UDC 611.811.-611.41

CHANGES IN THE IMMUNE SYSTEM IN BRAIN INJURIES

(Review article**)**

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✓ ***Resume.***

This article presents a review of the literature, which presents the various manifestations that occur in the immune system after a traumatic brain injury.

Key words: traumatic brain injury, immunity, cytokines, lymphocytes, interleukins.

ИЗМЕНЕНИЯ ПРОИСХОДЯЩИЕ В ИММУННОЙ СИСТЕМЕ ПОСЛЕ ЧЕРЕПНО-МОЗГОВОЙ ТРАВМЫ

(обзор литератур**)**

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✓ ***Резюме***

В этой статье представлен обзор литературы, в котором рассмотрены различные проявления, происходящие в иммунной системе после черепно-мозговой травмы.

Ключевые слова: черепно-мозговая травма, иммунитет, цитокины, лимфоциты, интерлейкины.

ТРАВМАТИК МИЯ ЖАРОҲАТИДАН КЕЙИН ИММУНИТЕТ ТИЗИМИДА ЮЗАГА КЕЛАДИГАН ЎЗГАРИШЛАР

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✓ ***Резюме***

Ушбу мақолада травматик мия жароҳатидан кейин иммунитет тизимида юзага келадиган турли хил кўринишларни ўрганганган олимларнинг адабиётлари кўриб чиқилди.

Калит сўзлар: травматик мия шикастланиши, иммунитет, цитокинлар, лимфоцитлар, интерлейкинлар.

Relevance

Traumatic brain injuries, high mortality and disability of the victims, the real increase in the number of neurosurgeons, as well as long-term forecast data prioritize the problem of Neurosurgery [5,11]. Neurosurgery statistics require a more stringent study of the medical and social aspects of this problem, with a constant increase in numbers, significant disability and high mortality. In order to further improve organizational measures to provide neurotraumatic assistance to the population, it is important to study this problem under a wide epidemiological coverage column [6,15]. At the beginning of the 21st century, injuries still remain relevant. The problem of injury is determined by its prevalence, medical, social and economic importance (high cost of medical care, high level of death and disability, significant direct and indirect losses due to the loss of the Labor potential of the society) [2, 11]. Every year, the world receives 1.5 million dollars from various injuries.more than 2,4 million people die.more than one person becomes disabled. [15].

The World Health Organization estimates that around 80 million accidents occur annually in the European region. The weight of the injury load is almost 2,200 injuries per day or more than 90 cases per hour. Approximately 30 hospitalizations and 300 outpatient treatments are required for each case of death from an injury [11]. In Russia, for a year, the total economic and medical-social harm inflicted on society, the rate of death from injuries among people of working age, in the first place in the total composition of mortality indicators

(52%), ahead of cardiovascular and Tumor Diseases [13,18]. Brain injury is the leading cause of disability and temporary disability in the population, accounting for 30-40% of injuries, and cardiovascular and oncological diseases are also the leading causes of death among people of active age [14,12].

In developed countries, injuries in the structure of the causes of death of the population follow cardiovascular and oncological diseases, and according to the total economic and medical-social damage caused to the society, head injuries are in the first place [6,7]. In order to obtain information about the true prevalence of a brain injury, a population survey is conducted, which is organized specifically to take into account all cases of injury from a population living in a particular area, that is, a brain injury. The amount of head injury prevalence varies in different regions of the country and abroad, depends on many factors, an incomplete report due to frequent non-renewal, an incomplete report due to the fact that the victims of the injury were not registered in the registry, and other occlusive causes. [15,23]. In recent decades, traumatic brain injury has been one of the most important social and medical problems. This is due to the increased incidence of injuries and the severity of the injuries, the predominance of combined injuries in their composition and the high incidence of death [12,13,14]. Among the survivors, disability is high, and its leading causes are mental disorders, psychopathic states, gross motor and speech disorders, and epileptic seizures [1,15,21].

It is shown that already in the early period after TBI, leuko-, lympho - and monocytopenia develop, the activity of the effector link of cellular immunity decreases with an increase in the relative amounts of CD8+, CD20+, CD95+ cells and the levels of cytokines regulating inflammation. To restore disturbed neuroimmune interactions after TBI, it is possible to use immunomodulators that have neuroprotective capacity and the potential to stimulate the regenerative activity of the central nervous system [20, 29]. One of the immunomodulators that have neuroreparative and neuroprotective activity is a drug of recombinant human rencoleukin — rencoleukin. It is known that in the immune system, rencoleukin is produced by T cells in response to antigenic and mitogenic stimulation, ensuring their proliferation. However, the essential growth factor of rencoleukin is only for the regulatory suppressor T-lymphocytes, the function and viability of which it supports. Rencoleukin deficiency in the immune system of animals leads to the spontaneous development of an autoimmune disease characterized by T-cell infiltration (and in some cases, the deposition of autoantibodies), affecting certain organs and systems [23].

