Медицинская иммунология
2021, Т. 23, № 4,
стр. 825-830

Краткие сообщения
Short communications

Medical Immunology (Russia)/
Meditsinskaya Immunologiya
2021, Vol. 23, № 4, pp. 825-830

КЛЕТОЧНЫЙ ИММУНИТЕТЕ И ЕГО РОЛЬ В ПАТОГЕНЕЗЕ УШИБА ГОЛОВНОГО МОЗГА

Норка А.О.[1, 3], Воробьев С.В.[1, 5], Кузнецова Р.Н.[3, 4], Серебрякова М.К.[2], Кудрявцев И.В.[2, 3], Коваленко С.Н.[6]

[1] ФГБОУ ВО «Санкт-Петербургский государственный педиатрический медицинский университет» Министерства здравоохранения РФ, Санкт-Петербург, Россия
[2] ФГБНУ «Институт экспериментальной медицины», Санкт-Петербург, Россия
[3] ФГБОУ ВО «Первый Санкт-Петербургский государственный медицинский университет имени академика И.П. Павлова» Министерства здравоохранения РФ, Санкт-Петербург, Россия
[4] ФБУН «Научно-исследовательский интситут эпидемиологии и микробиологии имени Пастера», Санкт-Петербург, Россия
[5] ФГБУ «Национальный медицинский исследовательский центр имени В.А. Алмазова» Министерства здравоохранения РФ, Санкт-Петербург, Россия
[6] ФГБВОУ ВО «Военно-медицинская академия имени С.М. Кирова» Министерства обороны РФ, Санкт-Петербург, Россия

Резюме. Черепно-мозговая травма (ЧМТ) является одной из наиболее распространенных патологий центральной нервной системы в мире, а применение методов структурной нейровизуализации – компьютерной томографии (КТ) и магнитно-резонансной томографии (МРТ) – зачастую не позволяет оценить тяжесть, полученной при травме головного мозга. Это предопределяет необходимость поиска новых методов дифференциальной диагностики степени тяжести и прогнозирования риска последствий. Одно из таких перспективных направлений является изучение иммунного статуса, так как черепно-мозговая травма характеризуется высокой частотой осложнений.

Помимо этого известно, что тяжесть при ЧМТ в значительной степени определяется вовлеченностью иммунокомпетентных клеток. Реакции со стороны иммунной системы, которые развиваются после травмы мозга и, возможно, направлены против собственных антигенов, в раннем периоде заболевания имеют отношение к повреждению нервной ткани. Однако, по последним имеющимся данным, впоследствии способны стимулировать процессы репарации и регенерации в ткани головного мозга. При повреждении нервной ткани в ответ на эндогенные молекулы, которые образуются при разрушении клеток и внеклеточного матрикса, будут активироваться клетки иммунной системы.

Современные данные указывают, что Т-клетки иммунной системы играют роль как в формировании вторичных повреждений, так и в механизмах восстановления. Они способны защищать нейроны посредством продукции нейротрофических факторов, таких как нейротрофический фактор мозга (BDNF), который стимулирует рост нейронов и формирование синапсов. С помощью многоцветного

Адрес для переписки:

Норка Анна Олеговна
ФГБОУ ВО «Первый Санкт-Петербургский государственный медицинский университет имени академика И.П. Павлова» Министерства здравоохранения РФ
197022, Россия, Санкт-Петербург,
ул. Льва Толстого, 6-8.
Тел.: 8 (911) 218-85-00.
E-mail: norka-anna@mail.ru

Address for correspondence:

Norka Anna O.
First St. Petersburg State I. Pavlov Medical University
197022, Russian Federation, St. Petersburg,
L. Tolstoy str., 6-8.
Phone: 7 (911) 218-85-00.
E-mail: norka-anna@mail.ru

Образец цитирования:

А.О. Норка, С.В. Воробьев, Р.Н. Кузнецова, М.К. Серебрякова, И.В. Кудрявцев, С.Н. Коваленко «Клеточный иммунитете и его роль в патогенезе ушиба головного мозга» // Медицинская иммунология, 2021. Т. 23, № 4. С. 825-830.
doi: 10.15789/1563-0625-ROT-2355

For citation:

A.O. Norka, S.V. Vorobyev, R.N. Kuznetsova, M.K. Serebriakova, I.V. Kudryavtsev, S.N. Kovalenko "Role of the cellular immunity in the pathogenesis of brain contusion", Medical Immunology (Russia)/Meditsinskaya Immunologiya, 2021, Vol. 23, no. 4, pp. 825-830.
doi: 10.15789/1563-0625-ROT-2355

