

Abstract

Volodymyr Lychko,

¹⁾**Volodymyr Malakhov**

Sumy State University,

2, Rymyskogo-Korsakova st.,

Sumy, 40007, Ukraine

¹⁾*Kharkiv Medical Academy of*

Postgraduate Education

58, Korchaginцев st., Kharkiv,

61176, Ukraine

MAIN INDICES OF BLOOD-BRAIN BARRIER DAMAGE AT ACUTE PHASE OF ISCHEMIC STROKE

Introduction: An acute ischemic stroke causes expressed disruption of blood-brain barrier (BBB), which significantly affects prognosis. One of the indicators of the effect is the level of albumin in the cerebrospinal fluid (CSF).

The **purpose** of the study was to examine the level of albumin in the CSF in patients with ischemic stroke and to assess the role one as index of BBB dysfunction. In the study were involved 121 patients who had first incident of brain infarction (mean age was 64.4 ± 0.9 years) were comprehensively examined and the concentration of albumin in serum and CSF were determined.

The **results** of the study show level of albumin in CSF was clearly elevated in patients with increased severity of infarction. Under treatment, there was a general trend of increase in level of CSF albumin in patients of all groups, remarkably in those with severe condition.

Conclusion: The onset of brain infarction is characterize by significant functional changes of the BBB confirmed by a sharp increase in the level of CSF albumin (34.6 %) which directly correlated with the severity of patients. Dynamics of treatment have shown unfavorable prognostic signs due to increase in levels of albumin by 1.7 times observed in patients with severe condition.

Key words: albumin, cerebrospinal fluid, barrier, stroke, prognosis, dysfunction.

Corresponding author: *vladlychko@ya.ru

Резюме

Володимир Личко,

¹⁾**Володимир Малахов**

Сумський державний

університет,

вул. Римського-Корсакова, 2,

Суми, 40007, Україна

¹⁾*Харківська медична академія*

післядипломної освіти

вул. Корчагинців, 58, Харків,

61176, Україна

ПРОВІДНІ ПОКАЗНИКИ ПОШКОДЖЕННЯ ГЕМАТОЕНЦЕФАЛІЧНОГО БАР'ЄРУ В ГОСТРОМУ ПЕРІОДІ ІНФАРКТУ ГОЛОВНОГО МОЗКУ

Актуальність: В гострому періоді інфаркту головного мозку відбувається виражена дезорганізація гематоенцефалічного бар'єру, що значно погіршує прогноз захворювання. Одним із індикаторів цієї дисфункції є рівень альбуміну в цереброспінальній рідині.

Методи та матеріали дослідження: Нами були комплексно обстежені 121 хворий із першим у житті інфарктом головного мозку (середній вік склав $64,4 \pm 0,9$ років). Визначали вміст альбуміну в сироватці крові та цереброспінальній рідині.

Результати: Рівні альбуміну в цереброспінальній рідині чітко підвищувалися зі зростанням ступеня тяжкості хворого. У динаміці лікування спостерігалася загальна тенденція до підвищення рівнів альбуміну ліквору в усіх групах хворих, особливо у тяжкому стані.

Резюме**Владимир Лычко,**¹⁾**Владимир Малахов***Сумский государственный университет,**ул. Римского-Корсакова, 2, Сумы, 40007, Украина*¹⁾*Харьковская медицинская академия последипломного образования**ул. Корчагинцев, 58, Харьков, 61176, Украина*

Висновки: В дебюті інфаркту головного мозку характерні значні функціональні зміни ГЕБ, про що свідчить різке зростання рівнів альбуміну в лікворі (на 34,6 %) та на пряму корелюють із ступенем тяжкості хворих. Несприятливою прогностичною ознакою було підвищення рівнів альбуміну в 1,7 рази в динаміці лікування, що спостерігалось у тяжких хворих.

Ключові слова: альбумін, цереброспинальна рідина, бар'єр, інсульт, прогноз, дисфункція.

