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MOLECULAR BIOMARKERS OF COGNITIVE IMPAIRMENT IN ISCHEMIC STROKE

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МОЛЕКУЛЯРНЫЕ БИОМАРКЕРЫ КОГНИТИВНЫХ НАРУШЕНИЙ ПРИ ИШЕМИЧЕСКОМ ИНСУЛЬТЕ

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At the review systematize modern ideas about biomarkers of cognitive impairment in ischemic stroke were performed. The metabolic changes underlying the ischemic cascade were combined into three basic processes: excitotoxicity, oxidative stress, and inflammation. Studies of the possible relationship between key metabolites and mediators of acute ischemic stroke and the state of higher cortical functions are analyzed. The search for sensitive and specific biomarkers of cognitive impairment will make it possible to predict the rehabilitation potential and will promote the earliest possible start of cognitive rehabilitation measures. Besides, it will enable the development of modern methods of drug correction and prevention of vascular dementia.

Keywords: higher cortical functions, cognitive impairment, biomarkers, ischemic stroke, excitotoxicity, oxidative stress, inflammation

Систематизированы современные представления о биомаркерах когнитивных нарушений при ишемическом инсульте. Метаболические изменения, лежащие в основе ишемического каскада, объединены в три базовых процесса: эксайтотоксичность, оксидативный стресс и воспаление. Проанализированы исследования, в которых определяется взаимосвязь ключевых метаболитов и медиаторов острого периода ишемического инсульта с состоянием высших корковых функций. Поиск чувствительных и специфичных биомаркеров когнитивных нарушений позволит прогнозировать реабилитационный потенциал и будет способствовать максимально раннему началу мероприятий когнитивной реабилитации. Кроме того, определяется возможность разработки патофизиологически обоснованных методов медикаментозной коррекции и профилактики сосудистой деменции.

Ключевые слова: высшие корковые функции, когнитивные нарушения, биомаркеры, ишемический инсульт, эксайтотоксичность, оксидативный стресс, воспаление

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BDNF – Brain Neurotrophic Factor
D-serine – the right-rotating optical isomer of serine
ESR – Erythrocyte Sedimentation Rate
IL – Interleukin
NMDA-receptors – N-methyl-D-aspartate receptors
NR2-peptide – N-terminal domain of NMDA receptor
RAGE-receptor – Advanced Glycation End Products receptor
TNF-α – Tumor Necrosis Factor

Poststroke cognitive disorders are moderately expressed in 37–71 % of observations, and in 4–40 % of cases reach the degree of dementia [1]. At the same time, they are pathogenetically and clinically heterogeneous, which affects their curability and prognosis [2]. The study of cognitive status by traditional neuropsychological methods in the acute period of stroke is difficult due to the severity of patients' condition, misinterpretation of testing results is possible in patients with apathy (20–25 % of observations), depression (30–40 % of observations), anxiety disorders [3]. All this dictates the need to search for sensitive and specific biomarkers to predict the development of poststroke cognitive impairments. M. Riverol and co-authors have combined the criteria inherent in the ideal biomarker: specificity for the disease, ability to reflect the severity of its course and effectiveness of treatment, economic accessibility, and minimal invasiveness [4, 5]. Metabolomics is a new branch of knowledge acting by measuring large arrays of metabolites with low molecular weight in biological media (liqueur, blood plasma, urine) and tissues of the body [6]. To date, data on the links of metabolic changes with cerebral ischemia has been accumulated.

Exaytotoxicity markers. Excitotoxicity is a universal phenomenon of the second nerve cell damage caused by hyperproduction or reduction of the reuptake rate of excitation neurotransmitters [7]. The essential, exciting transmitter is glutamate. In a healthy organism, glutamate provides a realization of many cognitive processes, among which are training and consolidation of memory trail. Persistent activation of NMDA-receptors is a universal link to the pathogenesis of both acute cerebral ischemia and dementia of various etiologies [8, 9]. Data on the dynamics of glutamate concentration in the blood plasma in the acute stroke period are contradictory. Some authors reported an increase in glutamate levels [10]; others noted that there was no increase in its concentration, explaining this phenomenon with low permeability for the hematoencephalic barrier mediator [11]. There was revealed a rise in the level of glutamate-glutamine precursor in the acute period of ischemic stroke, and its degree correlated with the severity of cognitive impairments [10]. This allowed suggesting glutamine as a potential biomarker of poststroke cognitive deficiency. It was revealed that a fragment of NMDA-receptors NR2-peptide in the first hours of stroke is fragmented by serine protease and enters the blood plasma, where it is possible to determine it by rapid methods [12].