DOI: 10.15789/1563-0625-ROT-2355

цитофлуометрического анализа было проведено исследование по определению количества основных субпопуляций лимфоцитов среди CD45RA-negative $CD3^+CD4^+$-клеток. Относительное количество Th17 ($CXCR5^-CXCR3^-CCR6^+CCR4^-$) и Th17/Th22 ($CXCR5^-CXCR3^-CCR6^+CCR4^+$), Th1/Th17 ($CXCR5^-CXCR3^+CCR6^+CCR4^-$) среди общего количества CD45RA-negative $CD3^+CD4^+$-клеток у пациентов с ушибом головного мозга достоверно повышено в сравнении со значениями в контрольной группе в свою очередь, а относительное количество Th1 ($CXCR5^-CXCR3^+CCR6^-CCR4^-$) среди общего количества CD45RA-negative $CD3^+CD4^+$T-клеток достоверно снижено в сравнении со значениями в контрольной группе. Полученные к настоящему времени результаты позволяют рассматривать иммунные ответы среди ключевых звеньев патогенеза ушиба головного мозга. И, возможно, комплексное иммунологическое обследование пострадавших в первые сутки после травмы позволит определить параметры, которые помогут прогнозировать характер возможных осложнений у пациентов с ушибом головного мозга.

Ключевые слова: черепно-мозговая травма, проточная цитометрия, ушиб головного мозга, воспаление, клеточное звено системы иммунитета, субпопуляции $CD3^+CD4^+$-лимфоцитов

ROLE OF THE CELLULAR IMMUNITY IN THE PATHOGENESIS OF BRAIN CONTUSION

Norka A.O.[a, c], Vorobyev S.V.[a, e], Kuznetsova R.N.[c, d], Serebriakova M.K.[b], Kudryavtsev I.V.[b, c], Kovalenko S.N.[f]

[a] *St. Petersburg State Pediatric Medical University, St. Petersburg, Russian Federation*
[b] *Institute of Experimental Medicine, St. Petersburg, Russian Federation*
[c] *First St. Petersburg State I. Pavlov Medical University, St. Petersburg, Russian Federation*
[d] *St. Petersburg Pasteur Research Institute of Epidemiology and Microbiology, St. Petersburg, Russian Federation*
[e] *V. Almazov National Medical Research Centre, St. Petersburg, Russian Federation*
[f] *S. Kirov Military Medical Academy, St. Petersburg, Russian Federation*

Abstract. Traumatic brain injury (TBI) is one of the most common pathologies of the central nervous system in the world, and the use of structural neuroimaging methods – computed tomography (CT) and magnetic resonance imaging (MRI) – often doesn't allow assessment of the severity of the brain injury that has occurred. This situation predetermines the need to search for new methods of differential diagnosis of the severity of TBI and predicting the risk of consequences.

One of these promising areas is the study of the immune status, since traumatic brain injury is characterized by a high rate of complications.

One of these promising areas is the study of the immune status in patients with TBI in the acute period. It is now known that in response to brain damage, a response from the immune system is triggered.

The reactions from the immune system, which develop after brain injury and directed against its own antigens, in the early period of the disease are related to damage to the nervous tissue. However, according to the latest available data, they are subsequently able to stimulate the processes of repair and regeneration in the brain tissue. In the course of damage to the nervous tissue, in response to endogenous molecules formed during the destruction of cells and the extracellular matrix, the cells of the immune system are activated.

Current evidence indicates that T-cells play a role in both the formation of secondary damage and repair mechanisms. They are able to protect neurons through the production of neurotrophic factors such as brain neurotrophic factor (BDNF), which stimulates the growth of neurons, the formation of synapses.

Using multicolor cytometric analysis within the framework of this work, a study was carried out to determine the number of the main subpopulations of $CD3^+CD4^+$-lymphocytes. The relative number of Th17 ($CXCR5^-CXCR3^-CCR6^+CCR4^-$) and Th17/Th22 ($CXCR5^-CXCR3^-CCR6^+CCR4^+$), Th1/Th17 ($CXCR5^-CXCR3^+CCR6^+CCR4^-$) among total CD45RA-negative $CD3^+CD4^+$-cells population is significantly increased in comparison with the values in the control group, in turn, the Th1($CXCR5^-CXCR3^+CCR6^-CCR4^-$) subpopulations among total CD45RA-negative $CD3^+CD4^+$-cells are significantly decreased with the values in the control group. The results obtained so far make it possible to consider immune responses among the key

links in the pathogenesis of brain contusion TBI. And, perhaps, a comprehensive immunological examination of the victims in the first day after the injury will determine the parameters that will help predict the nature of possible complications in patients with brain contusion.

