S100B PROTEIN CONTENT IN ISCHEMIC STROKE AND ITS PROGNOSTIC VALUE IN PATIENTS SUBJECTED TO INVASIVE INTERVENTIONS

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The authors declare that they have no conflicts of interest

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ischemic stroke; protein S100B; prognosis

Abstract

The aim of the study *is to determine the levels of the S100B protein in patients with ischemic stroke and evaluate its relationship with the size of brain tissue damage, stroke severity, and clinical outcomes.*

Materials and methods. *The study included 113 patients with acute ischemic stroke, hospitalized within the first day after its onset and subjected to invasive treatment. 101 men and 12 women were examined, including 32 at the age of 50-60, 64 at the age of 61-70, 17 at the age of 71-80. parameters and degree of functional deviations according to the NIHSS scale.*

Results. *The content of S100B during the initial determination on average for the group significantly exceeded the level determined in the control by 3.22 times (p=0.025). There was a direct dependence of the content of S100B on the size of the stroke. A moderate increase in the indicator on the 3rd day relative to the determined one on the 1st day and a decrease on the 7th day after the development of the stroke were revealed. There was no significant dependence of S100B content on the presence of comorbidities. The influence of the studied parameter on the degree of neurological deficit was determined only in patients with a large stroke size.*

Ишемиялық инсульттегі S100B протеинінің құрамы және инвазивті араласуларға ұшыраған науқастардағы оның болжамдық мәні

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Түйінді сөздер:
ишемиялық инсульт; ақуыз S100B; болжау

Аңдатпа

Зерттеудің мақсаты *- ишемиялық инсультпен ауыратын науқастарда S100B протеинінің деңгейін анықтау және оның ми тінінің зақымдану аймағының өлшемімен, инсульттің ауырлығымен және клиникалық нәтижелерімен байланысын бағалау.*

Материалдар мен тәсілдер. *Зерттеуге жедел ишемиялық инсультпен ауыратын, оның басталуынан кейінгі бірінші тәулікте ауруханаға жатқызылған және инвазивті емге ұшыраған 113 пациент қамтылды. NIHSS шкаласы бойынша 101 ер және 12 әйел тексерілді, оның ішінде 50-60 жаста - 32, 61-70 жаста - 64,*

71-80 жаста - 17. Параметрлері мен функционалдық ауытқу дәрежесі.

Нәтижелер. *Топ бойынша бастапқы анықтау кезінде S100B мазмұны орта есеппен бақылауда анықталған деңгейден 3,22 есе (p=0,025) айтарлықтай асып түсті. S100B мазмұнының инсульт өлшеміне тікелей тәуелділігі болды. 1-ші күні анықталғанға қатысты 3-ші күні көрсеткіштің орташа жоғарылауы және инсульт дамығаннан кейін 7-ші күні төмендеуі анықталды. S100B мазмұнының қатар жүретін аурулардың болуына айтарлықтай тәуелділігі болған жоқ. Зерттелетін параметрдің неврологиялық тапшылық дәрежесіне әсері тек инсульт мөлшері үлкен науқастарда анықталды.*

Содержание белка S100B при ишемическом инсульте и его прогностическое значение у больных, подвергнутых инвазивным вмешательствам

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Ключевые слова:
ишемический инсульт; белок S100B; прогноз

Аннотация

Цель работы *- определение уровней белка S100B у пациентов с ишемическим инсультом и оценка его связи с размером области поражения мозговой ткани, тяжестью инсульта и клиническими исходами.*

Материалы и методы. *В исследование включены 113 пациентов с острым ишемическим инсультом, госпитализированных в течение первых суток после его начала и подвергнутых инвазивному лечению. Обследован 101 мужчина и 12 женщин, из них в возрасте 50-60 лет – 32, 61-70 лет – 64, 71-80 лет – 17. Осуществляли определение белка S100B на 1, 3 и 7 сутки, а также комплекса клинико-лабораторных параметров и степени функциональных отклонений по шкале NIHSS.*

Результаты. *Содержание S100B при первичном определении в среднем по группе значимо превысило уровень, определенный в контроле, в 3,22 раза (p=0,025). Имелась прямая зависимость содержания S100B от размера инсульта. Выявлено умеренное повышение показателя на 3 сутки относительно определенного на 1 сутки и снижение на 7 сутки после развития инсульта. Не было выявлено существенной зависимости содержания S100B от наличия сопутствующей патологии. Влияние исследованного показателя на степень неврологического дефицита определено только у пациентов с большим размером инсульта.*

Introduction

Stroke is one of the leading causes of death in developed countries and up to now can take the first place among diseases leading to disability [1, 2]. The frequency of strokes in the population increases with age, up to 80% of them are ischemic [3].

