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PATHOPHYSIOLOGICAL FEATURES OF GLIAL CELL CHANGES AND MARKERS OF BRAIN TISSUES DAMAGE IN TBI

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Abstract. Traumatic brain injury (TBI) is the leading cause of mortality and psychiatric disorders among neurologic pathology. In many patients, TBI leaves long-term sequelae that may involve both mild cognitive impairment and severe disability. It is known that the mechanisms of damage in traumatic brain injury can be primary, related to the mechanical impact on the brain, and secondary, mainly caused by astrocytes, microglia and infiltrated immune cells from peripheral tissues that lead to neuronal and vascular dysfunction. Because these mechanisms, particularly secondary injury, remain incompletely understood, there are difficulties associated with the diagnosis and treatment of TBI. In search of a solution to this problem, substantial data on the quantification of biomarkers of traumatic brain injury have accumulated in recent decades, which may provide a clinically accessible window to study the mechanisms, diagnosis, monitoring, and prediction of brain injury outcomes. The article is a brief review of posttraumatic changes in brain tissue associated with ionic disturbances, activation of astro- and microglia, involvement of immune system cells, and major biomarkers of brain injury isolated from blood and cerebrospinal fluid.

Key words: traumatic brain injury; astroglia; microglia; damage; biomarkers.

ПАТОФИЗИОЛОГИЧЕСКИЕ ОСОБЕННОСТИ ИЗМЕНЕНИЯ ГЛИАЛЬНЫХ КЛЕТОК И МАРКЕРЫ ПОВРЕЖДЕНИЯ ТКАНЕЙ МОЗГА ПРИ ЧЕРЕПНО-МОЗГОВОЙ ТРАВМЕ

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Резюме. Черепно-мозговая травма (ЧМТ) является основной причиной смертности и психических расстройств среди неврологической патологии. У многих пациентов ЧМТ оставляет долгосрочные последствия, которые могут

быть связаны как с легкими нарушениями когнитивных функций, так и с тяжелой инвалидизацией. Известно, что механизмы повреждения при ЧМТ могут быть первичными, связанными с механическим воздействием на головной мозг, и вторичными, в основном вызванными астроцитами, микроглией и инфильтрированными иммунными клетками из периферических тканей, которые приводят к нейрональной и сосудистой дисфункции. Ввиду того, что эти механизмы, в частности вторичное повреждение, остаются не до конца изученными, существуют сложности, связанные с диагностикой и лечением ЧМТ. В поисках решения этой проблемы в последние десятилетия накопились существенные данные о количественной оценке биомаркеров ЧМТ, что может обеспечить клинически доступное окно для изучения механизмов, диагностики, мониторинга и прогнозирования исходов травмы головного мозга. Представлен краткий обзор посттравматических изменений в ткани головного мозга, связанных с ионными нарушениями, активацией астро- и микроглии, участием клеток иммунной системы, а также основных биомаркеров повреждения головного мозга, выделенных из крови и цереброспинальной жидкости.

Ключевые слова: черепно-мозговая травма; астроглия; микроглия; повреждение; биомаркеры.

Traumatic brain injury (TBI) is a global problem of public health service in the modern world. Traumatic injuries of the brain are the most relevant forms of neurologic pathology [7]. Epidemiological studies identify a stable increase of the number of traumatic brain injuries, particularly in big cities [6]. The prevalence of traumatic brain injury in the Russian Federation is 130–400 cases per 100 thousand population [9]. The risk of head injury has increased taking into account new dynamics of modern technological society development. Car accidents, extreme sports, and armed conflicts have increased the frequency of TBI [6].

According to the World Health Organization TBI is annually diagnosed in over 10 million patients worldwide within the period of 5 years, and 200–300 thousand people die. The principal causes of the population disabilities following TBI are considered mental and cognitive disorders, severe motor and speech impairments, posttraumatic epilepsy, etc. A stable rise of disability following TBI in able-bodied population (mean age 20–40 years old) has increased [13, 14]. Due to this fact there is a negative increase in realization of labour potential of the country (budget loss of about 495 milliard roubles a year), but at the same time huge resources are spent to provide medical institutions with everything required for the treatment and rehabilitation of disabled people [1, 12].

Disability in case of traumatic brain injury is caused by both primary involvement of the brain, and development of new clinical syndromes of dysregulation mechanisms and decreased adaptable reserves after some time period and during the period of complications [3].

