UDC 616

[https://doi.org/10.32689/2708-7530-2020-3\(3\)-162-172](https://doi.org/10.32689/2708-7530-2020-3(3)-162-172)

Makarenko Oleksandr Mykolayovych Doctor of Medical Sciences, Professor of the Interregional Academy of Personnel Management, Predslavinska str., 14, Kyiv, 03150, tel.: (096) 209-61-16, e-mail: makarenko.alexander.1954@gmail.com, <https://orcid.org/0000-0002-6892-2314>

Kyrychenko Anastasiia Volodymyrivna 1st year student of the National Medical University named after O. O. Bogomolets, Vysotskoho boulevard, 6, Kyiv, 02232, tel.: (098) 311-33-55, e-mail: akyrychenko373@gmail.com, <https://orcid.org/0000-0002-5587-048X>

DISORDERS OF THE GLIAL SYSTEM OF CELLULAR FORMATIONS (GLIOM) OF THE BRAIN IN CONDITIONS OF NEUROTRAUMA

Abstract. Neurotrauma is damage to various structures of the central and peripheral nervous system (CNS and PNS), including isolated and combined craniocerebral trauma, isolated and combined spinal cord injury (SCI), as well as multiple limb trauma with isolated or combined injury bones, ligamentous apparatus, vessels and peripheral nerves.

Trauma is always the result of external influences.

Traumatic injury can be caused by various factors. Since the nervous system is very well protected, especially the central nervous system, then in the overwhelming majority we are talking about mechanical action. Thermal damage, chemical damage, and radiation damage are rare.

Both the central and peripheral nervous systems are subject to traumatic injuries. Trauma can be both acute and chronic. [1]

Glial cells are in close interaction with neurons, and their common function is to maintain homeostasis in the brain, which is optimally combined with the performance of specific functions of a wide range of "housekeeping" in the central nervous system. The importance of the interaction between neurons and glia in neurogenesis and in the mature brain is clear. The key role of glia in the pathogenesis of spinal cord injury, ischemia, neuropathic pain, and neurodegenerative diseases was revealed. In this case, glia reacts ambiguously and can participate in both defensive and pathological reactions. There is sufficient evidence for the role of glia in maintaining homeostasis and in protecting the brain from damaging factors. [2]

If the brain is injured, endogenous protective and ruinous mechanisms are triggered. Brain injury also triggers pathological processes that can potentially threaten cells. These mechanisms include excitotoxicity, free radical formation, inflammation, and apoptosis.

The self-protective mechanisms that are induced include the synthesis of heat shock proteins, anti-inflammatory cytokines, growth factors, and endogenous antioxidants. [3]

Keywords: neurotrauma, glial cells, inflammatory process, pathological reactions.

Макаренко Олександр Миколайович доктор медичних наук, професор Міжрегіональної академії управління персоналом, вул. Предславинська, 14, м. Київ, 03150, тел.: (096) 209-61-16, e-mail: makarenko.alexander.1954@gmail.com, <https://orcid.org/0000-0002-6892-2314>

Кириченко Анастасія Володимирівна студентка 1-го курсу Національного медичного університету імені О.О. Богомольця, бульвар Висоцького, 6, м. Київ, 02232, тел.: (098) 311-33-55, e-mail: akyrychenko373@gmail.com, <https://orcid.org/0000-0002-5587-048X>

ПОРУШЕННЯ ГЛІАЛЬНОЇ СИСТЕМИ КЛІТИННИХ УТВОРЕНЬ (ГЛІОМА) МОЗКУ В УМОВАХ НЕЙРОТРАВМИ

Анотація. Нейротравма - це пошкодження різних структур центральної та периферичної нервової системи (ЦНС і ПНС), включаючи ізольовану і поєднану черепно-мозкову травму (ЧМТ), ізольовану і поєднану хреботно-спинномозкову травму, а також множинну травму кінцівок з ізольованим або поєднаним пошкодженням кісток, зв'язкового апарату, судин і периферичних нервів.

Травма - це завжди результат зовнішнього впливу.