There is a complex of pathogenetic mechanisms of ischemic stroke, including regular changes in cerebral hemodynamics and, further, metabolic disorders of nerve and glial tissues.

Recently, biochemical markers have become important in the identification of brain damage. Among the family of Ca2+-modulated proteins, S100B is mainly produced by astrocytes. S100B plays an important role in the growth, differentiation and repair of nerves [4, 5, 6, 7]. At physiological levels of concentration, this protein causes a protective effect, but elevated extracellular concentrations lead to cell damage, which may be associated with the pathophysiology of neurodegenerative processes [6]. With brain damage, S100B easily spreads into the cerebrospinal fluid, as well as into the blood [5, 6]. A number of studies have reported an increase in S100B levels due to trauma and various ischemic conditions [8].

Purpose of the study is to determine the levels of the S100B protein in patients with ischemic stroke and evaluate its relationship with the size of brain tissue damage, stroke severity, and clinical outcomes

Materials and methods

The study included 113 patients with acute ischemic stroke, hospitalized during the first day after its start. 101 men and 12 women were

examined, including 32, 61-70 aged 50-60 years years - 64, 71-80 years - 17.

The study was conducted in 2019-2022.

The control group consisted of 40 clinically healthy individuals, comparable in sex and age.

Criteria for inclusion in the study:

- instrumentally verified ischemic stroke;
- the full scope of the examination according to the Study Protocol;
- invasive intervention in all patients. Exclusion Criteria:
- hospitalization more than 24 hours after the onset of a stroke;
- the development of a stroke due to trauma, tumor, infectious process;
- the presence of a diagnosed brain tumor or a malignant neoplasm of another localization,
- transient ischemic attack,
- epidural, subdural or subarachnoid hemorrhage;
- history of head trauma or acute myocardial infarction within the last 3 months.

The risk assessment criteria for the examined patients included age, gender, concomitant cardiovascular risk factors, radiological data, and results of a neurological examination on the 1st, 3rd, and 7th days from the onset of a stroke. Neurological examinations were recorded using the NIHSS scale.

The NIHSS score was divided into main grades: 0–1: normal, 2–7: mild, 8–14: moderate, 15 and above: severe [9].

On the 1st, 3rd and 7th days from the development of a stroke, venous blood was taken (5 ml each). After incubation at room temperature for about 20 minutes to achieve complete coagulation, the serum was separated by 10 minutes of centrifugation at 4000 rpm. Serum samples were stored in Eppendorf tubes at -80°C until analysis. Results were reported in ng/mL after sample analysis according to the kit protocol using the ELISA method and the Human S100B ELISA kit (S100B; BioVendor Research and Diag). Nostic Products, Brno, Czech Republic).

Stroke subtypes were grouped as TACI (total anterior circulation stroke), PACI (partial anterior circulation stroke), POCI (posterior circulation stroke), and LACI (lacunar stroke) according to the OCSP classification [10].

Magnetic resonance imaging (MRI) was performed on an MRI tonometer (MAGNETOM Avanto; Siemens Healthcare, Erlangen, Germany) with a field strength of 1.5 T.

The volume of the lesion was calculated from the slice thickness of 5 mm in the axial plane and the gap between the cross sections of 1.5 mm in diffusion-weighted images. At discharge from the hospital, patients were divided into two groups of functional impairment according to the modified Rankin scale: normal-mild and moderate-to-severe [11].

Statistical analysis. The SPSS 20 program was used. Descriptive statistical methods (mean, standard deviation), Friedman test for repeated measures of several groups, Kruskal-Wallis test for comparison of several groups, Mann-Whitney U-test for comparison of two groups, correlation were used to evaluate the data. Spearman's test and Pearson's exact $\chi 2$ test for comparing qualitative data. The boundary level of the presence of statistical significance was taken $p<0,05$.

Results

The results were evaluated by the average values of laboratory and clinical parameters at various times. They are presented in the charts (Figure 1, 2, 3) and in the table 1.

