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CENTRAL NERVOUS SYSTEM DAMAGE MARKERS IN CHILDREN: CURRENT STATE OF THE PROBLEM

© M.S. Panova, A.S. Panchenko

Chita State Medical Academy, Ministry of Healthcare of the Russian Federation, Chita, Russia

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Pathology of the central nervous system (CNS) occupies one of the leading places in the structure of childhood morbidity and mortality. In the modern world the diagnosis of central nervous system diseases is based not only on the a thorough history, identification of certain neurological symptoms during an objective medical examination of the child and data from various neuroimaging methods, but also on the use of laboratory research methods with the identification of specific markers which indicate a pathological process occurring in the tissues of the brain and spinal cord. The article presents modern data on the biochemical parameters indicating damage to the nervous tissue, as well as their role in conditions of homeostasis and the prospects for further research. We analyzed the latest domestic and foreign literature on the properties and role of such indicators as neurotrophic growth factor, vascular endothelial growth factor, monocytic chemotactic protein, trigger receptor expressed on myeloid cells-1, trigger receptor expressed on myeloid cells-2, transforming growth factor, fractalkin, a nerve growth factor, which is a promising direction in the study of damage to nerve tissue. We can conclude that a study of the level of these markers will help diagnose the presence of damage to the nerve tissue, its severity, and therefore, select the right individual therapy for each specific child, thereby preventing the development of severe neurological consequences.

Keywords: neurodamage; children; neurotrophic growth factor; vascular endothelial growth factor; monocytic chemotactic protein; trigger receptor; transforming growth factor; fractalkin; nerve growth factor.

МАРКЕРЫ ПОВРЕЖДЕНИЯ ЦЕНТРАЛЬНОЙ НЕРВНОЙ СИСТЕМЫ У ДЕТЕЙ. СОВРЕМЕННОЕ СОСТОЯНИЕ ПРОБЛЕМЫ

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Федеральное государственное бюджетное образовательное учреждение высшего образования «Читинская государственная медицинская академия» Министерства здравоохранения Российской Федерации, Чита

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В структуре детской заболеваемости и смертности патология центральной нервной системы занимает одно из ведущих мест. В современном мире диагностика заболеваний нервной системы основывается не только на тщательном сборе анамнеза, выявлении определенных неврологических симптомов при объективном обследовании ребенка и данных различных методов нейровизуализации, но и использовании различных лабораторных методов исследования с определением специфических маркеров, которые указывают на патологический процесс, происходящий в тканях головного и спинного мозга. В статье представлены современные данные отечественных и зарубежных литературных источников о биохимических показателях, указывающих на нейроповреждение, а также их роль в условиях гомеостаза и перспективы дальнейшего исследования. Изучение таких маркеров, как нейротрофический фактор роста, сосудистый эндотелиальный фактор роста, моноцитарный хемотаксический протеин, триггерный рецептор, экспрессируемый на миелоидных клетках-1, триггерный рецептор, экспрессируемый на миелоидных клетках-2, трансформирующий фактор роста, фракталкин, фактор роста нервов является перспективным направлением в диагностике повреждения нервной ткани. Определение уровня этих маркеров у пациентов позволит выявлять наличие повреждения нервной ткани, его степень выраженности, а следовательно, подобрать правильную индивидуальную терапию для каждого конкретного ребенка, тем самым предупреждая развитие тяжелых неврологических последствий.

Ключевые слова: нейроповреждение; дети; нейротрофический фактор роста; сосудистый эндотелиальный фактор роста; моноцитарный хемотаксический протеин; триггерный рецептор; трансформирующий фактор роста; фракталкин; фактор роста нервов.

Among the causes of childhood disability, the attack rate of central nervous system (CNS) affections is 50%, of which 40% are children with disabilities after a perinatal affection of CNS (PACNS) [4]. The occurring neurological symptoms from brain affection lead to a social maladaptation of children and, consequently, a decrease in their quality of life at an early age. However, the consequences of a hypoxic brain injury may also appear at an older age (after 7 years) [11, 33]. In this regard, children with a burdened history (for example, intrauterine hypoxia, asphyxia during childbirth, etc.) should be more thoroughly and objectively examined not only to identify abnormalities in neuropsychological development at early stages but also for various markers of CNS injury. Early laboratory diagnostics of nerve tissue damage will allow the development of an individual approach to the treatment and rehabilitation of children with PACNS.