Травматичне ушкодження може бути викликано дією різних факторів. Оскільки нервова система захищена дуже добре, особливо центральна нервова система, то в переважній більшості мова йде про механічний вплив. Термічне пошкодження, хімічне пошкодження, променеве ушкодження спостерігаються рідко.

До травматичних ушкоджень схильні і центральна, і периферична нервова система. Травма може бути як гострою, так і хронічною. [1]

Гліальні клітини знаходяться в тісній взаємодії з нейронами, і їх загальною функцією є підтримання гомеостазу в мозку, що оптимально поєднується з виконанням конкретних функцій широкого спектра з ведення «домашнього господарства» в ЦНС. Важливість взаємодії між нейронами і глією в нейрогенезі і в зрілому мозку очевидна. Виявлено ключова роль глії в патогенезі травми спинного мозку, ішемії, нейропатичного болю і нейродегенеративних захворюваннях. При цьому глія реагує неоднозначно і може брати участь як в захисних, так і в патологічних реакціях. Представлено достатньо доказів ролі глії в підтримці гомеостазу і в захисті мозку від руйнуючих факторів. [2]

Після травми мозку запускаються ендogenousні протективні і руйнівні механізми. Травма мозку запускає також патологічні процеси, які потенційно можуть загрожувати для клітин. Ці механізми включають ексайтотоксичність, утворення вільних радикалів, запалення і апоптоз. Аутопротективні механізми, які індуються, включають синтез білків теплового шоку, протизапальних цитокінів, факторів росту, ендogenousних антиоксидантів. [3]

Ключові слова: нейротравма, гліальні клітини, запальні процеси, патологічні реакції.

Formulation of the problem. The level of neurotraumatism is quite high everywhere and reaches 18-20%. Neurotrauma is accompanied by high mortality and disability of the victims, the severity of the consequences with persistent or temporary disability, economically burdensome for the family, society and the state. This necessitates early effective rehabilitation treatment for this pathology. [4]

Analysis of recent publications on the problem. According to the World Health Organization, there is an annual increase in the number of victims of neurotrauma by 2%.

Brain trauma often becomes the cause of a disease of the body as a whole, because it violates the complex regulatory relationship of cork-subcortical, cork-trunk structures between themselves and the performing organs, forming a traumatic disease of the body. Therefore, an injury to the nervous system cannot be regarded as a local damage caused by mechanical influence; it is defined as a general disease of the nervous system. During the acute period of injury, diffuse changes in nerve cells, synapses occur, vascular regulation is disrupted, which leads to edema and swelling of the brain. Sometimes an infection joins, which, in turn, entails a number of complications. [5]

The purpose of the article is to study the quantitative change, phenotypic changes and uniqueness of the reactions of the four main types of glial cells at different stages of neurotrauma.

Presenting the main material.

Microglia.

Microglia proliferate and is maximally activated after 3-5 hours. [6, 7, 8] In recent years, there has been a growing interest in the role that the immune system plays in the pathogenesis of traumatic brain injury (TBI). The classical ideas about the immunopathological significance of immune reactions, such as secondary post-traumatic immunodeficiency, the development of autoimmune reactions to neuroantigens, the induction of neurodegeneration, which complicate the course of trauma, have replaced the ideas about the immunosuppressive and reparative-restorative effects of immune processes in the body. Such a transformation of ideas about the role of immune reactions is due to data obtained in studies carried out in the last 10-15 years, on the structure of the immune system, functions of cells of innate and acquired immunity, mechanisms of development of both damaging and protective, stimulating tissue regeneration, the influence of immune processes in the body as a whole and in particular with TBI. [9] The immune response develops within a few minutes after TBI and includes the activation of innate immune cells, namely microglia in the brain, followed by the synthesis of cytokines and the attraction of peripheral immune cells to the brain parenchyma, which cause an inflammatory cascade and specific immune responses that develop from time, and have both a useful, stimulating neuron repair, and a pathogenic effect on the course of injury, which can affect the outcome of TBI. [10] Taking into account the double possible influence of immune responses on the course of neurotrauma, it is important to understand the mechanisms underlying immune activation and functioning of innate and acquired immunity in the early and late periods after TBI. It is assumed that active management of the immune process in the post-traumatic period and targeted

immunomodulation can significantly change both the course and clinical outcome in patients with TBI. [11]