D-serine, involved in the norm in the implementation of higher cortical functions, is a coagonist of NMDA-receptors. However, in cerebral ischemia, excessive formation of D-serine from L-serine with the help of serine racemase enzyme aggravates excitotoxicity, and some authors consider inhibition of serine racemase as a promising mechanism of neuroprotection, which allows, among other things, to reduce the severity of cognitive deficiency [13].

Oxidative stress markers. Oxidative stress-cell damage due to oxidation processes involving reactive oxygen forms [6, 14]. As a result, increased concentrations of oxidation products are recorded in the plasma. The mechanisms of lipid peroxidation during acute ischemic stroke were studied in a sufficiently deep way; a study involving 3726 patients showed that a high level of oxidized lipoproteins of low yield correlates with a pronounced cognitive deficiency [15]. According to other data, the estimation of the dynamics of oxidized modifications of proteins (the primary ketone and aldehyde derivatives of dinitrophenylhydrazones) can also serve as a biomarker for the prediction of poststroke neuropsychological impairments [16]. The study of the concentration of malondialdehyde and 8-hydroxydeoxyhanosine – common products of lipid and deoxyribonucleic acid oxidation – demonstrated a significant excess of their level in observations with cognitive impairments [17]. A more detailed assessment of their role as biomarkers of cognitive deficiency is required. One of the key mediators of impairment of the integrity of the hematoencephalic barrier and hemorrhagic transformation is matrix metalloproteinase-9. Its transition to the active form as a result of the proteolytic splitting of the predecessor molecule is carried out due to oxidative stress [6]. As a result of studies of brain tissue, and a liqueur of patients who have vascular dementia, a significant increase in the level of this mediator was found [18]. The works on the relationship between the concentration of matrix metalloproteinase-9 and poststroke cognitive deficiency are few. However, the analysis of 558 observations with ischemic stroke revealed that its high levels on the first day after cerebral circulation impairment correlate with impairments of higher cortical functions [19]. Probably, the excess activity of matrix metalloproteinase-9 contributes to proteolytic degradation of the hematoencephalic barrier and subsequent diffuse damage to the white matter of the brain [20]. Hyperhomocysteinemia is not only a recognized risk factor for ischemic stroke but also a marker of brain endothelial damage during acute ischemia [6, 21]. The connection between the level of homocysteine in acute stroke and the risk of vascular dementia is proved [22]. An important role is given to post-translational modification of proteins called homocysteinylation, and impairments of formation of astrocytic contacts with capillaries, which leads to ionic and osmotic imbalance [22]. Folic acid, remethylating homocysteine in methionine, was proposed as a biomarker of ischemic stroke [23]. The effect of its concentration in the acute ischemia period on the further state of cognitive functions is not fully determined, but it is proved that its deficiency in the poststroke period reliably correlates with the deficiency of higher cortical functions [22, 24].

