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Review

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The Use of Neuromarker NSE, S100-B, GFAP Proteins in the Diagnosis and Treatment of Cerebral Ischemia in Patients with Aneurysmal Subarachnoid Hemorrhage

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ABSTRACT The incidence of non-traumatic subarachnoid hemorrhage due to rupture of cerebral aneurysms and subsequent disability motivates the search for predictors of severe course and unfavorable outcome of the disease for early intensive treatment. NSE, S100-B, GFAP markers have proven themselves well for assessing the dynamics of treatment for diseases of the nervous system and detecting neurological nosologies. The use of the above proteins in aneurysmal hemorrhage opens up new perspectives in assessing the clinical status of the patient in the early stages, developing further treatment strategies, as well as helps draw conclusions about the outcome of the disease and possible disability of the patient. The studies collected in the review motivate continued research of the neuromarkers in aneurysmal hemorrhage.

Keywords: subarachnoid hemorrhage, neuromarkers of nontraumatic subarachnoid hemorrhage, S100-B, NSE, GFAP, prognostic factors of nontraumatic subarachnoid hemorrhage

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ACVA — acute cerebrovascular accident
ALS — amyotrophic lateral sclerosis
BBB — blood-brain barrier
CA — cerebral aneurysms
CNS — central nervous system
CSF — cerebrospinal fluid
CT — computed tomography
EBI — early brain injury
GCS — Glasgow Coma Scale
GFAP — glial fibrillar acid protein
GOS — Glasgow Outcome Scale
H-H — Hunt-Hess

mRs — modified Rankin scale
m-GCS — motor component of the Glasgow Coma Scale
nSAH — non-traumatic subarachnoid hemorrhage
NSE — neuron specific enolase
S100-B — protein, tumor marker
TBI — traumatic brain injury
WFNS — World Federation of Neurosurgical Societies

INTRODUCTION

Mortality from cardiovascular diseases in Russia is 517 per 1000 people per year [1]. The number of patients with the established diagnosis of "Stroke - acute cerebrovascular accident" (ACVA) in this country is about 500,000 people per year, with non-traumatic subarachnoid hemorrhages (nSAHs) accounting for 3–7% of all ACVA cases [2]. Disability of patients remains quite high, and 50% of cases end in death [3]. It has been noted that up to 85% of nSAHs occur as a result of rupture of arterial aneurysms of cerebral vessels [4].

The average age of patients with cerebral aneurysm (CA) rupture is 40–60 years. That is, this is the age of the most able-bodied group of the population, which indicates the high socio-economic significance of the problem [5]. This state of affairs motivates the search for new methods for timely diagnosis and increasing the effectiveness of treatment for aneurysmal SAH.

The search for highly selective instrumental and laboratory predictors of severe course and unfavorable outcome of the disease for early intensive therapeutic and surgical treatment is of particular importance. This group of diagnostic methods is characterized by non-invasiveness (blood is tested in vitro), high reliability, and low cost. A significant aspect is the possibility of performing them in express mode (the entire procedure can be carried out within a period of up to 40 minutes from the moment of taking biological material).

Over the past decades, a large number of articles have appeared in the literature on the use of neuron specific proteins as markers for brain injury.

NEURON SPECIFIC PROTEINS. S100B AND NSE, GFAP. DIAGNOSTIC SIGNIFICANCE

Neuromarkers perform the function of synaptic transmission, cellular recognition, and reception. Currently, more than 60 such proteins are known, which include S100B and NSE, GFAP [6].

S100 protein family was discovered by B. Moore (1965) while studying proteins in the brain and liver. The protein received the name of S100 due to its ability to dissolve in a saturated (~100%) solution of sulfuric acid [7]. At the time of the discovery of the protein, it was believed that S100 was a neuron specific protein found exclusively in nervous tissue.

Further studies showed that S100 may occur in tissues of neuroectodermal origin [8]. Up to 80% of the S100B protein contained in the central nervous system (CNS) is located in the glial cells of the CNS, the remaining 20% is directly in the neurons of the CNS, but they can also occur in neoplastic processes. Intracellularly, S100 is found in the cytoplasm and in the nucleus of neurons [9].