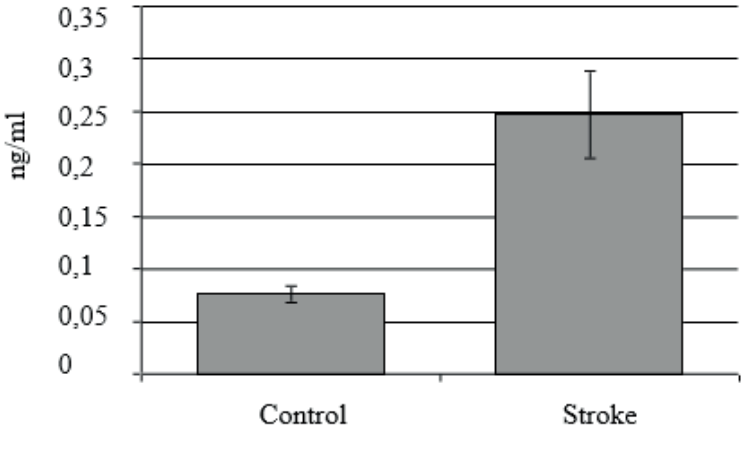
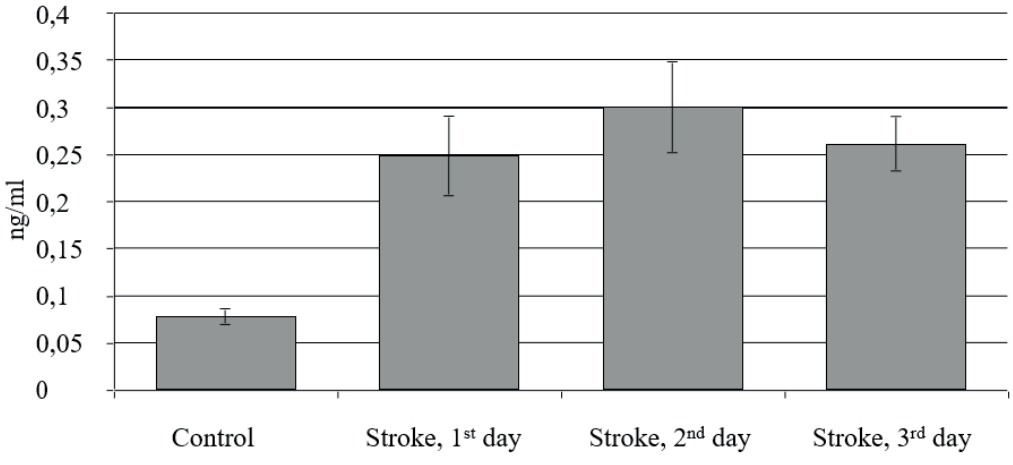


Figure 1.
The level of S100B content at the initial determination in comparison with the control

The content of S100B during the initial determination on average for the group significantly exceeded the level determined in the control by 3.22 times (p=0.025).

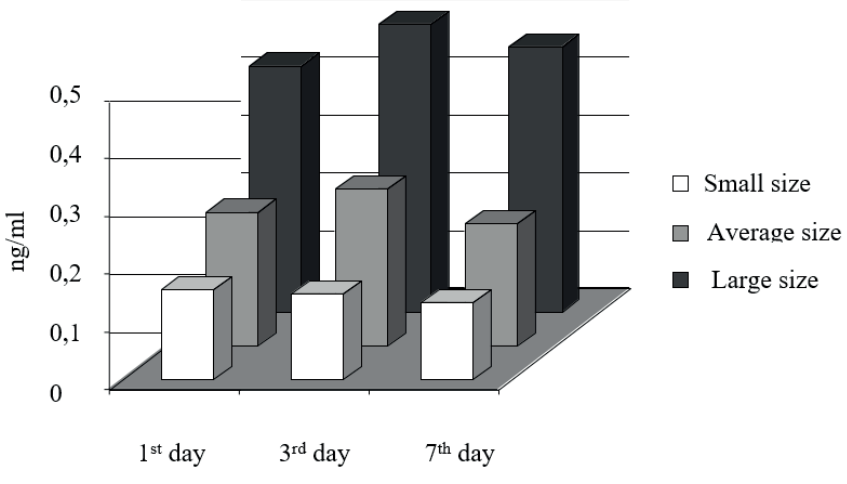
There were significant differences in the content of S100B depending on the size of the stroke. Thus, the average value of the indicator for small strokes exceeded the control one by 2.01 times, with medium ones by 2.99 times and with large ones by 5.55 times (p=0.043, p=0.003 and p<0.001, respectively). There were also significant differences between all groups of patients with stroke, except for small and medium stroke.

Figure 2. Dynamics of S100B content in the general group



A certain dynamics of S100B content in the blood was observed. Initially (up to 3 days), its value increased, and by 7 days it decreased. However, there were no significant differences between the indicators for this period.