Markers of inflammation. Inflammatory response induced by impaired cerebral circulation causes an increase in the production of pro-inflammatory cytokines activating indolamine-2,3-dioxygenase; this enzyme causes a decrease in concentrations of tryptophan AA and kynurenine hyperproduction [6]. Growth in the concentration of kynurenine metabolites and exhaustion of tryptophan is a marker of adverse prognosis of ischemic stroke. Low tryptophan level is associated with a significant cognitive deficit in Alzheimer's disease [25]. A similar study conducted with the participation of stroke patients showed a link between increased kynurenine to tryptophan ratio and the degree of severity of poststroke cognitive impairment [26]. A possible explanation of this phenomenon is hyperproduction of toxic metabolites of kynurenine, such as quinoline, hydroxyanthranyl, and kynurenic acid. These compounds can interact with NMDA-receptors, which confirms the unity and interdependence of the fundamental processes of the ischemic cascade. Attempts of pharmacological correction of kynurenine metabolism for the prevention of impairments of higher cortical functions are carried out [26, 27]. The inflammatory response also modifies the metabolism of phospholipids: phosphatidylethanolamine, phosphatidylcholine, and lysophosphatidylcholine [6]. Their plasma concentration is reduced in chronic cerebral ischemia, as well as in Alzheimer's disease, but with acute ischemic damage it may increase [28]. A stable relationship between the level of lysophosphatidylcholine (18: 2) and the degree of severity of poststroke cognitive deficiency was described [9], but further in-depth studies

are needed to recommend this metabolite for use as a biomarker. Regulation of the inflammation process is carried out by the whole ensemble of cytokines. It was revealed that low level of IL-10 and IL-6, as well as the dominance of IL-1β in liqueur are predictors of stable cognitive status; high level of IL-10 in liqueur, as well as prevalence of IL-10 over IL-1β in plasma is a predictor of positive dynamics; prevalence of IL-1β over IL-10 in plasma is a marker of possible progression of cognitive impairments [29]. Another study showed that high levels of IL-8 in plasma were independently associated with early formation of poststroke cognitive deficiency, and elevated IL-12 concentrations were associated with gradual cognitive decline [29]. These compounds, however, can only be used as biomarkers in combination with other indicators due to their low specificity. Several studies have shown a link between poststroke cognitive deficiency and the level of C-reactive protein, as well as ESR [28, 30]. Prognostically unfavorable role of high concentration of rheumatoid factor in acute ischemia for formation of subsequent cognitive deficiency was also determined [31]. The hypothesis about the effect of inflammation intensity on higher cortical functions needs to be further checked; it seems promising to develop preventive measures aimed at this link of pathogenesis.

The biochemical commonality of poststroke cognitive impairments and Alzheimer's disease. Often stroke is the cause of decompensation of a long-running neurodegenerative process, and poststroke cognitive impairments are nothing but a manifestation of Alzheimer's disease [1]. There is a certain commonality of the pathogenesis of these diseases: on the one hand, risk factors of cerebral circulation contribute to amyloidogenesis, on the other hand, amyloid angiopathy inherent in Alzheimer's disease in itself increases the risk of stroke [2]. It is proved that the plasma level of amyloid β 40 increases in vascular cognitive impairments; the correlation between the rise in its concentration in blood plasma during the acute stroke period and the degree of severity of neurological impairments was revealed [32]. All this makes it possible to consider β-amyloid as a potential biomarker of the development of mixed cognitive impairments during the acute stroke period. It was established that the level of amyloid β 40 in liqueur negatively correlates with the state of higher cortical functions [33]. It was suggested that the fraction β 40 is related to vasomotor impairments in acute ischemia, while amyloid β 42 is specific to neurodegenerative processes [34].

Neurospecific biomarkers. Determination of concentration of neurospecific biomarkers in different biological media is a promising direction in early diagnosis of ischemic stroke. Acute ischemic damage to the brain leads to leakage of neurospecific proteins into liqueur and further into plasma. One of the most studied is protein S100B, belonging to the group of calcium-binding proteins [35]. The concentration of S100B increases in plasma and liqueur in the first hours after stroke. Some researchers suggested the mechanism of protein participation in the development of cognitive deficiency by activating the RAGE-receptor of the final products of glycosylation and the subsequent increase of the expression of TNF-α [35]. Attempts were made to determine the relationship between the concentration of S100B during carotid endarterectomy and the subsequent cognitive deficiency, but the degree of correlation did not reach the expected level [35]. In the experiment, transgenic mice with increased production of S100ß were characterized by a decrease in short-term memory, impairment of visual and spatial gnosis, and attention [36]. As a fundamentally new biomarker of impairments of higher cortical functions can be considered protein S100A9: it was revealed that it's blocking in observations with Alzheimer's disease contributed to the partial restoration of cognitive abilities [37].