The half-life of the molecule averages 2.5 hours. One of the most studied functions of S100B is the attachment of ionized calcium which is necessary for the conduction of nerve impulses and the regulation of cellular protein expression in neurons [10]. However, the role of this protein in the functional systems of neurons and glial cells has not been fully established. Literary sources report the participation of S100B in calcium homeostasis, proliferation, cell differentiation and influence on the formation of the cell cytoskeleton [11–15].

In clinical practice, S100B was first used by Michetti F. (1979) when testing cerebrospinal fluid (CSF) in a patient with exacerbation of multiple sclerosis [16]. This paved the way for the study of other biological fluids: blood, urine, amniotic fluid and saliva. Protein elevation varies depending on the type of pathology and the degree of damage to the CNS [17–19]. High protein concentrations are found in Alzheimer's disease, traumatic brain injury (TBI), CNS tumors, amyotrophic lateral sclerosis (ALS), schizophrenia and ACVA [17–20]. If the presence of a neoplastic process is suspected, the

level of S100B is determined to assess the nature of the disease over time [21]. The appearance of S100B in plasma is a sign of disruption of the integrity of the blood-brain barrier (BBB), which is confirmed by a series of studies using computed tomography of the brain [22]. At the same time, the elevation of S100B in the CSF in case of the intact BBB is not accompanied by an automatic increase in its concentration in plasma [23].

One of the algorithms for the effective use of S100B in clinical practice is presented in the dissertation of E.A. Sosnovsky (2014) [24]. The author reveals the diagnostic capabilities of this neuromarker for TBI. Assessing the concentration of S100B in the blood serum in mild TBI can be an additional diagnostic criterion in the differential diagnosis between the diagnosis of "Concussion" and "Brain contusion". Assessment of the concentration of S100B in the blood serum, based on the findings of E.A. Sosnowsky, is a more sensitive method for diagnosing mild brain contusion than computed tomography (CT) of the brain. In patients with mild TBI, when the concentration of S100B in the blood serum increases, brain damage is detected on CT in 72.7%, and on MRI in 100% of cases.

Another neuromarker deserves attention: neuron specific enolase. There are three isoforms of enolase found in the human body: alpha, gamma and beta. Brain tissue contains gamma enolase which differs from the other two isoforms [25]. In the specialized literature, the name of gamma enolase is firmly established - neuron specific enolase (NSE). This name reflects the NSE content in mature differentiated neurons and neuroendocrine cells [26]. The protein was used in assessing the effectiveness of treatment for tumors in the tissues of which neuroendocrine cells are present. Such tumors include neuroblastoma, lung cancer, pheochromocytoma and others. The half-life—the time during which 50% of the protein is broken down in plasma—is 48 hours [27]. Determining the level of NSE in oncology is important for making a diagnosis, assessing the stage of the disease, and the effectiveness of the response to therapy [28]. The neuromarker is specific for many diseases of the central nervous system (CNS) [29]. NSE blood levels increase in diseases such as tick-borne encephalitis [30], cluster headache [31], migraine [32], neonatal hypoxia [33], bacterial meningitis [34], TBI [35], ischemic stroke [36], and a number of other CNS diseases.

NSE can also be found in other tissues such as skin, connective tissue. At the onset of acute CNS diseases, the concentration of NSE increases gradually in the first 24–48 hours, and its peak values are detected on average after 96 hours. In ischemic stroke, a repeated peak in the rise of NSE on days 5–7 may indicate hemorrhagic transformation of the lesion due to an additional violation of the integrity of the BBB [37]. A correlation was found between the volume of the ischemic lesion and the increase in the level of NSE in the blood plasma - the larger the volume of the lesion, the higher the concentration of the neuromarker [38].

Glial fibrillary acidic protein (GFAP) is a protein of astrocytes of the CNS, but can be found in Schwann cells of the peripheral nervous system [39–41]. GFAP is involved in the formation of the cytoskeleton, regulates cell proliferation, and ensures the functioning of the BBB [42–44]. GFAP belongs to the group of type III intermediate filament proteins [45]. To date, more than 10 GFAP isoforms have been described, but the GFAP-α isoform is used in clinical practice [46]. GFAP is a 50 kDa protein [47]. Under physiological conditions, astrocytes do not synthesize and do not allow GFAP to penetrate beyond the BBB [48].