Figure 3. The level of S100B in dynamics depending on the size of the stroke



In the dynamics, an unambiguous, but insignificant trend towards a decrease in the indicator was revealed in case of a small stroke, while with an average size of the lesion and with a large stroke, an increase in the S100B protein content was noted within 3 days and a tendency to decrease after 7 days from the development of a stroke.

Table 1. Relationships of S100B content in dynamics, risk factors and sizes of ischemic stroke

	Groups								
	Mild stroke, n=47			Average stroke, n=38			Large stroke, n=28		
	1 day	3 day	7 day	1 day	3 day	7 day	1 day	3 day	7 day
Gender male, n=101	0,151	0,163	0,149	0,229	0,237	0,235	0,442	0,497	0,458
Female	0,129	0,147	0,133	0,201	0,218	0,199	-	-	-
Age 0-61 y., n=32	0,199	0,185	0,176	0,255	0,270	0,242	0,436	0,488	0,430
61-90 y.	0,106	0,130	0,115	0,187	0,209	0,201	0,470	0,519	0,467
BP, n=96	0,148	0,153	0,146	0,234	0,258	0,248	0,481	0,493	0,470
No BP	0,138	0,147	0,137	0,227	0,222	0,195	0,399	0,420	0,419
Ischemic heart disease, n=27	0,154	0,156	0,155	0,244	0,253	0,251	0,490	0,528	0,500
No	0,132	0,140	0,129	0,215	0,218	0,197	0,421	0,455	0,432
DM, n=18	0,169	0,172	0,161	0,249	0,260	0,245	0,442	0,497	0,458
No DM	0,126	0,135	0,124	0,208	0,212	0,207	-	-	-

As a result of comparing the content of S100B in dynamics in the presence of various risk factors, it was found that in men this marker of tissue damage is more pronounced than in women. It was also found to be higher in relatively young individuals, with the exception of those who had large ischemic brain damage.

The presence of arterial hypertension,

coronary heart disease and diabetes mellitus did not significantly affect the values of the studied indicator. There were only tendencies to excess in all compared pairs of values in the presence of aggravating factors, especially coronary artery disease.

When determining the severity of disorders on the Rankin scale, it was determined that 94 patients had no clinical symptoms or they were mild, 19 had moderate or severe symptoms. Its distribution depending on the content of S100B during the initial determination is shown in Table 1.

In the structure of functional outcomes, a certain dependence on the content of the S100B protein is noticeable. It can be traced in all selected subgroups and reaches a degree of significance in large stroke (p=0.043). However, it should be noted that no significant differences were found on average across the group.

Discussion

Recently, many studies have been conducted to determine the frequency of post-stroke injuries and assess their impact on the prognosis of the diseas. Neurological examination or repeated neuroimaging may not be sufficient if cooperation with the patient cannot be established or if the patient is in a coma. In these circumstances, the presence of a marker that can be controlled in serum may provide convenience. One of the latest studied neurobiochemicals is S100B, a complex protein that modulates neuroglia interaction [11]. The correlation between lesion size and serum levels of this protein, as well as its association with early clinical and/or functional outcome in acute post-stroke patients, has been noted in several studies. Miao Y et al. [12], determined that serum level of Hyc altered slightly whatever the type of the heart disease, but it did not change in cases of minor cases; nevertheless, CRP level is significantly raised in all types of inflammations and in AMI.

However, when comparing the percentage change in S100B values on days three and five with that on day one, no significant difference was found between the mild and moderate and severe groups. Unlike other studies, we found approximately the same high levels of S100B during the first and third days and suggest that late (at the end of the first day) the time of admission of patients to the hospital or inaccurate timing may lead to disease progression. inflammation in the area of necrosis. Measurements of the highest levels of S100B on the third day may be associated with the effect of edema occurring 2-3 days after ischemic stroke, in which there is necrosis of a large number of astrocytes and the progression of inflammation, causing deterioration of the blood-brain barrier.