Further study of the S100A9 in the context of ischemic stroke is required. Neuronspecific enolase is a tissue isoform of an enzyme involved in glycolysis processes [38]. It is assumed that measuring the level of this enzyme can be informative in terms of predicting post-stroke cognitive impairments, but it is necessary to have a deeper understanding of its kinetics in acute ischemia period. Considerable attention is paid to the determination of levels of neurotrophic factors. In the observations with severe craniocerebral injury, the relationship between rehabilitation potential and the concentration in plasma of the brain neurotrophic factor (BDNF) was found [39]. The introduction of exogenous BDNF in ischemic stroke, Parkinson's disease, and Alzheimer's disease, according to some reports, improves the cognitive status of patients; however, information on the direction of the dynamics of the postischemic expression of BDNF is contradictory.

Other potential biomarkers. The independent predictor of the formation of postischemic cognitive impairments is, according to the results of many studies, the precursor of vasopressin copeptin [40]. A-1-antitrypsin and plasminogen-1 activator inhibitor are proposed as markers of vascular dementia [30]. There was an increase in the ratio of α-1-antitrypsin to creatinine in urine in patients with postoperative cognitive deficiency [41]. The possibility of application of 6-sulfaoxymelatonin and other melatonin metabolites as biomarkers of impairment of higher cortical functions is being studied. A link was demonstrated between low triiodothyronine levels in the acute period and cognitive deficiency a month after a vascular disaster [42]. Attempts are made to use polymorphism of specific genes, such as presenilin and apolipoprotein E, involved in the excretion of amyloid, to predict poststroke cognitive impairments [30]. Finally, the evaluation of peripheral microRNA profiles, non-coding small molecules regulating gene expression, seems to be a promising method. It was found that microRNK-31, -93, -143, and -146a expression profile can serve as a non-invasive biomarker for the diagnosis of Alzheimer's disease [30]. In one of the studies, microRNC-132 was proposed as a predictor of adverse cognitive outcomes in ischemic stroke [43].

Conclusions. Thus, to date, there is no sufficiently sensitive and specific biomarker of cognitive impairments in ischemic stroke. However, a large number of modern studies on this issue, the variety of compounds proposed for solving this problem, allow us to hope for future success. Application of a complex of several biomarkers, development of panels to determine the degree of risk of cognitive deficiency, a competent combination of biochemical technologies with the interpretation of results of neuropsychological testing will increase the accuracy of predicting poststroke cognitive impairments.

Disclosures:
The authors declare no conflict of interest.

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EXTRACTION OF TEXTURE FEATURES FROM MEDICAL IMAGES: OSTEOARTHRITIS CASES REVIEW

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ВЫДЕЛЕНИЕ ТЕКСТУРНЫХ ОСОБЕННОСТЕЙ ДАННЫХ ИЗ РЕНТГЕНОВСКИХ ИЗОБРАЖЕНИЙ ПРИ ОСТЕОАРТРОЗЕ

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Texture features of osteoarthritis quantitatively represent patterns of interest in image analysis and interpretation in medicine. Texture features can widely vary so that the analysis can lead to interpretation errors and undesirable consequences. In such cases, finding of informative features becomes problematic. In medical imaging, the texture features of bones were useful for representing variations in patterns of pixel intensity, which were correlated with pathological changes. In this paper, we review existing approaches to extracting the texture features and conclude on usability, including machine learning.

Keywords: texture features, osteoarthritis, medical imaging, pattern recognition, machine learning

Точная визуализация и интерпретация рентгенологической картины текстуры остеоартроза представляет интерес в современных условиях. Особенности изменений текстуры костной ткани могут сильно варьировать, и поэтому проводимый компьютерный анализ может приводить к ошибкам в интерпретации данных и к неправильной постановке диагноза. В таких случаях поиск информативных признаков становится проблематичным. В медицинской визуализации особенности текстуры строения кости чрезвычайно важны для представления вариаций паттернов