This paper presents a review of relevant studies aimed at understanding the problems connected with TBI diagnosis. The paper gives an analysis of such problems as damage of the brain cells in case of TBI, participation of microglia and astroglia in TBI pathogenesis, , as well as the issue connected with the study of TBI biomarkers.

ETIOLOGY AND PATHOPHYSIOLOGY OF TRAUMATIC BRAIN INJURY

TBI results from intense collision, acceleration-delay and rotary motion of the brain that leads to its functioning disorder. It is possible to make pathophysiological differentiation between primary and secondary brain damage. Primary brain damage can be caused by: a) direct action of mechanical force leading to local damage, characterized by fractures, cerebral hemorrhage, and local neuron necrosis, or b) fast accelerating and slowing forces which determine stretching of the brain tissue with associated diffuse axon damage mainly manifested on the level of brainstem and callous body that can remain there within several months after the trauma. The secondary brain damage caused by biochemical and cellular changes, which are secondary to primary damage, is connected with numerous factors, including lipid peroxidation, mitochondrial dysfunction, oxidative stress, excitotoxicity, neuroinflammation and axonal degeneration.

DAMAGE OF THE BRAIN CELLS IN CASE OF TRAUMATIC BRAIN INJURY

Direct mechanical exposure leads to immediate appearance of irreversible mechanical damages of the skull bones, its coats, the brain vessels and tissues,differing in severity [2]. In case of primary damage there is a disorder in the structure of neurons and glial cells, followed by axon synaptic ruptures or distensions formation, damage of blood-brain barrier, vascular thrombosis appearance, and the integrity of vascular wall is disturbed [47].

After the trauma a perifocal zone is formed around the centre of the primary damage where the cells remain viable [16], but become extremely sensitive to the mildest changes of oxygen and nutrition transportation (penumbra zone) [8].

Due to considerable oxygen and glucose demand by the brain tissue there is a displacement of perfusion in the area of damage that leads to lack of substrates and accumulation of toxic metabolites. The speed of energy production by brain cells is changed which means failure of ionic gradients, decreased membrane potentials.

The involved cells release glutamate from intracellular reserves [25, 53]. Glutamate causes death of nervous cells by some mechanisms. It initiates both types of glutamate receptors, NMDA (*N*-methyl-D-aspartic acid) and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) that leads to Na^+ afflux, K^+ efflux, and intensive Ca^{2+} afflux to neurons [29]. This process is called excitotoxicity. It leads to uncontrollable and stable increase of cytosolic calcium that causes disorders in mitochondrial transportation of electrons and stimulates the functioning of many calcium-dependent enzymes, including lipases, phospholipases, calpains, nitrogen oxide synthase, protein phosphatase and different protein kinases [15].

In case of prolonged lack of energy neurocytes and glial cells are depolarized, being changed functionally and structurally [34]. Damage and energy deficiency of cells in tissue leads to disorders in their interaction, change of intercellular fluid components, release of proinflammatory agents that causes glia activation.

ROLE OF MICROGLIA IN NEUROINFLAMMATION

Microglia is a subtype of CNS glial cells that have the function of resident macrophages [36]. They usually utilize the accumulated metabolism products and also influence the processes of training and memory, regulating destruction of cells and neurogenesis.

Similar to peripheral cells, microglia releases pathogen recognition receptors, such as toll-like receptors (TLR) and NOD-like receptors (NLR), and, therefore, reacts to pathogen-associated molecular patterns (PAMP), and endogenously produced damage-associated molecular patterns (DAMP) that are secreted by broken neurons and other CNS cells [32]. They also express receptors of some other factors that are released by broken neurons, including adenosine triphosphoric acid, glutamate, growth factors and cytokines. Microglia is composed by antigen-presenting cells and interacts with T-lymphocytes and activates markers of cellular surface, such as MHC II and CD86, as well as molecules of adhesion and complement receptors [32].

There are known to be two phenotypes of activated microglia: pro-inflammatory M1 and anti-inflammatory M2. Activation according to M1 type leads to the synthesis of tumor necrosis factor α (TNF α), interleukins (IL)-12, -6, -1 β, NO, oxygen active forms (OAF), chemokines CCL2, CXCL9, CXCL10 [23]. M2-microglia produces anti-inflammatory IL-4, IL-13 that have neuroprotective action [52]. However, it is obvious that highly reactive condition of activated microglia according to M1 type in response to DAMP and other extracellular signals of damage leads to release of high levels of proinflammatory and cytotoxic mediators that promote the dysfunctions of neurons and death of cells [24, 38]. After TBI activated microglia quickly migrates to the zone of damage and creates a barrier between involved and healthy tissue and stimulates phagocytosis in the involved tissue that, consequently, is a positive side of microglia participation.

