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New Understanding in the Pathophysiology of the Development of Cerebral Edema after Stroke and Traumatic Brain Injury

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Abstract: In this literature review the main attention is paid to the current understanding of the role of the glymphatic system (GS) in the development of brain edema (BE) in traumatic brain injury (TBI) and ischemic stroke. We discussed recent studies suggesting that glymphatic function is down regulated in brain pathologies and that glymphatic deficiency may in turn contribute to BE in TBI and ischemic stroke. A new understanding of how behavior, genetic predisposition, drugs affect HC function and how this function is decompensated in brain pathologies should lead to the development of new preventive and diagnostic tools and new therapeutic targets.

Keywords: GS, astrocytes, ischemic stroke, traumatic brain injury, BE.

Currently, there is no complete picture of the conjugation of cerebral blood flow, liquor circulation and interstitial space in brain edema (BE). This review of the literature is devoted to the recently discovered system of purification in the brain - the GS in ischemic stroke and traumatic brain injury (TBI).

BE is a complication of many diseases, and not only neurological ones. BE is the leading mechanism of thanatogenesis in patients with severe cerebral and extracerebral processes in intensive care units. BE has been described since before our era, but so far we know little about this universal process. In the historical aspect, interest in BE either appeared or disappeared for many years and was renewed only with the appearance of new research methods. Currently, there is renewed interest in the problem of BE, this is due to the ability to see morphological changes using neuroimaging methods and to study the molecular genetic mechanisms of BE formation using various experimental models [2,8].

After damage to the central nervous system (CNS), for example, in stroke, trauma, intracranial volumetric lesions, inflammatory reactions, metabolic disorders, the blood-brain barrier (BBB) is destroyed, exudation and accumulation of water and macromolecular substances. In perivascular and interstitial cells. Brain tissue hypoxia, cell membrane dysfunction, or intracellular electrolyte and osmotic changes lead to intracellular edema in the injured brain. In an injured nervous system, obstruction of the cerebrospinal fluid (CSF) circulation pathway causes ventricular enlargement or periventricular leukoencephalopathy. Brain edema after stroke and TBI increases intracranial pressure (ICP), which in turn exacerbates BE,

An important step in understanding the significance of the accumulation of excess fluid in the cranial cavity was the work of the Scottish anatomist A. Monro Secundus (1733–1817). The author introduced the concept of intracranial pressure (ICP), which occurs as a result of the impact of the contents of the skull (brain substance, blood in arterial and venous vessels) on its rigid walls, and described the mechanism of cerebral hernia formation. In his work "Observations on the structure and functions of the nervous system". In 1824, the A. Monro hypothesis, after multiple tests, was supported by G. Kellie (1770–1829) and subsequently became known as the Monro–Kelly doctrine [1,11].

Clinical diagnosis and monitoring of BE remain an unresolved problem. Both the development and course of BE is an asymptomatic process. Only the addition of complications of BE in the form of ICH is accompanied by the development of cerebral and focal neurological symptoms as a result of compression and displacement of cerebral structures by edema, as well as the formation of secondary

ischemia [1,13,27]. Currently, the method of choice for diagnosing BE is neuroimaging (computed tomography - CT and magnetic resonance imaging of the brain) [31,36,39,46]. One of the early markers of BE is a decrease in the volume of the sulci [29]. However, the limitations on the use of radiological methods and the discontinuity of the study do not allow monitoring of BE [39].

Developments are underway to isolate potential biochemical markers of BE from the blood. Endothelin-1, which is involved in the pathogenesis of brain damage in various diseases and contributes to an increase in BBB permeability, is considered as such a marker. Cellular fibronectin, one of the components of the basement membrane, and matrix metalloproteinase-9, a proteolytic enzyme that causes remodeling of the basement membrane and destruction of close junction proteins in the structure of the BBB, can be recognized as other indicators of the development of pronounced BE and hemorrhagic transformation [20,26,55].

The GS (GS) is one of the missing links for understanding the conjugated functioning of all components of the central nervous system (intracranial blood volume, cerebrospinal fluid, cell mass, interstitial space) in normal and pathological conditions. The name “glymphatic system” was coined by the Danish scientist M. Nedergaard in recognition of the dependence of GS on glial cells and the similarity of its functions with those of the peripheral lymphatic system [42].

The structure of the GS. According to a study conducted at the University of Rochester, subarachnoid CSF quickly enters the brain through the paravascular spaces surrounding the penetrating arteries and then exchanges with the surrounding ISF. In the same way, the ISF is cleared of metabolic products of the brain parenchyma through the paravascular spaces surrounding the large draining veins [42]. Where the PVR ends in the brain parenchyma, the CSF can continue to move along the basement membranes surrounding the arterial vascular smooth muscles to reach the basal plate surrounding the cerebral capillaries. perivascular spaces between the basement membrane, pericytes, astrocyte pedicels; system of aquaporin receptors of astrocytes; structures, producing and resorbing CSF; interstitial space of the brain; CSF circulation space [42,50].

