxon signed test, p= 0.005, p=0.005; P=0.026, respectively; see table 2).

Eleven of 20 (55%) acute CI patients had cerebral oedema, but only one patient (patient 13) had shift and was in coma (see table 2).

Mean S100 B values in cerebral oedema patients were higher than the patients' values of acute CI without oedema (in cerebral oedema patients: 0.87 ± 0.70 µg/L; in acute CI patients without oedema: 0.59 ± 0.62µg/L; with mean Whitney U test, p= 0.006). Also, in this group of patients, S100 B values on 24-48 and 72nd hours were found higher than compared with the values on the 2nd hour (for 24th hour: 0.31± 0.20 µg/L, for 48th hour: 0.80 ± 0.77µg/L, for 72nd hour: 1.18±1.42 µg/L; with Wilcoxon sign test; p= 0.037, p=0.016, p=0.041; respectively).

The highest S100 B value was found in the patient with cerebral oedema and shift (see table 2).

## DISCUSSION

In this study, we compared serum S-100 B levels of patients with acute and chronic ischaemic lesions. There are few reports about this subject. Additionally, this study researched the levels of S-100 protein in blood change over time after CI. Elevated levels of serum S100 B has been reported in patients after head injury, stroke, and cardiac surgery who had neurological complications (1-9). Studies on CSF concentrations of S100B in patients with neurological lesions indicated a quantitative relation with the degree of cell damage in the central nervous system (CNS) (10).

Serum S100 B protein values in acute stroke patients was first reported by Persson et al (4). They investigated 47 patients with cerebral infarction, transient ischemic attack, intracerebral or subarachnoid hemorrhage, and head injury. Temporal changes in serum S-100 concentrations reflected the clinical course in 4 patients. The authors commented that these protein concentrations might reflect the extent of brain damage and could be useful in selecting patients with major stroke for more aggressive treatment during the acute phase. Kim et al (7) measured 7 of 19 acute cerebral infarction patients' serum protein on days 1,3 and 7 with peak values after 3 days. Missler et al (3) investigated 44 acute stroke patients on days 3-4-7 and found peak values after 2.5 ± 1.3 days. Büttner et al (1) examined 26 patients' S100 B levels with an acute infarction on days 0,2,3,4,5,7,8 and 10. The highest level was observed on days 2 and 3. Elting et al (6) measured this protein levels in 21 ischaemic stroke patients. The peak levels of this protein were on day 3 or 4 in almost all stroke patients.

The results of our study were in concordant with those previous studies. We measured protein levels of acute CI patients on 2-24-48 and 72 nd hours. An elevated concentration of the protein in serum was found in almost all of the acute stroke patients. Although, the highest mean S100B value was measured on the 48 th hour, statistically significant elevation was found on 24-48 and 72nd hours. Mean S100 B values in cerebral oedema patients were found higher than acute CI patients without oedema supporting that these protein concentrations might reflect the extent of brain damage.

However, the highest S100 B value was found in the patient with cerebral oedema and shift.

Histological assessment of experimental brain infarction demonstrated tissue necrosis extending into the capillary endothelium followed by diapedesis during the first 3 days of cerebral ischemia (11). Leakage of glial cells may cause functional impairment of the blood-brain barrier, which could allow the transport of S100B from brain tissue to the vascular compartment (12). When S100B levels reach a maximum level 2 - 3 days after stroke, irreversible morphological alterations such as tissue necrosis and neuronal death could be observed by histological examination (13).

70 percent of our patients had elevated protein levels on the 2nd hour after acute CI. The possible explanation for this early peak levels could reflect reperfusion. The core of the infarct releases the S100B produced by adenosine and glutamate which might lead to early peak levels (6).

The level of diagnosed S100B protein value at which stroke or any cerebral complication is not entirely clear (9). In our study, the level of mean S100 B protein in acute CI group was 0.59±0.62 µg/L and in old CI patients was 0.09±0.6 µg/L. With forward studies with much more patients will put the clear level of diagnosed S100 B protein value.

Higher S100 B values were observed in 30 % of

the control group, peri-infarctional reactive gliotic lesions may produce S100 B (6,14).

In conclusion, we agree that elevated levels of the protein were not specific for CI and could indicate any cell damage in the central nervous system (3). With further studies, clearing the basic value of the protein and time related changes after acute stroke that would make it a useful marker for the diagnosis and follow-up the progression of acute stroke.

REFERENCES:

1. Büttner T, Weyers S, Postert T, Sprengelmeyer R, Kuhn W. S-100 protein:serum marker of focal brain damage after ischemic territorial MCA infarction. Stroke 1999, 28:1961-1965.
2. Reynolds MA, Kırchıck HJ, Dahlen JR, Anderberg JM, McPherson PH, Nakamura KK, Laskowitz DT, Valkirs GE, Buechler KF. Early biomarkers of stroke. Clinical Chemistry 2003, 49: 1733-1739.
3. 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, 28:1956-1960
4. Persson L, Hardemark HG, Gustafsson J, Rundstrom G, Mendel-Hartvig I, Esscher T, Pahlman S. S-100 Protein and Neuron-Specific Enolase in Cerebrovascular Fluid and Serum: Markers of Cell Damage in Human Central Nervous System. Stroke 1987,18:911-918.
5. Abraha H, Butterworth R, Bath P, Wassif WS, Garthwaite J, Sherwood RA. Serum S-100 protein relationship to clinical outcome in acute stroke. Ann Clin Biochem 1997, 34:366-370.
6. Elting JW, de Jager AE, Teelken AW, Schaaf MJ, Maurits NM, van der Naalt J, Sibinga CT, Sulter GA, De Keyser J. Comparison of serum S-100 protein levels following stroke and traumatic brain injury.J Neurol Sci 2000 Dec 1;181(1-2):104-110.
7. Kim JS, Yoon SS, K,m YU, Ryu JS. Serial measurement of interleukin-6, transforming growth factor-B, and S-100 protein in patients with acute stroke. Stroke 1996, 27:1553-1557.
8. Ali MS., Harmer M, Vaughan R. Serum S100 protein as a marker of cerebral damage during cardiac surgery. Br J Anaesth 2000, 85:287-298.
9. Raabe A, Grolms C, Sorge O, Zimmermann M, Seifert V. Serum S-100 B Protein in severe head injury. Neurosurgery 1999, 45:477-483.
10. Sindic C, Chalon M, Cambiaso C, Laterre E, Masson P. Assessment of damage to the central nervous system by determination of S-100 protein in the cerebrospinal fluid. J Neurol Neurosurg Psychiatry 1982, 45:1130-1135.
11. Katzman R, Clasen R, Klatzo I, Meyer JS, Pappius HM, Waltz AG. Report of Joint Committee for stroke resources IV: Brain edema in stroke. Stroke 1977, 8:510-540.
12. Pollay M, Roberts PA. Blood brain barrier: a definition of normal and altered function. Neurosurgery 1980, 6:675-685.
13. Raichle ME. The pathophysiology of brain ischemia. Ann Neurol 1983, 13:2-10.
14. Kanner AA, Marchi N, FazioV, et.al. Serum S100 _ : A noninvasive Marker of Blood-Brain Barrier Function and Brain Lesions. Cancer; 2003, 97:2806-2813.