When damage to the nervous system develops, astroglial cells respond with reactive astrogliosis, a process by which the astrocyte increase in size and express GFAP [49]. Neuronal injury and neuroinflammation activate astroglial proliferation at the site of inflammation and, as a result, GFAP synthesis increases [50]. Moderate levels of astrogliosis promote brain recovery. Excessive gliosis and associated reactions have a negative impact on neuronal and glial repair [51]. When neurons are damaged, GFAP is released from cells,

and after the BBB permeability is disrupted, it enters the blood plasma and cerebrospinal fluid [52]. In TBI, the maximum concentration of GFAP occurs 8 hours after injury, and is a predictor of the clinical outcome of the disease [53].

Currently, the high diagnostic significance of GFAP has been established in the following types of pathology: in the early stages of multiple sclerosis [54], Alexander disease [55], ischemic stroke [56], hemorrhagic stroke [57], epilepsy and psychogenic diseases [58], Parkinson's disease [59], and optical myelitis [60].

GFAP testing is used for differential diagnosis in the early stages of ischemic and hemorrhagic stroke [61]. In hemorrhagic stroke, GFAP concentration in the blood plasma increases during the first 2–6 hours of the disease. In ischemic stroke, the protein remains within the reference values [62]. GFAP elevation in hemorrhagic stroke develops as a result of damage to neurons by the hematoma and its breakdown products, and also as a consequence of the destructive effect of increased intracranial pressure [63].

In ischemic stroke, vessel occlusion, necrosis and lysis of brain tissue cells begin after 6–12 hours, and from this time, the content of GFAP in the blood plasma increases and reaches a peak at 48 hours from the onset of the vascular accident [64].

Exceeding of the reference GFAP values is also detected in grade II–IV astroglial tumors [65].

S100B, NSE, GFAP IN ANEURYSMAL SUBARACHNOID HEMORRHAGE

The potential for using the neuromarkers in non-traumatic hemorrhage is high, as demonstrated by several studies [66–68]. The following reference values were used in the studies: no more than 0.12 μg/l for S100B; no more than 0.49 μg/l for GFAP; and no more than 21.5 μg/l for NSE [69–70]. In the article by Vos P.E. et al. (2006) [68], the researchers used the Glasgow Outcome Scale (GOS), World Federation of Neurosurgical Societies (WFNS) [72], and Fisher [73] scales. Blood sampling was carried out daily, starting from the day of admission to the hospital and up to the 9th day inclusive. The study group included 67 patients. According to data presented by Vos P.E., patients with hemorrhage detected on CT and a higher Fisher score had higher blood levels of S100B and GFAP. During the first 56 hours after aneurysmal hemorrhage, NSE remains within normal limits and is independent of hematoma volume [74]. However, NSE testing was shown to be effective as a marker for secondary ischemic complications [75] caused by vasospasm.

The average values of neuromarkers in the blood plasma upon admission of a patient with SAH were increased (S100B – by 2.8 times; GFAP – by 1.8 times). Higher concentrations of S100B, GFAP, and NSE correlated with WFNS scores. The mean serum S100B, GFAP (but not NSE) values were higher in patients with increased intracranial pressure. Non-traumatic SAH results in the loss of structural integrity of glial and neuronal cells, and the release of specific proteins into the bloodstream. The degree of glial protein release appears to reflect the clinical condition of the patient.

These data are consistent with a study by Wiesmann M. (1997), which established a correlation between serum S100B levels and the Hunt & Hess score at the time of hospitalization [76].

An article by Kaneda K. (2010) [66] stated S100B, NSE, GFAP as the most accessible proteins for clinical use [77]. The study included 32 patients whose condition was assessed using GOS, WFNS, and Fisher scales. Neuromarkers were collected on the 3rd, 7th and 14th days. After 6 months from the onset of the disease, the patient's condition was evaluated using GOS. Proteins were tested in cerebrospinal fluid because, according to the authors, changes in plasma may lag behind changes in cerebrospinal fluid [78, 79]. The authors conclude that the concentration of S100B and GFAP is higher in groups with 1–4 GOS score than in groups with 5 GOS score. It is indicated that delayed vasospasm is accompanied by an increase in S100B levels 4 days after its onset [80]. S100B and GFAP are part of astroglial cells, which are most susceptible to ischemic damage [81, 82]. The authors point out that the level of S100B and GFAP correlates with the outcome of the disease and neurological deficit [66, 83].