When neurons are dysfunctional or damaged, including TBI, microglia are activated and react to pathological events, acting as an inducer of neuroinflammation, secreting cytokines and chemokines, attracts immune cells from the blood to the focus of damage, and can also perform antigen-presenting functions for T-lymphocytes and thus participate in the development of a specific immune response to antigens of damaged nerve cells. The physical connection of microglia with synapses and axons of neurons is achieved by continuous processing of specific signals emanating from neurons and astrocytes to numerous receptors located on microglia. Signaling through these receptors can cause changes in membrane potential, intracellular calcium of neurons, cellular motility and release of cytokines by microglia, which is accompanied by changes in its phenotype (transition from a relatively calm state to an activated state). [12] Microglia may exhibit the pro-inflammatory M1 phenotype, which is observed immediately after TBI and is able to induce neurodegeneration and neuronal death, and the anti-inflammatory M2 phenotype, which is formed from the M1 phenotype and is responsible for the inhibition of inflammation and the restoration of damaged cells after TBI. The cytokines synthesized by M1-microglia after TBI include (TNF- α), IL-1 β , IL-2, IL-6, IL-8, IL-4, and IL-18. Free radical nitric oxide (NO) is synthesized with the participation of inducible NO synthase (iNOS), which is an important mediator of inflammation after injury. The chemokine CCL20 plays a special role. It specifically interacts with the CC-6 chemokine receptor (CCR6) and induces chemotaxis of dendritic cells, T cells and B cells in the brain, which induces neuroinflammation and specific autoimmune responses to brain antigens, reactivates the synthesis of inflammatory mediators, and aggravates nerve damage. cells. Increased expression of CCL20, along with other cytokines, was observed in humans one day after severe TBI. In addition, there are reports that CCL20 is a dual-acting chemokine with the ability to stimulate and inhibit inflammatory and immune responses, M2 microglial cells can be induced by IL-4 and synthesize anti-inflammatory cytokines such as IL-10 and β -transforming factor, and a number of trophic factors (insulin-like growth factor-1, nerve growth factor, incretin GLP-1, etc.), which ultimately stimulate regeneration and recovery. The ability of microglia to change the phenotype depends on the microenvironment, severity and time after traumatic brain injury. [13]

Thus, after neurotrauma, microglial cells are the first cells that respond to damage, which pass from a quiet to an activated state, exhibit phagocytic and cytokine synthesizing activity, and, depending on the phenotype, can have both protective and damaging effects on neurons.

Activated microglia and astrocytes and increased levels of inflammatory cytokines can be detected for months or years after brain damage. The prolonged existence of activated glial cells and the uncontrolled expression of cytokines for several months or years after TBI suggest that the immune response to TBI can persist for a long period after the initial injury, which is confirmed by the existence of a high level of autoantibodies to neuroproteins for a long time in the blood after TBI. [14]

Asrtocytes.

In the reactive changes in astrocytes after a brain injury, the initial and remote stages are distinguished. The initial stage (5-7 days) is characterized by moderately pronounced signs of hypertrophy of the bodies of astrocytes in the forming capsule, and in the separated (10-21 days) their pronounced hypertrophy and proliferation. Within 5-21 days of the study, damaged perivascular glial membranes and astrocyte processes were revealed. [15]

It has been shown that an increase in GFAP expression is found in most pathological conditions of the central nervous system, including ischemia, traumatic brain injury, inflammation, epilepsy, and neurodegenerative diseases. In this case, proliferation and hypertrophy of astrocytes is observed. This condition is called "reactive astrogliosis." It is believed that the response of astrocytes to the action of pathological factors is nonspecific and the intensity of GFAP expression depends on the strength and duration of the action of damaging factors, and not on their nature. An increase in GFAP expression also occurs with age (age-related gliosis), with an increase in both the number and size of astrocytes.