For example, after an experimental study of fluid-percussion TBI model in rats Iba-1 labelling demonstrates that microglia is hypertrophic and gets amoebiform in the cerebral cortex and thalamus that remains within 7 and 28 days after TBI and correlates with subacute and chronic course in experimental TBI model [22].

ROLE OF ASTROGLIA IN NEUROINFLAMMATION

Astrocytes of the brain are subdivided into fibrillar, located mainly in the brain white substance, and protoplasmic, located in the brain grey substance. Damage of these cells leads to disturbance of their basic functions: those of neuron energy supply, synaptogenesis, transportation of neurotransmitters, normal ionic balance maintenance, formation of blood-brain barrier (BBB).

In response to mild or moderate tissue damage astrocytes are exposed to hypertrophic reactive astrogliosis that includes molecular, structural and functional changes. Severe tissue damage causes degeneration of nervous and glial cells, destruction of vessels and intense immune answer that leads to formation of tissue compartments with various forms of reactive astrogliosis. Directly near the damage astrocytes proliferate and intertwine, forming astroglial cicatrix that surrounds and limits distribution of intensive inflammatory reaction in the damaged area [20].

Under the influence of DAMP, ionic changes and deficiency of energy there is transformation of cells to reactive astrocytes, and the amount of them increases in the damaged area after the trauma. Patients with TBI and experimental TBI mice had increased expression of endothelin-1 (ET-1) [42], and ET-1 increase promoted transformation to reactive astrocytes through ETB receptor in mice with fluid-percussion TBI model [42]. Some inflammatory cytokines and chemokines also cause astrogliosis. IL-1 provides transformation of astrocytes to the reactive form [30], at the same time IL-1 receptor antagonist reduces astrogliosis of hippocampus in such experimental TBI model, as controlled cortical damage [50].

Damaged neurons release high mobility group protein B1 (HMGB1) that induces IL-6 secretion by microglia cells, IL-6 activates the water channel of astrocyte aquaporine-4

(AQP4), participating in water absorption [39]. The negative side of reactive astrocytes is that they can directly increase intracranial pressure because of cytotoxic hypostasis and develop harmful mediators of inflammation which aggravate brain damage.

Activated astrocytes can also release matrix metalloproteinase-9 in response to mechanical pressure [48]. As a result of its activation intercellular contacts that influence the increase of penetration of blood neutrophiles, leukocytes and monocytes into the trauma center that leads to the increase of BBB permeability and, as a consequence, to edema aggravation.

To protect the neurons astrocytes produce soluble factors, such as transforming growth factor β (TGF-β) and prostaglandins which can inhibit microglia activation [37], as well as provide with nutrients and support homeostasis of extracellular liquid due to glutamate and potassium absorption increase [33].

According to the information above it could be said that glial cells can render various effects, both negative and positive that, in turn, will be reflected in restoration of neuron functions and plasticity during tissue reorganization. At the beginning glia activation has a protective character, delimiting the damage area and supporting viability of damaged neurons, stimulating neurogenesis, but subsequent prolonged release of proinflammatory cytokines and formation of glial cicatrix causes brain disorders. To understand these activities better, further studies of their participation in TBI pathogenesis are necessary.

By the present moment a considerable number of biomarkers that can indicate damages of neurons and neuroglia have been studied. The scientific community actively conducts researches on identification of the biomarkers unambiguously characterizing TBI which could be included further in its diagnostic criteria.

Search of these biomarkers is important to predict possible complications and to use them as indicators for assessing the severity of TBI in patients.

LIQUID BIOMARKERS

1. *Neurofilament light polypeptide (NfL),* released from damaged axons, was suggested as a viable biomarker of mild TBI [31, 51, 59].

2. *Soluble vascular adhesion protein 1 (sVAP-1)* is increased in plasma correspondingly with TBI severity [41]. The threshold value was 8,61 nmol/ml per hour, and those patients who had higher levels, presented 25% death rate increase.

3. *Galectin-3,* a member of lectins family, participating in microglia activation, has increased concentration in plasma in TBI patients, and is also an indicator of hospital mortality [46].