In the CNS, rencoleukin is synthesized in brain neurons, and the alpha chain of the high-affinity receptor (CD25) for this cytokine is expressed on microglial cells. In the case of impaired rencoleukin production only by brain cells (without a deficiency of this cytokine in the immune system), the number of T-cells entering all areas of the brain doubles, creating conditions for the development of autoimmune damage to the central nervous system [12, 19]. That is, with a deficiency of rencoleukin, disorders develop both in the immune system and in the central nervous system, and the correction of the processes occurring in the central nervous system is possible with the peripheral administration of rencoleukin. Thus, intraperitoneal administration of rencoleukin increases the activation of microglia, leading to metabolic changes and increased expression of the alpha chain of the rencoleukin receptor [29]

Clinical data have shown that severe traumatic brain injury causes a decrease in cerebral blood flow by 2-3 times due to an increase in the tone of the arteries and arterioles.The activity of the HPAX and the hypothalamic-pituitary-gonadal system (HGGS) as stress systems whose functional activity reflects the activation of regulatory mechanisms [12] aimed at overcoming the consequences of TBI was evaluated by the concentration of corticosterone and testosterone in the blood of animals after TBI. The results indicate that in the first hours after TBI, hormone levels change in different directions: the concentration of testosterone (Ts) in the blood significantly decreases ($p < 0.05$), while the concentration of corticosterone (Cs) after TBI increases sharply ($p > 0.05$). A decrease in testosterone levels, as well as an increase in corticosterone levels, are sensitive indicators of the development of stress and are adaptive in nature, aimed at optimizing protective reactions [17].

Further observation revealed that the level of corticosterone after a short-term peak significantly decreases to the level of intact animals by the 7th day, and then increases by the 14th day to a level 2 times higher than in animals in the control group. The level of testosterone after a short-term drop begins to increase by the end of the first day, almost reaching normal values by the 3rd day, the maximum values are recorded on the 7th day, after which they return to the level of intact animals by the 14th day after TBI.

After TBI, experimental animals develop neuroendocrine changes that reflect the activation of stress regulatory mechanisms, which is

manifested in a decrease in testosterone levels, a significant increase in the level of corticosterone secretion, followed by a pronounced suppression of the level of both hormones. It was previously shown that an increase in the concentration of endogenous corticosterone within physiological limits, for example, during the development of a stress reaction, not only does not inhibit, but also has a stimulating effect on proliferative processes, optimizes the implementation of the immune response, and also induces the release of a number of pro-inflammatory cytokines [27]. The observed absence of an adaptive increase in the level of Cs in injured animals can be regarded as unfavorable, associated with the risk of developing hyperactivity of immune responses, which can be accompanied by both increased inflammatory damage and the development of autoimmunity [18]. Prolonged inhibition of gonadal hormone function is also an unfavorable factor contributing to the development of depression and other stress-induced pathological conditions [20].

The hormonal imbalance observed in animals after TBI was associated with an increase in cytotoxic and proliferative activity of splenocytes, accompanied by an increase in apoptotic death of a significant part of the cells. The described disorders of neuroimmune interactions in traumatic brain injury were corrected to a certain extent in rats that received recombinant human roncoleukin (roncoleukin) after injury. Three-time administration of roncoleukin both normalized changes in the peripheral immune system by day 14 after injury (in terms of splenocyte proliferation and apoptosis), and restored testosterone levels and increased Cs levels in injured animals. Normalization of the ratio of the number of proliferating splenocytes to the number of cells that entered apoptosis when using roncoleukin may indicate that this indicator is informative for assessing the dynamics of immune processes after TBI. The published results of clinical studies indicate that the administration of roncoleukin to patients with TBI significantly improves T-cell parameters and reduces the intensity of post-traumatic inflammatory processes, determining a positive outcome of the disease [25].

The problem of long-term complications of severe traumatic brain injuries is in fact possible not only with the complex of pathophysiological changes formed in the immune system, but also with the development of post-traumatic complications of the brain, structural and functional changes in the central nervous system, as well as with the onset of delayed deleterious lesions to the structures of the brain. Currently, the nervous and immune systems are increasingly considered as the only psychoneuroimmune system to regulate general homeostasis and adapt the body to the changing conditions of the external and internal environment [16,22]. Molecular mechanisms of interaction between components of the psychoneuroimmune system have been well studied, along with hormonal factors provide them mediators of the ne yroimmune effect — cytokines [3,10].