The Middelheim Multidisciplinary Stroke Study reported that S100B protein levels in the cerebrospinal fluid of 89 stroke patients (68 ischemic strokes, 21 TIAs) obtained at admission (mean 8 hours) and 35 healthy volunteers correlated with the volume of brain tissue lesion, stroke frequency, outcome severity (NIHSS) [14]. Kenangil et al showed that S100B values in 26 patients with acute stroke assessed on days 1, 3 and 7 reached maximum levels in patients with strokes associated with closure of more than 2/3 of the area of the middle cerebral artery on day 3, and they defined these results as poor outcome and disability. Elting et al. compared the relationship of S100B protein levels to clinical findings in 21 patients with ischemic stroke, 18 with TIA, and 10 patients with traumatic brain injury with that of 28 healthy controls. A correlation was found between the highest S100B levels measured on day 3 and NIHS scores on days 1 and 10. In trauma patients, the highest levels of S100B were found during the first day, and a correlation was found with the Glasgow Coma Scale on admission. In a study 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 stroke in the anterior circulation region, as well as with a clinical condition. The highest levels of S100B were determined on days 2 and 3 after the onset of symptoms in patients with more extensive strokes and more severe neurological deficits on admission, but no relationship was found between these higher values and prognosis [13]. In two separate studies, Wunderlich et al. found a strong correlation between neurological conditions and serum S100B concentrations in patients with ischemic stroke and stated that it has high predictive value in assessing early prognosis. In a study by Fassbender K. et al, it was shown that S100 protein levels correlate with the size of damage in ischemic stroke, and, in addition, its concentrations measured after 10, 24, and 72 hours correlate well with the patient's neurological status.

Conclusion

In our study, there was a correlation between lesion size and increased S100B levels, as well as between stroke severity (according to the NIHSS scale) and S100B levels. Therefore, we concluded that stroke severity or clinical situation is associated not only with the number of neurons that have undergone necrosis, but also with critical locations of necrosis. The identification of a weak correlation between the functional status in the first month and the maximum level of S100B on the 3rd day led us to think about S100B as an insufficient prognostic marker. Another conclusion was that gender and concomitant systemic diseases such as diabetes, hypertension and HL in patients with ischemic stroke do not affect the level of S100B. This observation may mean that S100B is a possible marker of brain injury. Thus, high levels

of S100B protein in the peripheral blood after ischemic stroke were found, which correlated well with the size of the lesion, but weakly correlated with disability. Even if the S100B content may be insufficient to predict prognosis in traumatic brain injury, its content in peripheral blood can be used as a marker of brain damage in ischemic stroke.

References

1. Towfighi A, Ovbiagele B. Health Equity and Actionable Disparities in Stroke: 2021 Update. Stroke. 2022 Mar;53(3):636-642. doi: 10.1161/STROKEAHA.122.035816.
2. Russo E. et al. Mitochondrial targeting as a novel therapy for stroke. Brain circulation. 2018; 4(3):84.
3. Rexrode KM, Madsen TE, Yu AYX, Carcel C, Lichtman JH, Miller EC. The Impact of Sex and Gender on Stroke. Circ Res. 2022 Feb 18;130(4):512-528. doi: 10.1161/CIRCRESAHA.121.319915.
4. Holst, C. B., Brøchner, C. B., Vitting-Seerup, K., & Møllgård, K. Astrogliogenesis in human fetal brain: complex spatiotemporal immunoreactivity patterns of GFAP, S100, AQP 4 and YKL-40. Journal of Anatomy, 2019;235(3):590-615.
5. Gao L. et al. Neuron-specific enolase in hypertension patients with acute ischemic stroke and its value forecasting long-term functional outcomes. BMC geriatrics. 2023:23(1):294.
6. Gonzalez L.L., Garrie K., Turner M.D. Role of S100 proteins in health and disease. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research. 2020;1867(6):118677.
7. Michetti F. et al. The S100B story: from biomarker to active factor in neural injury. Journal of neurochemistry. 2019;148(2):168-187.
8. Mokhtarzade M. et al. Exercise-induced changes in neurotrophic factors and markers of blood-brain barrier permeability are moderated by weight status in multiple sclerosis. Neuropeptides.2018;70:93-100.
9. Abbas N. I. et al. D-dimer level is correlated with prognosis, infarct size, and NIHSS in acute ischemic stroke patients. Indian Journal of Critical Care Medicine: Peer-reviewed, Official Publication of Indian Society of Critical Care Medicine. 2021;25(2):193.
10. Jose J., James J. An MRI based ischemic stroke classification–A mechanism oriented approach. Annals of Indian Academy of Neurology. 2022;25(6):1019.
11. Matsuo H. et al. Dysphagia is associated with functional decline during acute-care hospitalization of older patients. Geriatrics & Gerontology International. 2017;17(10):1610-1616.
12. Miao Y., Liao J.K. Potential serum biomarkers in the pathophysiological processes of stroke. Expert review of neurotherapeutics. 2017;14(2):173-185.
13. He Y, Cai Z, Chen Y. Role of S-100β in stroke. Int J Neurosci. 2018 Dec;128(12):1180-1187. doi: 10.1080/00207454.2018.1481065.
14. De Vos A. et al. Neurogranin and tau in cerebrospinal fluid and plasma of patients with acute ischemic stroke. BMC neurology. 2017;17:1-8.