In the study by Kedziora J. (2021) [67], the assessment of S100B, NSE, GFAP levels was carried out in parallel with the evaluation of 55 patients' condition using the following scales: GOS, WFNS, Fisher, and APACHE II. Biomaterial was collected more often than in other studies: on the 1st, 2nd, 3rd, 4th, 5th, and 6th days after non-traumatic subarachnoid hemorrhage (nSAH). As in the article by Kaneda K. (2010) [66], patients were divided into two groups: with a favorable outcome (4-5 GOS score - 24 patients), and an unfavorable outcome (1-3 GOS score - 31 patients). A negative correlation was found between GOS score (at the time of discharge and 6 months later), S100B level on days 1–6, and NSE level on days 1–5. According to the researchers, S100B has a greater diagnostic value. They note the correlation of S100B and NSE with the GOS score at the time of transfer from intensive care in the acute period of nSAH, which makes it possible, according to the authors, to classify these indicators as predictors of early clinical outcome.

There was no correlation between the GOS score and GFAP. When the S100B concentration was more than 0.7 μg/L, the outcome was 100% fatal. The authors conclude that the issue of determining the timing of the highest predictive value of biomaterial collection for neuromarker testing remains a matter of debate.

In articles by various authors, testing of neuromarkers was carried out at different time periods, starting from the first day of the development of vasospasm, and then daily for 1–2 weeks [84, 85]. It should be noted that works on the use of neuromarkers in SAH were performed on the basis of one clinical center; we did not find studies that included observations from several research centers at once [67].

In addition to articles that included the study of the markers in a combination of NSE, S100B, GFAP, works were identified on determining the concentration of only one biomarker in SAH, and in various combinations [86–91].

Thus, in the publication of Nylen K. (2007) [88], 116 patients with aneurysmal SAH were examined with the interpretation of the same scales as in the above studies [66, 67, 68], but in comparison only with the level of one neuromarker - GFAP. GOS score was assessed 1 year later. Protein concentrations were measured during the first 15 days. It was possible to carry out the follow-up after 1 year in 94 out of 116 patients. It is noted that the highest GFAP values were obtained in patients with Fisher IV. Maximum protein concentrations were observed during the first 5 days followed by a gradual decrease. On the 3rd day from the onset of the disease, the correlation of the neuromarker blood level (above 0.15 μg/l) with an unfavorable outcome was 86%.

The work by Weiss N. (2006) [90] included 74 patients with non-traumatic SAH. The criteria for inclusion in the study were as follows: age over 18 years, no more than 48 hours from the onset of hemorrhage. The neurological status and clinical condition of the patients were assessed using the WFNS scale and GCS. Changes in brain CT data were interpreted using the Fisher scale. Clinical outcome was considered by the authors using GOS at the time of transfer from intensive care, and 6 months later. The researchers determined S100B values. The results were obtained from the 1st day of admission to the 8th day inclusive. S100B concentration in the deceased increased from the 1st day, and every day. In those who were transferred from the intensive care unit before day 8 (values below 0.4 μg/L), such results were not noted. The authors conclude that changes in S100B obtained over an 8-day period correlate with WFNS and Fisher scores, as well as GOS score 6 months later. The highest S100B concentrations were detected in patients with the ruptured middle cerebral artery aneurysm. Lower concentrations were obtained in patients with aneurysm rupture in the basin of the anterior cerebral artery/anterior communicating artery.

The data presented are comparable with publications on the influence of aneurysm localization on the clinical outcome assessed by GOS [92]. In a retrospective work, Kopera M. (1999) [91] found that in 32% of those examined with an aneurysm of the middle cerebral artery, an

intracerebral hematoma as a result of its rupture was detected, which is an unfavorable factor.

S100B values in the study by Weiss N. (2006) [90] correlated with troponin I values: in the examined patients with high initial troponin I levels (0.10 g/l), correspondingly high S100B levels, increasing over time, were recorded.

In the work by other authors, high troponin levels are also associated with the occurrence of neurological deficits [93–94]. This confirms that SAH is a multiorgan dysfunction, the consequences of which may affect not only the nervous system [95].