ОСНОВНЫЕ ПОКАЗАТЕЛИ ПОВРЕЖДЕНИЯ ГЕМАТОЭНЦЕФАЛИЧЕСКОГО БАРЬЕРА В ОСТРОМ ПЕРИОДЕ ИНФАРКТА ГОЛОВНОГО МОЗГА

Актуальность: в остром периоде инфаркта головного мозга происходит выраженная дезорганизация гематоэнцефалического барьера, значительно ухудшающая прогноз заболевания. Одним из индикаторов этой дисфункции является уровень альбумина в цереброспинальной жидкости.

Методы и материалы исследования: было комплексно обследовано

121 больного с первым в жизни инфарктом головного мозга (средний возраст составил

64,4 ± 0,9 лет). Определяли содержание альбумина в сыворотке крови и цереброспинальной жидкости.

Результаты: уровни альбумина в цереброспинальной жидкости четко повышались с ростом степени тяжести больного. В динамике лечения наблюдалась общая тенденция к повышению уровня альбумина ликвора во всех группах больных, особенно в тяжелом состоянии.

Выводы: в дебюте инфаркта головного мозга характерны значительные функциональные изменения гематоэнцефалического барьера, о чем свидетельствует резкий рост уровней альбумина в ликворе (на 34,6 %) и прямо коррелирует со степенью тяжести больных. Неблагоприятным прогностическим признаком было повышение уровня альбумина в 1,7 раза в динамике лечения, что наблюдалось у тяжелых больных.

Ключевые слова: альбумин, цереброспинальная жидкость, барьер, инсульт, прогноз, дисфункция.

Автор, відповідальний за листування: *vladlychko@ya.ru

Introduction

An integration of mechanisms such as depletion of neurons energy resources, excessive accumulation of excitatory amino acids and the associated "excitotoxicity", formation of reactive oxygen species with the development of oxidative stress, the advancement of endothelial dysfunction and functional changes of the blood-brain barrier (BBB) is the fundamental component in the pathogenesis of brain infarction [1, 3, 8].

All of these processes affect the cell membrane, intercellular structure and most importantly the vascular wall [6, 14]. There is damage to the vascular basement membrane, dense interendothelial

junctions and the endothelial lining of cerebral vessels and as a result, the development of functional disorders of BBB [9, 10, 15].

Presently, mechanisms of BBB permeability violations are disputed, but at the same time, changes that induce pathological cascade of reactions (lactic acidosis, "excitotoxicity" and oxidant stress), are a "shock discovery" to the obstacle in the nervous system being the cause of cell death and concomitant brain edema, which may further induce hypoxic necrobiosis and apoptotic gene expression [14, 18].



Therefore, the presented set of clinical and pathological criteria that indicate expressed BBB disruption is undoubtedly one of the major pathogenetic links of infarction [5, 16]. It should be noted that the cerebrovascular endothelium is the most susceptible area to injury, the degree and pattern of which is significantly influenced by the severity of morphological changes in basal membranes and adjacent neuronal-glia structures [11, 19].

The indicator of the degree of permeability of the BBB is the level of albumin in the cerebrospinal fluid (CSF) [2, 12, 17]. The latter, being a blood protein that is not locally synthesized are therefore "markers" of immunoglobulins that penetrate from the systemic blood flow due to impaired barrier function [4, 7, 13]. The aim of the study was to determine the characteristic functional changes of BBB in patients at the acute period of ischemic stroke and to create the diagnostic criteria for the disease.

Methods

The fundamental subject matter of the study was comprehensive survey of 121 patients: 69 (57 %) male and 52 (43 %) female with first incident brain infarction at an average age of 64.4 ± 0.9 years. A control group were 20 people: 11 men and 9 women, at a mean age of 58.3 ± 0.7 years, suffering from orthopedic pathologies other than CNS lesions, systemic diseases or thermoregulation disorders, who underwent peridural anesthesia and are homogeneous by gender and age with the test group were examined.

The task was carried out according to the guidelines of biotic Helsinki Declaration of the World Medical Association (1964.)