When developing a pathogenetically based prevention and correction of post hypoxic states, it is important to carefully study the processes of neuron injury and identify factors that protect them from the destructive effects of hypoxia. Nerve tissue is capable of regeneration. Neurotrophins are one of the substances that contribute to this process [4, 30].

A neurotrophic growth factor (Brain-Derived Neurotrophic Factor, BDNF) is a substance expressed in both the developing and mature brain. BDNF is synthesized in neurons, platelets, astrocytes, microglia, endothelium, and liver cells [1, 4, 5]. On the first day after a stroke, rare diffusely located astrocyte-like cells accompanying microvessels are detected in the nodules [13]. Pyramidal neurons in deeper layers have an increased immunoreactivity to BDNF. At the end of the third week, gliosis and areas of necrotic brain tissue resorption are formed. In the penumbra and surface layers, the number of BDNF-immunopositive neurons increases. A cerebral ischemia model in rats showed an increased BDNF content in the hippocampus 12–24 h after an 8-min cardiac arrest from asphyxia, and in the black substance after 1 week [1, 3, 5, 9]. A decrease in BDNF is associated with the development of various neurodegenerative diseases. It determines the participation of cannabinoids in dopamine reactions, responsible for the plasticity of thinking and associative learning [9]. Young people, due to high regenerative abilities, have decreased cognitive functions that are correlated with an increase in BDNF levels. In children with cerebral palsy, the more the expression of their motor disorders, the lower their BDNF level with a significant increase after the rehabilitation, showing that it is involved in restoring brain functions [12]. However, neurotrophins are not widely used in clinical practice because there is no way to deliver exogenous neurotrophic factors to the damaged locus of the brain: their large molecules cannot penetrate the blood-brain barrier and are immediately inactivated by blood enzymes.

Nerve Growth Factor (NGF) is a neurotrophin that plays a role in cell death, survival, angiogenesis, inflammation, and tissue remodeling [10, 31]. When vascular endothelial cells are damaged by oxidative stress, NGF shows angioprotective and antiapoptotic activities [10]. NGF can be a good diagnostic marker of the severity of neurological deficits in the first year of life. The more severe the CNS lesion was in infants of 1–3 months, the higher the NGF level. In the same study, a significantly lower NGF level in 4–6-months-old children was a prognostically unfavorable sign and reflected more severe damage to brain tissue in this group of children [7]. For children with autism, after a complex sanatorium-resort therapy including dolphin therapy, there was an increase in β-endorphin and NGF [3]. This neurotrophin also plays a major role in a prenatal and postnatal brain development and can affect birth outcomes and nervous system development. A study showed that the level of NGF did not differ statistically in the cord blood of full-term and large for gestation babies. This factor was however much lower in those with low weight for gestation. At the age of 4 months, children with a low birth weight who were artificially fed also showed lower NGF levels compared to children who were breastfed. Indeed, several studies have reported higher concentrations of trophic factors in maternal milk than in other biological fluids at different periods of maturation. Thus, it can be assumed that high levels of NGF in infants fed with breast milk may reflect the presence of a higher amount of NGF in it, acting as a compensatory mechanism aimed at preserving and/or improving the cognitive func-

tion of children. Breastfed children have a higher psychomotor development index compared to children receiving formula. Maintaining elevated NGF concentrations in children through breastfeeding in the first months of life can be one of the ways to prevent the development of cognitive disorders [31, 32].

Children with autism spectrum disorders have decreased NGF levels and increased serotonin levels. These data suggest that the implementation of the neuroprotective properties of the serotonergic modulating system of the brain is mediated by increased transcription of neurotrophins [14].

Vascular endothelial growth factor (VEGF) is one of the representatives of a family of structurally related proteins [8]. This family includes five types: placenta growth factor, VEGF-A/B/C/D. VEGF-A stimulates angiogenesis and neurogenesis along with neuroprotection. After ischemia, VEGF-A induces neurogenesis. This function makes it attractive for therapeutic use in the treatment of brain ischemia, but only in the delayed phase of the pathological process (in the early period this factor is also responsible for some damaging processes such as brain edema and increased permeability of the blood-brain barrier) [22].