4. *High mobility group box 1 protein* (HMGB1) is translocated from nucleus to cytoplasm at the beginning of TBI, later it penetrates phagocytic microglia and represents cytokine and inflammation marker which is a predictor of one-year death in patients with TBI [55, 56], like an increased level of *copeptin hormone* [26].

5. *S100B* is an endocellular calcium-binding protein found in astrocytes, which is one of the most widely studied TBI biomarkers [17]. It has been demonstrated that serum S100B concentration during an acute phase of TBI negatively correlates with brain communication at rest condition that is identified by functional MRI [54]. One study has shown that addition of S100B test to the clinical guidelines on TBI management can become economically effective and lower the frequency of CT [21]. It has been shown that serum S100B concentration is considerably changing in the course of time that is significant for early prognosis [28]. It is interesting that the patients who had surgeries due to their fractures of backbone or lower extremities, demonstrated essential increase of blood S100B concentration compared with presurgical concentration [57]. It has also been shown that the placement of external ventricular drainage influences the levels of S100B though this time S100B cerebrospinal fluid and serum levels above 0.7 mkg/dl correlate with 100% death in case of TBI and subarachnoid hemorrhage [35].

It has been identified that S100B levels vary depending on type and number of TBI lesions. S100B test can be used in a group of patients with mild TBI with alcoholic intoxication. S100B test was more accurate in sober patients compared with alcohol intoxication patients. Serum S100B 24-hour levels can be used as a screening tool for early identification of patients with brain death risk following severe TBI. S100B can be an effective tool of TBI treatment monitoring, and one study has shown that S100B levels decrease after hyperosmolar therapy. It has been supposed that S100B samples taken within 12 hours after traumatic damage, have smaller prognostic value compared with S100B samples taken 12–36 hours after the trauma. It was also suggested that urine S100B levels had prognostic value compared with serum S100B levels. It has been shown that the combination of S100B levels with glial fibrillary acidic protein levels (GFAP) leads to precise prognosis of one-year death following TBI.

6. *Tau-protein* (Microtubule-associated protein tau, MAPT) is a protein that has its role in neuron development, axon stabilization and neuron polarity. It has been noticed that serum and cerebrospinal fluid tau-protein levels can be considered as TBI biomarker, because pathologicoanato-

mic examination demonstrated the increased levels of tau-protein even if macroscopically visible damages were not noticed, this means that some damages nevertheless could occur [45].

It has also been shown that the levels of the split serum tau-protein are significantly higher in case of severe TBI compared with control group [49]. The levels of total tau correlated positively with clinical and radiological TBI indicators [18]. Poor outcomes in case of severe TBI were identified in patients with higher level of blood serum tau-protein [40].

7. *Neuron-specific enolase (NSE)* increases similarly to S100B in TBI patients [44], and it is progressive depending on the trauma severity [60]. Medicine treatment (memantine) of patients with moderate TBI leads to significant decrease of blood serum NSE level and to the improvement of indicators according to Glasgow coma scale [43]. However, some foreign authors consider that NSE can be not so accurate or clinically useful compared with S100B [54]. But, again compared with S100B, the increase of NSE has been more closely connected with brain death prognosis after severe TBI [19].

8. *Nesfatin-1* is connected with inflammation and is an independent predictor of hospital mortality. Its concentration in plasma is connected with TBI severity, and it can become a reliable prognostic marker of these traumas [58].

9. *Resistin*, also called adipocyte-specific secretory factor (ADSF), is a secretory factor specific to adipose tissue. Plasma resistin levels increase from the 6th hour after the trauma, and reach its peak in 24 hours [27]. The study demonstrated that resistin is an independent predictor of one-month death of patients.

Experimental and clinical studies have shown that in case of TBI microglia cells and astrocytes more frequently produce such cytokines as [4]:

- *Interleukin-1 β* (IL-1 β) is an anti-inflammatory cytokine stimulating apoptosis and phagocytosis of the cells, causing fever. Active IL-1 β secretion after TBI contributes to the increase of excitability and excitotoxicity by glutamatergic and gamma-aminobutyric acid-ergic mechanisms and to change of concentration of calcium ions that can potentially lead to epilepsy development. Increased correlation of IL-1 β in liquor and blood serum during TBI acute phase is connected with an increased risk of posttraumatic epilepsy development [11]. Thus, IL-1 β plays a significant role in inflammatory processes in case of TBI and can be a marker of TBI severity and risk of posttraumatic epilepsy development.
- *Interleukin-6* (IL-6) is characterized by both proinflammatory, and anti-inflammatory features. IL-6 is considered to be the basic regulator of inflammatory responses which provides short-term protection against infectious process and tissue damage, has neuroprotective function. The role of IL-6 in case of TBI has been investigated in some clinical studies [5]:
  - The increase IL-6 in the cerebrospinal fluid of the ventricles patients with TBI, and also communication between IL-6 and production of the factor of neuronal growth was noticed that has allowed to assume considerable intracranial production IL-6 after TBI;
  - Blood IL-6 level increase within 48 hours after severe TBI is connected with unfavourable delayed clinical outcomes;
  - The analysis of serum IL-6 levels in patients with severe TBI has demonstrated that the highest IL-6 concentration has been found on the first day of hospitalization and was associated with the formation of multiple organ disfunction, sepsis and adverse neurologic outcome;
  - Liquor and blood IL-6 level reaches its peak in 24–28 hours after TBI;
  - IL-6 blood plasma concentration is increased by the time of making the diagnosis of the brain death.

Thus, high levels of IL-6 measured in blood and liquor, are associated with poor outcomes of trauma and higher risk of death outcome, being a possible predictor of intracranial hypertension after isolated TBI.

- *Tumor necrosis factor α (TNF α)* is involved in pathophysiological processes in case of many diseases and conditions, particularly systemic inflammatory response syndrome (SIRS), combined trauma, massive burns and rheumatoid arthritis [10]. The experimental studies have identified that:
  - TNF α activity is increased during the first hours after TBI and it is not found in blood serum on 3–7 days after the trauma;
  - Due to the influence of IL-1 on astrocytes and microglia there occurs the production of proinflammatory cytokines, including TNF α which will also stimulate IL-6 production by glial cells;
  - There is lack of studies describing the role of TNF α in TBI pathogenesis; TNF α concentration reaches its peak during the first hours after TBI and correlates with high mortality and formation of multiple organ disfunction;
  - Correlation of TNF α level and development of intracranial hypertension is noted.

In general, cytokines, belonging to the group of hormone-like proteins and peptides, which activation, according to the opinion of both Russian and foreign scientists, leads to various phenomena which can be observed in the brain after TBI, for example pyrexia, neutrophilia, edema,

disorders in BBB permeability, that have an important role in intercellular communications and stimulate reparative processes, such as gliosis.

However, gliosis, in its turn, causes further production of cytokines by hypertrophied astrocytes and microglia cells, in addition to mediators secreted by cells of peripheral immune system: polymorphonuclear leukocytes which penetrate through the weakened BBB that can lead to further brain damage.

Despite a considerable number of biomarkers known nowadays that can be associated with damages in case of TBI, most part of them are not highly specific and can be characteristic for other pathologies. Thus, among the above described biomarkers it is possible to allocate a number of the most perspective for diagnosis and assessment of dynamics in patients with TBI. They are neurofilament light polypeptide, neuron-specific enolase and glial fibrillary acidic protein. So, for example, GFAP was included in TBI diagnostic criteria by U.S. Food and Drug Administration [61].

CONCLUSION

TBI still remains one of the most severe types of trauma, even in case of mild TBI patients are likely to have prolonged disorder of cognitive functions that can be connected with a prolonged neuroinflammation course which types differ in pathology and outcome.

Detailed studies and evidences are needed to have a clear idea about the damage and regeneration of nerves. The available data do not make it possible to specify a definite role of inflammation after TBI due to its complex molecular and cellular interactions. The studies demonstrate that the mechanisms provoked by the trauma, have a protective function during acute inflammation and influence negatively in long-term prospect. The basic participants starting the cascade of these responses, are astrocytes and microglia, that is why biologically active factors and functional molecules, formed by them are, therefore, likely to be attractive targets for studying.

Pathophysiological markers of the brain tissue damage give evidence to a variety and mosaic structure changes in case of different types of trauma that underlines importance of continuation of TBI and its markers study. Allocation of the spectrum of the basic biomarkers — TBI indicators of different severity levels — could help to simplify diagnostics and further control of patients after trauma.

Thus, future studies of neuroinflammation mechanisms will allow to develop new algorithms of treatment, able to limit influence of secondary brain damage and to improve a long-term prognosis for patients.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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