The role of astrogliosis is controversial. On the one hand, activated astrocytes, forming a kind of protective shaft and forming a glial scar, delimit the viable brain tissue from the damaged area and prevent the spread of the pathological process. In this case, the formation of an astrocytic scar can occur not only due to cells migrating to the lesion focus from proliferative zones, but also in situ due to mitotic division of existing astrocytes. On the other hand, activated astrocytes produce proinflammatory cytokines, in particular IL-1, IL6, TNF- α , exerting a toxic effect on oligodendrocytes and contributing to post-traumatic demyelination processes. Therefore, in the case of diffuse axonal trauma (DAT) and in demyelinating diseases, astrocytes act as antagonists of oligodendrocytes, preventing the restoration of nerve conductors and their remyelination. [16]

Astrocytes are activated in response to brain injury, infection, inflammation, and ischemia. In this case, reactive astrocytes are formed, which have both positive and negative effects on the microenvironment.

Reactive astrocytes enhance the immunoreactivity to the acidic protein of the fibril, increasing their size and number. It is assumed that activated astrocytes are involved in reparative processes, for example, through the secretion of nerve growth factor, squandering neuronal survival and inhibiting the activity of microglia by secretion (TGF β).

Damage to axons does not induce granulocytic infiltration.

As a result of ischemia, Icam-1, P- and E- are expressed on the endothelium.

selectins. These molecules interact with receptors on neutrophils, as a result of which these cells adhere to the epithelium, migrate through the vascular wall to the brain parenchyma. The peak of neutrophilic infiltration occurs after 24 hours, after which the number of granulocytes decreases rapidly. On days 5-7, monocytes and macrophages begin to dominate in the area of ischemic lesion. Leukocyte infiltration is associated with the activation of resident cells of the central nervous system. Experimental studies have shown PMNL infiltration in the early stages and monocytic-lymphocytic infiltration during the later stages of trauma. It is known that brain damage is associated with the emergence of various immune mediators in plasma. Various studies describe elevated

levels of various soluble mediators such as S-100, ICAMs, selectin, IL-4, IL-6, IL-8 and IL-10 after a variety of brain damage. In clinical studies of patients with brain damage have shown a significant neuroendocrine and inflammatory response shortly after the acute phase. [17]

Spinal cord injury leads to more severe inflammatory reactions than with brain damage, according to the degree of recruiting of neutrophils, the expression of adhesion molecules, the number of infiltrating macrophages and the degree of BBB disturbance.

In 5–7 days after injury, astrocytes near hemorrhages were characterized by moderately pronounced signs of hypertrophy. In contrast to the sections of the sections remote from hemorrhage and control, the astrocyte bodies were increased in size due to the cytoplasm expressing GFAP somewhat more strongly than usual. Cell nuclei, also larger, were located mainly slightly eccentrically. The processes of astrocytes became thicker, shorter and more discontinuous. GFAP of perivascular membranes, in contrast to control, was thinned and also looked intermittent. The relief of the cell bodies located near the damaged area was smoother than in the remote part of the nucleus and control, but their stellate shape was preserved. After 10–20 days of the recovery period, an increase in the number of astrocytes, more pronounced signs of hypertrophy than before, and a certain polymorphism of cells were observed in the forming capsule. Some of the astrocytes looked fusiform, less large than the rest; they expressed GFAP much more intensively than others and had the most thickened and shortened processes. Continuous GFAP + perivascular membranes were not detected. [18]

Oligodendrocytes.

Demyelination of nerve fibers is another factor that predetermines impaired conduction of the spinal cord after injury. It is the myelin sheath that is the anatomical substrate that is necessary for the rapid conduction of impulses along the nerve conductors. There are several hypotheses regarding the mechanism of demyelination of nerve fibers in traumatic brain injury. Behind one of them, with traumatic damage to the myelin sheath, an autodestructive process occurs in the body, which consists in the formation of autoantibodies to myelin breakdown products. The concentration of antibodies to myelin in the damaged area is very high, and in some cases (if recognition is impaired) they destroy the intact myelin sheath, which leads to an increase in tissue necrosis. Already 24 years after the injury, a microgliocyte is activated in the damaged area with the participation of the complement system, which, turning into macrophages, actively absorbs detritus. [19]