VEGF regulates brain plasticity, recruitment, and proliferation of neuronal precursors that allow tissues to adapt after a stroke. Rapid VEGF secretion contributes to endothelial damage after an ischemic event. Early VEGF inhibition reduces vascular permeability and together with a decrease in the volume of infarction, increases the functioning of neurons [41]. VEGF plays an important role in the regulation of neuroinflammation. Microglia in chronically affected areas of the CNS increases VEGF expression [23, 26]. Angiogenesis in newborns occurs along the VEGF concentration gradient and within 4–7 days after cerebral ischemia at the border of the ischemic nucleus. This may be important for brain recovery after ischemia [21, 26]. A significant increase in the VEGF concentration in the acute period was detected in children of different ages with brain ischemia and compared with healthy children. The highest levels of this factor were in children with severe clinical appearances (paresis, paralysis, impaired consciousness, epilepsy). Because of the presence of such neuroprotective effects, VEGF has recently been considered as a therapy for post hypoxic conditions in the rehabilitation period [34].

The most promising therapeutic direction is to modulate the inflammatory response by limiting its neurotoxic effect, enhancing neuroprotective properties, and stimulating the regeneration of damaged nerve tissue. As for the wide range of inflammatory mediators associated with CNS functions, chemokines have new roles in both physiological and pathological conditions. The multidirectional action of neurochemokines includes participation in the embryogenesis of the nervous system, modulation of synaptic conduction, plasticity, and their function in the pathogenesis of neurodegenerative disorders.

Monocytic chemotactic protein (CCL2) is a cytokine belonging to the group of CC chemokines and is the most powerful factor in the chemotaxis of monocytes, memory T cells, and dendritic cells. It is secreted by monocytes, macrophages, dendritic cells, fibroblasts, endotheliocytes, and other cells, and is also involved in the pathogenesis of neurodegenerative diseases [6, 42]. Thus, the expression of CCL2 in glial cells increases in epilepsy, brain tissue ischemia, Alzheimer›s disease, experimental autoimmune encephalomyelitis, and traumatic brain injuries [20, 42]. Together with other cytokines, CCL2 is involved in the pathophysiological process of perinatal ischemic stroke [25].

An increase in CCL2 was detected in severe hereditary diseases including the destruction of the CNS: Sandhoff, Farber, and Gaucher diseases [40].

The chemokine CX3CL1 (fractalkine) and its receptor CX3CR1 are expressed by immune and non-immune cells. In the brain, CX3CL1 is mainly expressed by neurons, and in the case of inflammation is expressed in astrocytes [28]. CX3CR1 is expressed in parenchymal microglia and perivascular and subdural macrophages of the meningeal and vascular plexus. The structural relationship of CX3CL1–CX3CR1 transmission signals reflects the influence on synaptic transmission in certain neuroanatomic regions in processes such as learning, memory, and behavior. CX3CL1 protects the brain during ischemia by controlling inflammation and organizing a neuroprotective response [29, 35]. High levels of CX3CL1 are constantly produced by neu-

rons within the terminal and intermediate brain, in the cerebral cortex, hippocampus, amygdala, basal ganglia, and olfactory bulb. In the ventricular system, their expression is associated with the vascular plexus. In newborn mice, inflammatory chemokines such as CCL1, CCL17, and CXCL12 were temporarily enhanced 24 h after brain ischemia. Increased production of other chemokines such as CCL5, CCL9, and CXCL1 was extended to 3 weeks after brain damage, but most of them disappeared over time. In response to the introduction of umbilical cord blood cells, an additional increase in CCL2, CCL12, CCL20, and CX3CL1 levels was recorded, which may be associated with new recruitment and differentiation of neural stem cells leading to the induction of tissue regeneration [19].