Plasma S100B concentrations decreased significantly more rapidly in patients who underwent endovascular treatment compared with those treated with clipping. These data are consistent with the results of the International Subarachnoid Aneurysm Trial [96]. Some authors suggest that during open vascular neurosurgery, the S100B content increases due to nonspecific secretion from astrocytes [97]. According to the authors, S100B values for 8 days of observation are equivalent in patients with vasospasm (n=27; 36%) and without it (n=47; 64%). In 17 subjects with vasospasm, average daily concentrations of S100B below 0.4 μg/L were recorded. Of this subgroup of 17 people, none of the cases were fatal. In another subgroup of 10 people with vasospasm (S100B above 0.4 μg/L), there were 5 deaths. The authors conclude that S100B concentrations greater than 0.4 μg/L are predictive of poor clinical outcome in 6 months. Weiss N. et al. [90] point out that due to the short half-life of the S100B protein (about 2 hours), it cannot be excluded that S100B peak values could have been missed by the researchers.

Balança B. (2020) [89] assessed S100B on admission and after the first 24 hours. 81 patients were examined and treated. Inclusion criteria for the study were the presence of aneurysmal hemorrhage confirmed by CT data and age over 18 years. The WFNS, GCS, Hijdra and Fisher scales were used. The article introduces the concept of early brain injury (EBI), first described in 2004 by Kusaka G. [98]. The patients were divided into three subgroups: mild EBI (with minor neurological deficit, without impairment of consciousness), moderate EBI (with moderate neurological deficit and loss of consciousness, which soon recovered), high EBI (with prolonged loss of consciousness). In order to apply the above approach, an early assessment of the clinical outcome was carried out on the 3rd day of the study, for which the Glasgow coma scale (GCS) was used, namely the motor component of the scale - motor GCS (mGCS). Based on the m-GCS values at admission to the intensive care unit and on day 3, the authors identified three groups: mild EBI group for patients with m-GCS score of 6 at the time of admission and on day 3; moderate EBI group for patients with m-GCS score of less than 6 on day 1 and equal to 6 on day 3; and high EBI group for patients with m-GCS score of less than 6 on day 3, regardless of the m-GCS value at admission. At the time of admission, 56 out of 81 subjects had m-GCS score of 6. With m-GCS score of 6 on days 1 and 3, 53 patients were classified into the mild EBI group, and 16 into the moderate EBI and high/severe EBI group. S100B testing material was taken from the patients upon admission to assess the diagnostic ability to predict early clinical outcome on day 3 using the m-GCS score. Mean S100B values were higher in the high/severe EBI group (0.467 μg/L) than in the moderate EBI group (0.134 μg/L) and in the mild EBI group (0.098 μg/L). S100B values determined on day 1 using the modified Rankin scale (mRs) at the time of transfer from the intensive care unit were also assessed. The mean S100B protein value was higher in the group with severe disability (mRs score 5, 0.340 μg/L) or death (mRs score 6, 1.5 μg/L) compared to those with little or no disability (mRs score less than 2, 0.093 μg/L). The researchers conclude that the maximum serum S100B concentration on admission and after the first day predicts the severe consequences of early brain injury [99].

Tawk R.G. et al. (2016) [85] studied the first NSE elevation in 71 patients with the correlation of outcome according to modified Rankin score (mRS) after 6 months. The researchers identified an NSE limit of 15 μg/L, at which the probability of an

unfavorable outcome correlated with the WFNS, H-H, and initial GCS and mRs scores. The subjects were divided into three groups: NSE up to 15 μg/l (within normal limits), from 15 μg/l to 30 μg/l, and more than 30 μg/l. The authors found that 2 groups with the NSE level of more than 15 μg/L at the time of inclusion in the research had worse outcome when assessed by mRs, WFNS, H-H and GCS. These data are promising; however, additional research is necessary, since according to a number of authors [100–101], elevated serum NSE was found in cases of severe damage to internal organs.

Quintard H. (2016) [86] believes that an excess of the S100B level on the 5th day of the disease above 0.13 μg/L is an independent factor of unfavorable outcome 6 months after nSAH. It was indicated that on the 7th day in the group of unfavorable outcome there was a repeated rise in the neuromarker, which can be regarded as a result of secondary complications. The author suggests that higher S100B values are due to ischemic lesions. However, this issue is not discussed in more detail in this article.