GS performs a number of functions, the most important of which is currently considered "cleansing", that is, the removal of metabolic products, toxic substances from the central nervous system. Evaluation of GS activity after acute cerebrovascular accident or traumatic brain injury can determine whether its activity correlates with neurological recovery. A new understanding of how behavior, genetic predisposition, and drugs affect GS function and how this function is decompensated in various pathologies should lead to the development of new preventive and diagnostic tools and new therapeutic targets [4].

Astrocytes play an important role in the removal of metabolites. They express water channels called aquaporins. However, until recently, no physiological function has been identified to explain their presence in mammalian CNS astrocytes. Aquaporins are a family of proteins that consist of six membrane domains and have a molecular weight of 30 kDa. They selectively let water molecules through, allowing it to enter and leave the cell, while at the same time blocking the flow of ions and other soluble substances. Compared to simple diffusion, the presence of aquaporins in biological membranes contributes to an increase in water permeability by a factor of 3–10 [21, 58, 59, 63]. To perform a lymphatic function, the subarachnoid CSF must enter the brain and exchange contents with the ISF, and then return back to the CSF-conducting spaces. The study of these pathways and mechanisms has been the subject of intensive study over the past few decades [24,32,40,44,52].

According to a new hypothesis, CSF follows the paraarterial spaces, mixes with the ISF and substances dissolved in it, and is removed from the brain through the paravenous spaces [42]. This pathway is based on the movement of fluid through AQP4 channels located on astrocytic stalks surrounding the parenchymal circulatory network. The second hypothesis states that the outflow of interstitial fluid and solutes occurs along the middle layers of the basement membrane of arterial smooth muscle cells in the direction opposite to the flow of substances in the paravascular pathway [25].

In 2015, a number of researchers suggested that eventually interstitial solutes leave the brain through the meningeal lymphatic vessels flanking the venous sinuses along the sheaths of the cranial and spinal nerves [22,47]. The exchange of solutes between the CSF and the ISF is mainly due to arterial pulsation and is regulated during sleep by the expansion and contraction of the extracellular space of the brain.

Functions of the GS. GS performs a number of functions, the most important of which is currently considered to be “cleansing”, that is, the removal of metabolic products, decay, and toxic substances from the central nervous system. In mice with reduced AQP4 function and, accordingly, GC, the clearance of solutes, including mannitol and Aβ, is significantly impaired. In addition, increased glymphatic clearance has been found to be responsible for the decrease in brain lactate levels that accompanies the transition from wakefulness to sleep [42]. Inhibition of glymphatic clearance has been observed in anesthetized mice, in AQP4 deletion treated with acetazolamide, on cistern puncture or head repositioning, resulting in elevated lactate levels in the brain and in the lower cervical lymph nodes [48]. Apart from the clearance, this path is as shown

GS is involved not only in the excretion of metabolites, but also in the distribution of glucose, lipids, amino acids, various growth factors, and neuromodulators in the brain [23]. A decrease or increase in the level of ICP is mainly due to changes in the volume of intracranial contents, primarily blood and CSF. However, as mentioned above, the ISF is capable of migration, so it can be assumed that in the case of an increase in the level of ICP, this mechanism may be part of a compensatory reaction [27,33,54].

Glymphatic dysfunction, characterized by a lack of interstitial clearance of solutes, is a central feature of natural brain aging, as well as a wide segment of CNS diseases, including storage diseases (Alzheimer's, Parkinson's), traumatic brain injury, ischemic and hemorrhagic stroke [37,41,45,51 ,53,61].

Neuroinflammation reduces glymphatic clearance [35,43]. Inadequate expression of defensins (defensins are peptides that are released as part of the immune response to protect the brain from pathogenic microorganisms) [65] leads to the penetration of T-lymphocytes, viruses, and mediators into the CNS, disruption of the integrity of the BBB, and accumulation of Aβ [58]. Modern ideas about the pathogenesis of TBI are based on the identification of primary and secondary factors of brain damage [6,7,15,38]. If the primary damage in TBI is due to the direct impact of mechanical energy on the substance of the brain, then the secondary damage to the brain is an inflammatory reaction developed in the process of evolution, which develops in response to the primary mechanical damage. Such lesions are induced at the time of injury and develop over time, leading to irreversible ischemic damage to cells located in the immediate vicinity of the focus of primary damage (in the penumbra zone); at the same time, initially intact cells are involved in the pathological process [6]. The action of the primary traumatic agent triggers the development of biochemical and immunological reactions that lead to destructive processes.

The action of factors of secondary brain damage leads to a disruption in the delivery of oxygen and nutrients to brain cells and causes their insufficient utilization. There are disorders of cerebral microcirculation, oxygenation and metabolism of neurons, brain edema and its ischemia develop [6,7,14]. Secondary ischemic brain damage, according to different authors, develops in 36.0–42.6% of patients with TBI, the severity of which corresponds to an average degree, and in 81.0–86.4% of patients with severe TBI. In this regard, prevention and timely correction of secondary brain damage factors remain the most important task in the treatment of patients with severe TBI [6,7,38].