The highest level of regulation in this system leads to complex control disorders of the immune system functions, accompanied by the development of traumatic brain injury, posttraumatic immunodeficiency, brain and immune diseases posttraumatic encephalopathies fatal processes of the brain. [11,18] all of the above, indicating the presence of a single Psycho-neuroimmun system, should be considered in terms of the presence of differences in higher nerve activity and immune response types in mammals. However, very few studies have been conducted in this direction, the effect of traumatic brain injury on the psycho-neuroimmune system, depending on the type of nervous system, there are relatively few comparative studies, and in this respect there is little data on the study of the long-term post-traumatic period. [1, 9, 26.]

In addition, the lack of clear criteria for Central dysregulation of the immune system, limiting the possibility of targeted correction. In this regard, the use of natural brain regulators of active substances and peptides (or their synthetic analogues) is promising, the main purpose of which is to protect against stress damage, to coordinate the work of analgesia and tissues, to receive signals from the relevant systems of organs, systems and tissues of the body as a whole, and to carry out the coordination [10,17,24.].

Traumatic brain injury is a multifunctional disease characterized by high mortality and disability of a large part of the victims. Primary lesion in the central nervous system is more extensive, secondary lesion and leads to the development of neuroinflammation, which ultimately determines the level of neurodegeneration, the development of Neurological Disorders and behavioral disorders [17,21,23]. Against the background of a head injury in the immune system, multidirectional seizures that affect the composition of T-and V-lymphocytes develop, which leads to bronchopulmonary complications and autosensibilization of the body, in particular, the appearance of autoantibodies to antigens of brain structures [10,26].

In general, in the lesion of brain tissue, the primary action begins with the activation of

resident cells of the immune systemitet (microglia and pericitis), the dendritic cells, macrophages, as well as other cells and molecular components are involved in the immune response. [19, 24].

Corticosteroids are the most important negative regulator of congenital adaptive immune responses and the acute stage of inflammation. Activation of corticosteroid production begins by proinflammation cytokines by triggering the hypothalamic-pituitary-adrenocortical system (HPAS). In experimental brain injury, the activation of this adaptive system leads to an increase in the level of corticosteroids and a decrease in the functional activity of immunocompetent cells [8,27]. It is shown that in the first period after brain injury, the activity of T-lymphocytes in the cellular immune system decreases with the increase in the relative amount of subpopulations and the level of cytokines, regulates the mediators of intercellular interactions in the blood, developing Leuko -, lympho-and monocytopenia [9, 20]. To restore the disturbed neuroimmune system after a head injury, it is possible to use immunomodulators in combination with the potential to stimulate neuro-ability and regenerative activity. It is possible to use immunomodulators with neuroprotektiv capabilities and the potential to stimulate the regenerative activity of the central nervous system to restore the impaired neuroimmune system after a head injury [16, 19].

It is known that in the immune system, interleukin-2 is produced by T-cells in response to antigen and mitogen stimulation and promotes their proliferation. However, interleukin-2 is only an indispensable growth factor for regulating suppressor T-lymphocytes, supporting its function and viability [8, 10]. Lack of interleukin-2 in the immune system of animals leads to the spontaneous development of autoimmune disease, characterized by T-cell infiltration (and in some cases the deposition of autoantitelles), affects some organs and systems [11,15]. In the central nervous system, interleukin-2 is synthesized in brain neurons, which are expressed in receptor microglial cells that have a high effect on cytokine. Only in the case of suppuration of interleukin -2 production by brain cells (without this cytokine deficiency in the immune system), the number of T-cells in all areas of the brain doubles in order to develop autoimmune damage to the central nervous system [19,22].

Active management of the immune process in the post- traumatic period and targeted immunomodulation can significantly change both the course and the clinical outcome in patients with TBI . In the pathogenesis of TBI, there are several periods: a) primary damage caused by direct or indirect bruising, which leads to a shift or stretching of brain tissue and immediate (necrotic) cell death, subdural hematoma and cerebral ischemia, b) secondary damage with diffuse damage to axons, local and systemic inflammatory reactions [3,8]. A number of authors distinguish a third period, which is characterized by regeneration and restoration of brain function or slowly progressing degenerative changes in the central nervous system [10,14].

The phase of non-mechanical damage, which is progressive and lasts from several hours to many days or months, significantly contributes to the development of neurological disorders. Damage to the brain vasculature at the time of TBI disrupts the integrity of the blood-brain barrier(BBB), leads to rapid penetration of immune cells into the brain parenchyma and the lesion site, and the development of local and systemic inflammatory reactions [13,15]. Acute and chronic inflammatory reactions caused by the activation of local and systemic immune responses have a dual character and can either aggravate pathological disorders after injury, or contribute to the process of recovery and regeneration [2,14]

The distinguishing features of secondary brain damage reactions after TBI may be the destruction of the BBB, the infiltration of the injury site by immune cells, oxidative stress, glutamate excitotoxicity, and the development of neuroinflammation, which may develop immediately after the primary mechanical injury [3, 17]. The production of inflammatory mediators is normally influenced by the mechanisms of neuroendocrine and immune regulation based on the feedback principle with the hypothalamus-pituitary-adrenal system and efferent cells of the sympathetic nervous system [28,30]. With TBI an imbalance between these regulatory factors can increase the suppression of immunity and lead to immunological dysfunction, immune insufficiency or increased susceptibility to infection, on the one hand, and to the development of neuro-autoimmune reactions of the cellular and humoral type, on the other [26,29]. .