Abboud T. (2017) [87] presented data on the possibility of early prediction of outcome using NSE and S100B in patients with GOS 1–3. The work included 43 patients. The author showed that the determination of proteins during the first 3 days is sufficient for the subsequent prognosis of the unfavorable outcome. Referring to the work by P. Sancez-Pena (2008) [102], which assessed the average S100B value for 15 days from the onset of aneurysmal SAH, the researcher concluded that the mean S100B concentration exceeding the 0.23 μg threshold during the first two weeks was a predictor of poor outcome. Abboud T. [87] suggests a diagnostic window in the first 3 days after the onset of nSAH. The author argues that mean S100B values greater than 1.888 μg/L or NSE values over 19.95 μg/L are a definite signal of poor clinical outcome.

The article by Ramont L. (2005) describes the effect of hemolysis [103]. Red blood cells contain one of the NSE isoforms. In the case of hemolysis, laboratory values may not reflect the actual clinical picture. By measuring NSE in biological media, Ramont L. et al. recommend to take into account possible hemolysis.

Oertel M. (2006) demonstrates the relationship of S100B and NSE levels with vasospasm [104]. But the article does not contain data on the real correlation between the markers and the resulting vasospasm. The study included 51 patients. Proteins in blood plasma were measured in the first 3 days from the onset of the disease. Clinical outcome – 6 months after the onset of the disease. The type of surgical intervention did not affect the results of measuring neuromarkers: endovascular intervention/clipping: S100B 0.75±1.8 μg/l and 0.7±0.9 μg/l, NSE 13.9±15.1/8, 7±9.3 μg/ml, respectively. Vasospasm developed in 26 patients included in the study. Emphasis is placed on developing secondary complications in those patients [105]. Clinically significant vasospasm causes secondary ischemic complications in 20–30% of surviving patients with aneurysmal hemorrhage [106]. The group of those patients seems to be the most interesting for the use of neuromarkers, given that the search for drugs to prevent the development of vasospasm is very active. In the study results, the authors emphasize that vasospasm developed mainly in the group of patients with low (less than 0.12 μg/l) and medium (0.12–0.99 μg/l) S100B values.

Neither author describes CT perfusion in the context of using neuromarkers as predictors of vasospasm and clinical outcome. A study by Lefournier V. [107] (2016) indicated the ability of CT perfusion to accurately detect clinically significant hemodynamic changes and vasospasm. A more detailed research by Sun H. [108] concluded that all six CT perfusion parameters can be used to diagnose secondary ischemic complications on days 4–6.

The S100B neuromarker is extremely promising as an early prognostic factor for poor clinical outcome in aneurysmal hemorrhage. The use of protein markers as predictors of early complications of nSAH in patients with ruptured aneurysms was not sufficiently studied.

The utility of GFAP as an early predictor for clinical outcome has not been well researched.

Available evidence suggests the likely use of GFAP as an early predictor for poor outcome. However, the authors emphasize the need to carry out new trials with a larger sample and a more detailed study of the neuromarker's behavior in nSAH. Difficulties in using this neuroprotein in clinical practice are also associated with the high cost of its testing.

The literature sources we found differ significantly in assessing the diagnostic significance of NSE for early diagnosis of the course of the disease. Many researchers point out the impossibility of using NSE as a predictor for early clinical outcome, in contrast to S100B, GFAP. Others believe it is possible to use NSE in predicting clinical outcome. We have not found any information on the use of this neuromarker as an early predictor for secondary complications of nSAH in aneurysmal hemorrhage. This motivates new studies to obtain data on the feasibility of using NSE in the early period of nSAH.

CONCLUSION

The works discussed in this literature review do not answer the question of whether it is worth determining all three proteins simultaneously or only one of them should be used. Further research with a larger sample and criteria is needed. Works reflecting the interaction of the three proteins open up opportunities for a more detailed study of each of them and the correlation of each marker with the outcome. The obtained values in the studies are not interpreted in relation to the secondary complications that arise. This opens up the prospect of studying the significance of changes in neuromarker concentrations for the diagnosis and prediction of secondary complications in clinical practice.

The reviewed works did not take into account hemodynamic changes during the acute period of subarachnoid hemorrhage. There is no data on the correlation of vasospasm with neuromarker levels and clinical outcome. Instrumental studies such as CT perfusion reveal abnormalities in the hemodynamics of the brain, and a joint study with laboratory changes in neuroproteins during nSAH opens up new opportunities in understanding the mechanisms of vasospasm, the possibilities of its prevention, reducing mortality and disability. This is a motivating factor for further research of the neuromarker informative value in aneurysmal hemorrhage.

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