Factors contributing to the development of secondary ischemic brain damage are divided into intracranial and extracranial. Intracranial factors include: intracranial hypertension, disorders of cerebral hemodynamics, occlusive hydrocephalus, ischemia, BE, and dislocation syndrome [16]. Many researchers, using the example of clinical cases, proved that after severe TBI, glymphatic outflow significantly decreased [75]. Reduced excretion of neuroinflammation mediators could be a key factor

in the accumulation of tau protein aggregates in the damaged area and, consequently, the processes of memorization and storage of information [19,28,34,56,57].

Acute treatment of BE and increased ICP is a common problem in patients with neurological damage. Practical recommendations for the selection and monitoring of therapy for the initial treatment of BE for optimal efficacy and safety are generally not available. Clinicians should be able to select appropriate treatments for initial BE based on available evidence, balancing efficacy and safety [30].

Evidence suggests that hyperosmolar therapy may be beneficial in reducing the increase in ICP or BE in patients with SAH, TBI, IIS, ICH, and HE, although neurological outcomes do not change. Corticosteroids help reduce BE in patients with bacterial meningitis but not in those with ICH. Differences in therapeutic response and safety may exist between HTS and mannitol. The use of these agents in these critical clinical situations requires careful monitoring of side effects. There is an urgent need for high-quality research to better inform clinicians about the best options for individualized care for patients with BE [8].

Despite the fact that BE was visually described more than 2 thousand years ago, understanding its formation and control over it remain an unresolved problem until now. In recent decades, people have learned to measure ICP and control its increase, but ICH is already a complication of BE. The GS is a newly discovered CSF transport system. Through the perivascular space and aquaporin 4 (AQP4) on astrocytes, it promotes the exchange of cerebrospinal fluid and interstitial fluid (ISF), cleanses the brain of metabolic waste, and maintains the stability of the internal environment in the brain. Excessive accumulation of fluid in the brain tissue causes BE, but the GS plays an important role in both the intake and removal of fluid within the brain. Changes in the GS after stroke may be an important factor in BE [9,10,17,64].

In an injured nervous system, obstruction of the CSF circulation pathway causes ventricular enlargement or periventricular leukoencephalopathy. BE after a stroke increases ICP, which, in turn, exacerbates BE, causes functional and structural damage to the brain tissue, leads to epilepsy, paralysis, aphasia, and other symptoms of brain damage. With further aggravation of BE or diffuse progression, herniation of the brain and damage to the brain stem occur, which ultimately leads to brain death. Thus, timely and effective control of BE is useful for improving the symptoms and prognosis of patients with stroke. It was believed that, unlike other parts of the body, the brain lacks lymphatic vessels. However, recent studies have shown that the GS transports metabolic waste andregulates the flow of CSF [3,18,62].

Studies by several authors have shown that the GS can remove excess water, ions, and various solute molecules from brain tissue. On the one hand, the degree of BE decreases due to the outflow of water, ions and proteins from the lymphatic tract. On the other hand, with a decrease in BE, the function of the GS is gradually restored, which, in turn, contributes to the recovery of the central nervous system from BE and other pathological conditions. Recovery of the GS is associated with long-term prognosis in patients with BE after ischemic stroke [3,5].

Imaging studies of the GS and meningeal lymphatics using imaging techniques have confirmed that the meningeal lymphatics are downstream of the glymphatic pathway in humans. Therefore, the dural lymphatics are important pathways for the removal of intracranial solutes and CSF [65].

The discovery of the GS expanded the understanding of brain transport pathways. In addition, the GS is not isolated, as it plays a role in the formation and regression of BE by interacting with other pathways for the transport of solutes and fluids in the CNS. Generally speaking, the study of BE is the study of the transport pathways of solutes and fluids in the CNS. Various molecules, including AQP4, transporters, ion channels, and vascular permeability factors, are believed to be associated with cytotoxic and vasogenic edema after CNS injury [13,17].

Thus, understanding the mechanisms of the GS in BE after stroke and TBI can provide a new goal and opportunities for treatment, thereby contributing to the restoration of neurological function and improving the prognosis of patients after stroke and TBI. Evaluation of GS activity after acute

cerebrovascular accident or traumatic brain injury can determine whether its activity correlates with neurological recovery. A new understanding of how behavior, genetic predisposition, drugs affect GS function and how this function is decompensated in various pathologies will lead to the development of new preventive and diagnostic tools and new therapeutic targets. Further study of the pathophysiological and regulatory mechanisms of the GS in BE after stroke will help to find an innovative goal and direction of treatment. More clinical trials are needed to test drugs aimed at regulating the GS.

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