In addition, TBI causes a systemic inflammatory response in the body against the background of a damaged BBB and this can lead to an increase in the number of infiltrating immune cells in the brain and cytokines in the body. These cells and molecules gain access to the brain parenchyma, primarily in the damaged area, and worsen the pathogenesis of TBI [24,30]. Thus, in studies on rats, a systemic and intracerebral increase in the level of neutrophils (neutrophilia) was shown against the background of increased

BBB permeability in traumatic damage to the cerebral cortex and administration of granulocyte - colony-stimulating factor to animals. Impaired BBB function after TBI can cause not only the entry of inflammatory cells and cytokines into the brain, but also the release of pro-inflammatory molecules, such as cytokines, arachidonic acid metabolites, complement factors, acute phase proteins, and especially autoantigens and proteins of damaged nerve cells through the damaged BBB from the brain to the circulation. This can lead to the development of a systemic autoimmune and inflammatory response syndrome [22,23], which is characterized by the occurrence of a hyper-inflammatory reaction in the body and the production of long-existing autoantibodies to brain antigens, which can enter the brain and damage nerve cells. In TBI, it is possible for lymphocytes and macrophages of the peripheral blood and brain to secrete anti-inflammatory molecules that can block the production of pro-inflammatory cytokines, such as interleukin (IL)-1β, IL-6 and tumor necrosis factor-α (TNF-α), which can block the development of an inflammatory response and inhibit the regeneration of nerve cells in the area of brain damage . An uncontrolled increase in the content of inflammatory cytokines in the blood and brain parenchyma after TBI can lead to multiple organ dysfunction syndrome and insufficiency up to death [25,28].

The mechanisms of the development of various immune responses of pro-and anti- inflammatory orientation in CHTM, despite the almost century-old history of studying the immunology of neurotrauma, have not been sufficiently studied. This is probably due to both the nature and pathogenesis of CHTM itself, the peculiarities of BBB disorders, and the constantly changing ideas about immune reactions, their role in neurodegenerative and regenerative processes in the body [23,26,30].After primary damage , cellular endogenous inflammatory responses are triggered in the brain to repair the damaged tissue, but often excessive production of proinflammatory cytokines is likely to become an important driver of pathological progression in TBI [21,27].

Thus, after TBI, despite post- traumatic immunosuppression, there is activation of cells of the systemic immunity and local immunity of the brain, increased secretion of a large number of inflammatory mediators, such as cytokines, chemokines, which are involved in the implementation of the inflammatory response and the interaction between the innate and acquired immunity. The exact role of cytokines and the nature of immune processes in TBI have not been established. The presented clinical and experimental data indicate that cytokines synthesized by immune cells play a regulatory role in determining both the pathological and protective effects of local and systemic immune processes in trauma. Establishing the dual role of immune responses in TBI expands our understanding of the pathogenesis of neurotrauma. We can conditionally distinguish several stages of their formation: 1) the initial activation of innate immune cells, namely micro-glia in the brain and the removal (phagocytosis) of damaged tissue, 2) the synthesis of cytokines by microglia and the involvement of peripheral immune cells in the brain parenchyma, 3) the development of systemic, specific immune and inflammatory reactions in the body. At each of these stages, the phenomenon of "duality" and the switching of the direction of immune responses from pro - inflammatory to anti-inflammatory, from immunopathological, is possible on immunosuppressive, from neurodegenerative to stimulating the regeneration of damaged brain tissue immune processes. Expanding the understanding of the functions of immune cells and their different effects on the brain allows a broader approach to assessing the significance of immune responses in the pathogenesis of TBI. Further study of the multidirectional nature of immune responses in TBI will clarify their pathogenetic and compensatory significance, find methods of their immunomodulation, which will help to reduce neurodegeneration, disability of patients and improve the results of treatment of neurotrauma.

The data presented in this review on the various variability of regulatory subpopulations of T-lymphocytes in traumatic brain injuries indicate that the subtypes of immune process regulation have not yet been fully studied by the researchers. Regulatory cells of the immune system play an important role in the pathogenesis of traumatic brain injury, autoimmune diseases, recurrent and recurrent infections, allergic diseases and oncological diseases. These cells further explore the possibilities of further investigation of the methods of development and functioning of subpopulations, developing new approaches in the treatment tactics for traumatic brain injuries.

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Entered 09.04.2021