In the event of damage to the nerve fibers of the leading pathways of the spinal cord by a traumatic factor, the process of degeneration and demyelination of the axon is triggered distal to the site of damage by the type of Valerian degeneration, as occurs with damage to peripheral nerves, and ascending, retrograde degeneration at the proximal end of the axon 2-3 segments above the injury. Axotomy can lead to complete degeneration with subsequent necrosis of the neuron or cause only dystrophic changes in it. In dystrophic altered neurons, the process can occur in two ways: dystrophic changes can deepen, which over time predetermines cell atrophy, or vice versa, the process of renewal of cellular elements and regeneration of the damaged axon takes place. It has been proven that axotomy acts as an inducer of cell apoptosis. [20]

Development of autoimmune processes.

Traumatic brain injury can induce development autoimmune processes. Immune system that is normal counteracts infectious agents that enter our body externally, begins to act in a similar way against the substance of the nervous system (myelin) and the cells that produce it (oligodendrocytes), and causes the formation of a focus of inflammation in the central nervous system. That is, the cells of the body begin to destroy their own tissues, as foreign ones, a target for such destruction becomes myelin. [21]. At the sites of damaged myelin, hardened scars that can completely block conduction, resulting in multiple dysfunctions of the nervous systems: visual, motor, coordinating, pronunciation, genitourinary system.

Mechanical damage to the central nervous system manifests itself in the primary destruction of neurons that have succumbed to direct influence, and is often accompanied by a secondary loss of unharmed neurons. It was shown in different models of CNS injury in rats that CNS-specific autoreactive T cells protected against secondary neuronal damage. Autoimmune T cells specific to myelin basic protein can prevent the spread of neuronal death caused by primary spinal cord injury. Passive and active immunization with myelin peptides protects spinal cord neurons from death. Various authors have discovered the accumulation of T cells at the site of degeneration and secondary regeneration. [22] It is assumed that autoreactive CNS-specific Th1 lymphocytes trigger autoimmune diseases such as multiple sclerosis. CNS injury has been shown to trigger a response to self antigens within the nervous system, in particular to myelin basic protein. Thus, damage to the white matter, namely the optic nerve, leads to an increased accumulation of T cells (between 3 and 21 days), regardless of their antigenic specificity, therefore, this accumulation is not selective. [23]

Ependymocytes.

The problem of the pathomorphology of TBI is inextricably linked with the violation of the CSF circulation system (including its links with two liquor secretion and CSF circulation) and with dislocation processes, displacements and deformations of the brain, often leading to death in victims with head trauma. [24] Pathomorphological changes in the choroid plexus and ependymal lining are determined by topography and depend on the duration of the post-traumatic period. In this regard, microscopy of the choroid plexus can reveal varying degrees of changes, ranging from edema of the stroma of the villi to desquamation of the choroidal epithelium. Changes in the ependymal lining also range from the appearance of folding to the formation of deep "bays" and protrusions with disruption of the whole layer of ependymocytes. Features of the spatial (morphometric) characteristics of dislocation displacements of the midline structures of the brain are studied on the basis of a three-stage technique for sectional examination of the brain. [25]

Conclusions and prospects for further research. The issue of neurorehabilitation is burning and remains a crucial vector of researches for scientists. Neurorehabilitation is a system of socio-economic, medical, professional, pedagogical and psychological measures aimed at restoring or maintaining the health, personal and social status of the patient, which ultimately affects the main criterion of the patient's life - its quality.

Under the condition of neurotrauma, all the considered glial cell types are to changes. We can assert that the quantitative and qualitative changes in glial cells are somewhat different from those that are present in the pathology of acute stroke. This

topic was covered in a previously published article and referring to it, the following is clearly visible. In both cases, astroglia was activated and acquired a reactive character, its amount increased significantly. Also, astrocytes increased in size. In neurotrauma, demyelination of nerve fibers and the start of an autodestructive process take place. In turn, with an acute stroke, an increase in the amount of oligoglia will follow. Microglia, in the two pathologies considered, proliferate and is activated in the same way as astroglia. Ependyma after mechanical damage changes so, forming deep "bays" or the appearance of folding. In ischemic stroke, ependymal cells simply detach from the walls of the ventricles of the brain.

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