The assessment of severity of the patients was carried out according to the level of consciousness, the presence of cerebral symptoms and the severity of neurologic deficit on the National Institutes of Health Stroke Scale (NIHSS) and the Glasgow Coma Scale (GCS.) All patients were divided into 2 clinical groups on this basis: A (n = 79) – patients

in moderate state of severity (mean NIHSS score 14.24 ± 0.29) and B (n = 42) – patients in severe condition (mean NIHSS score 23.65 ± 0.45 .)

Neurological examination of the patients included collecting complaints, medical histories of previous illnesses, data on development of the current disease, risk factors, comorbidities, previous medications and records on somatic and neurological states describing specific symptoms and syndromes.

Paraclinical examination methods included laboratory biochemical tests (complete blood count, urinalysis, blood chemistry, blood lipid spectrum, coagulate) and instrumental methods (ECG, ophthalmoscopy, lumbar puncture and measurement of CSF pressure on the first and 10th day.) CT scan of the brain was performed to confirm diagnosis for "brain infarction" and to determine specificities of focus and the presence of mass effects.

The photolorimetry test was performed using a set of Liquick Cor-ALBUMIN, manufactured product of «Cormay» (Poland) to determine levels of serum albumin. ELISA was performed using test-system («Behring Nephelometer Analyser», Behringwerke, Marburg, Germany) to determine levels of CSF albumin.

Statistical analysis of the results was carried out using the statistical analysis package «Statistica 8.0 for Windows».

Results

According to recorded data it was possible to assess the degree of damage of BBB structures, which was reflected by increasing level of albumin CSF in both groups of patients with ischemic stroke before treatment measures (Table 1). The level of albumin clearly rose with increasing severity of the patient's condition. It was displayed in both groups of patients. The general trend observed during treatment was increase in level of CSF albumin ($p > 0.05$) in all groups of patients, which reached significant levels only in B group – from 0.58 ± 0.05 to 0.87 ± 0.04 g/l.

Table 1

Dynamics of CSF albumin in varying degrees of severity (M ± m, g/l)

Time of Research	Albumin (g/l)	
	A	B
Day 1	0,44±0,06	0,58±0,05*
Day 10	0,52±0,02*	0,87±0,04* ^
Control Group	0,3±0,02	

Notes:

- * – $p < 0.05$ in relation to the control group
- ^ – $p < 0.05$ parameters between the first and 10th days



The data may indicate that although the BBB dysfunction occurs in all patients with ischemic stroke, it is less pronounced and is subject to greater therapeutic effect in patients with moderate severity. However, the dynamics of treatment shows progressive degradation of the BBB, as attested by the elevated albumin level in B group patients.

Simultaneous determination of albumin level in CSF and blood serum allowed for calculation of albumin quotient: albumin quotient

$$(Q_{alb}) = \text{CSF albumin} / \text{serum albumin} \times 1000$$

The degree of functional changes in BBB was exhibit by elevated Qalb in both groups of patients with ischemic stroke before treatment measures (Table 2.) The figures distinctly increased in patients with more severe condition as displayed in both groups of patients. Nonetheless, the dynamics of treatment shows tendency of Qalb to decrease only in A group ($p < 0.05$).

Table 2

Dynamics of Qalb in varying degrees of severity (M ± m)		
Time of Research	Q _{alb}	
	A	B
Day 1	12,27±0,15	38,59±0,37
Day 10	10,35±0,19 ^	46,84±0,78 ^
Control Group	6,8±0,02	

Notes:

1. in all cases considerably from the control group
2. ^ – $p < 0.05$ parameters between the first and 10th days

The data suggests much less functional changes in the BBB of patients with moderate severity.

The study deemed appropriate to examine the

dynamics of albumin factor in acute brain infarction by sex and age groups. The data represents in Table 3.