Trigger receptors expressed on myeloid cells 1,2 (TREM 1,2) are innate immune receptors [38]. TREM1 is recognized as a critical immunomodulator in the inflammation of infectious and non-infectious etiology [43] and plays a role in the release of proinflammatory cytokines and T cells. Also, TREM1 was presented as a hypoxia-related protein involved in dendritic cell activation. The hypoxic tumor environment modulates the expression of TREM1, leading to immunosuppression. Microglia expression of TREM1 increases after ischemic brain damage. Blocking TREM1 can increase cell proliferation and synaptic plasticity, which leads to a long-term improvement in the functional activity of neurons [38, 39].

TREM2 is a cell surface receptor that plays an important role in phagocytosis and microglial function. Nucleotides and lipid mediators, key factors that are secreted in a hypoxic environment by apoptotic neurons, activate it. Also, TREM2 stimulates a Pro-regenerating phenotype shift [25]. It is involved in inhibiting neurodegeneration processes, for example, NASU-Hakol disease (polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy) develops in people with a mutation or loss of function of the *TREM2* gene. With this disorder, bone cysts are formed due to dysfunctional osteoclasts and progressive dementia, motor dysfunction, convulsions with reduced life expectancy occur. TREM2 deficiency suggests a more unfavorable outcome in ischemic brain damage. In an experiment with a model of multiple sclerosis with autoimmune encephalomyelitis, it was found that macrophages obtained with overexpression of TREM2 showed increased phagocytosis of apoptotic neurons, resulting in a more favorable outcome. Inhibition of TREM2 activation negatively affects the outcome of encephalomyelitis [24, 27, 37, 40]. In the occlusion of the middle cerebral artery and reperfusion, the level of TREM2 increases in primary microglia and the zone of ischemic penumbra of the cerebral cortex. TREM2 protects against cerebral ischemia and reperfusion damage through a post-ischemic inflammatory response and neuronal apoptosis. Given the above, TREM2 pharmacotherapy may provide a new approach for developing strategies for the treatment of various cerebrovascular diseases by suppressing the inflammatory response [24, 25, 27, 36, 38].

Transforming growth factor-beta (TGF-β) is a cytokine involved in the regulation of growth, adhesion, migration, apoptosis, proliferation, and differentiation [18]. They are presented in three isoforms with similar effects: TGF-β1, TGF-β2, and TGF-β3 [2]. It is involved in the development of many human diseases, including CNS pathology [18]. TGF-β plays a role in glial differentiation, embryonic and adult neurogenesis, survival and migration of neurons, fixation of the radial glial layer, and formation of the blood-brain barrier [15, 16, 18]. When TGF-β is deficient, neuronal death and microgliosis in the cerebellum increase [18]. This cytokine plays a major role in the early postnatal development of the cerebellum. When its structure and function change, emotional and cognitive disorders occur for patients with neuropsychiatric disorders [17, 18]. Patients with autism had an increase in the concentration of TGF-β after a therapy with positive dynamics in the form of a decrease in neurological deficit [18].

Thus, many markers indicate nerve tissue damage. Determining the levels of these indicators in children at risk for developing neurological diseases will help prevent the occurrence of clinical symptoms without reducing their quality of life in the future. The analysis of markers of neuroprotection in children with established neurological

diagnoses will allow the control of the quality of treatment, correcting it, and preventing severe disease outcomes.

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◆ Information about the authors

Marina S. Panova — Assistant Professor, Department of Propaedeutics of Children's Diseases. Federal State Budgetary Educational Institution of Higher Education Chita State Medical Academy, Chita, Russia. E-mail: merik2002@mail.ru.

Aleksandra S. Panchenko — MD, PhD, Dr Med Sci, Associate Professor, Head, Department of Propaedeutics of Children's Diseases. Federal State Budgetary Educational Institution of Higher Education Chita State Medical Academy, Chita, Russia. E-mail: sashawomen18@mail.ru.

◆ Информация об авторах

Марина Сергеевна Панова — ассистент, кафедра пропедевтики детских болезней. ФГБОУ ВО «Читинская государственная медицинская академия» Минздрава России, Чита. E-mail: merik2002@mail.ru.

Александра Сергеевна Панченко — д-р мед. наук, доцент, заведующий, кафедра пропедевтики детских болезней. ФГБОУ ВО «Читинская государственная медицинская академия» Минздрава России, Чита. E-mail: sashawomen18@mail.ru.