Table 3

Distribution of Q _{alb} dynamics by age and sex (M ± m)					
Group of Patients	Time of Research	Age			
		Women		Men	
		46-59 years	60-75 years	46-59 years	60-75 years
A	1 day	16,86±0,38	18,67±0,66	19,99±0,75^	22,11±0,95^
	10 day	19,34±0,47	20,29±0,75	22,16±0,84^	26,45±0,49^
B	1 day	17,09±0,28	18,32±0,98	20,46±0,73^	21,77±0,77^
	10 day	17,58±0,54*	17,98±0,48*	18,73±0,68*	20,88±0,61*^
Control Group		6,8±0,02			

Notes

1. in all cases significantly from the control group
2. * – $p < 0.05$ among the 1st and 2nd groups of patients on the 10th day
3. ^ – $p < 0.05$ among age groups

Analysis of the experimented patients showed significantly lower values of Qalb in both men and women aged 46-59 years compared to those aged 60-75 years. It can be explain by depletion of BBB transport systems with aging under increasing demand for vasoregulation amid concomitant vascular risk factors.

Meanwhile, significantly higher Qalb values were reveal in patients of both sexes in all age groups compared to the control group, indicating BBB dysfunction. There were no statistically significant differences between men and women observed in terms of Qalb within age groups, although slightly higher values of the index were record in

men.

Correlation analysis of interactions in the CSF protein system in patients with ischemic stroke revealed a number of features. The variation of albumin levels based on the severity of the disease showed a correlation. Thus inverse relation between the levels of albumin and total clinical score ($r = - 0.708$; $p < 0.05$) was observed. The dynamic findings of these indicators persistently led to a possible correlation, but did not reach statistically significant values ($p > 0.05$). The established inverse correlation between the levels of serum and CSF albumin levels ($r = - 0.70$) likewise did not reach statistically significant values ($p > 0.05$) during the



entire study. Elevated values of indices of BBB permeability in the development of an infarction

Conclusion

The onset of ischemic stroke characterize by significant functional change of BBB like increasing of permeability. Leading indicator is CSF albumin (34.6 %) that directly correlated with the volume of the affected area (focus more than 30 cm³) and severity of the patient's condition (more than 15 points on NIHSS scale, less than 7 points on Glasgow scale – GCS). Unfavorable prognosis

may reflect the degree of damage of membrane structures and be markers for barrier dysfunction.

was imply by further increase in levels of albumin by 1.7 times during treatment, which was observe in clinically severe patients.

Diagnostic criterion for the disease is the degree of severity of BBB dysfunction manifested by increased CSF albumin, which is directly dependent on the severity of patients and the volume of the damaged areas of the brain.

References (список літератури)

1. Ara Nazarian, F. Araiza Arroyo, Rosso C. Tensile properties of rat femoral bone as functions of bone volume fraction, apparent density and volumetric bone mineral density. *Journal of Biomechanics*. 2011; 44: 2482–2488.
2. Erdal N., Gürgül S., Demirel C. et all. The effect of insulin therapy on biomechanical deterioration of bone in streptozotocin (STZ)-induced type 1 diabetes mellitus in rats. *Diabetes Research and Clinical Practice*. 2012; 97: 461 – 467.
3. Geraets W.G.M., van Ruijven L.J., Verheij J.G.C., van der Stelt P.F. Spatial orientation in bone samples and Young's modulus. *Journal of Biomechanics* – 2008. - Volume 41, Issue 10. – P. 2206-2210.
4. Hamed E, Jasiuk I. Multiscale damage and strength of lamellar bone modeled by cohesive finite elements . *Journal of the Mechanical Behavior of Biomedical Materials*. 2013; 28: 94 – 110.
5. Lagerholm S, Park H-B, Luthman H et all. Genetic loci for bone architecture determined by three-dimensional CT in crosses with the diabetic GK rat. *Bone*. 2010; 47:1039 – 1047.
6. Sirois I, Cheung AM, Ward WE Biomechanical bone strength and bone mass in young male and-female rats fed a fish oil diet. *Prostaglandins, Leukotrienes and Essential Fatty Acids*. 2003; 68: 415 – 421.
7. Starnes JW, Neidre DB, Nyman JS. et all. Synergistic effect of exercise and statins on femoral strength in rats. *Experimental Gerontology*. 2013; 48: 751 – 755.
8. Wanyura H., Kowalczyk P., Bossak M, Samolczyk-Wanyura D. Finite element method for analysis of stresses arising in the skull after external loading in cranio-orbital fractures. *Neurologia i Neurochirurgia Polska*. 2012; 46: 344-350.

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