Keywords: traumatic brain injury (TBI), flow cytometry, contusion, inflammatory, cellular immune status, subpopulations of $CD3^+CD4^+$-lymphocytes

Introduction

Traumatic brain injury (TBI) is one of the leading causes of morbidity as well as mortality in the world. With regard to molecular and cellular mechanisms of TBI in the past 20 years, but immune status doesn't know. It is now known that cells of immunity play an important role in brain function, including the organization of cognition and neurogenesis [10]. The basis for this is that there is an interconnection between the main immune cells in the periphery and the brain, and this connection is strengthened in response to the immune response [5]. The data of the conducted studies indicate that signals from the immune system from the periphery cause an inflammatory response in the brain, while it increases with age, which, in turn, reduces the plasticity processes necessary for cognitive functions [3]. In this case, the triggering of the immune response occurs through Toll-like receptors (TLR), which are expressed on the cells of the macrophage system located in the circumventricular organs and the vascular plexus, reacting to circulating pathogen-associated molecular patterns, which further become to the formation of pro-inflammatory cytokines, or the flow of cytokines from the systemic circulation to the brain through the BBB, it is also possible that an inflammatory response is triggered through receptors for interleukin-1 (IL-1) expressed on perivascular macrophages and endothelial cells of cerebral venules [3, 8, 12].

Materials and methods

Within the framework of this study were explored 52 apparently healthy people aged 18-65 years without TBI, as well as any pathology that could lead to a change in the immunological status, and 22 patients with a diagnosis of brain contusion. Of these, 25 are men and 27 are women aged 20 to 46 years. All examination was conducted on the day of the patient's appointment. The examination included the collection of complaints, medical history, assessment of somatic and neurological status, neuropsychological testing. The number of subpopulations Th in percentage within CD45RA-negative $CD3^+CD4^+$-lymphocytes are demonstrated in quartile and medians ranges – Me ($Q_{0.25}$-$Q_{0.75}$), which were evaluated using multicolored cytometric analysis. The object of the study was venous blood from apparently healthy donors, obtained by puncture of a peripheral vein and collected in test tubes. Definition the severity of TBI was avowed in accordance with the established criteria. Moreover, the presence of concomitant severe damage to other organs and somatic pathology, as well as concomitant intoxication, are an exclusion criterion for recruitment into the group. Immunophenotyping of the main subpopulations of T-helpers of peripheral blood was leaded on the day of blood sampling. Preparation of peripheral blood and setting up the flow cytometer in accordance with the recommendations outlined by S.V. Khaidukov et al. [7].

To identify the main subpopulations of T-helpers, 200 μl of whole EDTA-stabilized peripheral blood was stained for surface antigens using the following combination of monoclonal antibodies conjugated to fluorochromes. Antibodies against CD3 (clone UCHT1) and CD4 (clone 13B8.2) were used to identify T-helpers – phenotype $CD3^+CD4^+$T-cells in peripheral blood. To separate the total pool of Th-cells at the main stages of maturation, antibodies against surface CD45RA (clone 2H4LDH11LDB9 (2H4)) and CD62L (clone DREG56) were used.

We used antibodies against CD3, CD4, CD45RA, and CD62L conjugated with APC-Alexa Fluor 750, Pacific Blue, FITC, and PE, respectively (Beckman Coulter, USA), and antibodies against CCR4, CCR6, CXCR3, and CXCR5 were conjugated with Brilliant Violet 510™, PE/Cy7, APC and PerCP/Cy5.5, respectively (Biolegend, USA). The destruction of erythrocytes was carried out using a VersaLyse lysis solution (Beckman Coulter, USA) – to 975 μl *ex tempore* was added 25 μl of IOTest 3 Fixative Solution (Beckman Coulter, USA), which was incubated at room temperature in a dark site for 15 minutes. After the destruction of erythrocytes, the samples were washed once with sterile saline (330 g for 7 minutes), after which the resulting cell pellet was resuspended in physiological solution with pH 7.2-7.4 containing 2% paraformaldehyde (Sigma-Aldrich, USA). For each of the samples, at least 40,000 $CD3^+CD4^+$-lymphocytes were analyzed. Coexpression of the chemokine receptors CCR4, CCR6, CXCR3, and CXCR5 was assessed using the "gating" tactic based on the construction of hierarchical dendrograms for CD45RA-negative Th memory [9]. The statistical comparisons of data between TBI patients and healthy controls were performed using the Mann–Whitney U-test. Differences were considered significant when

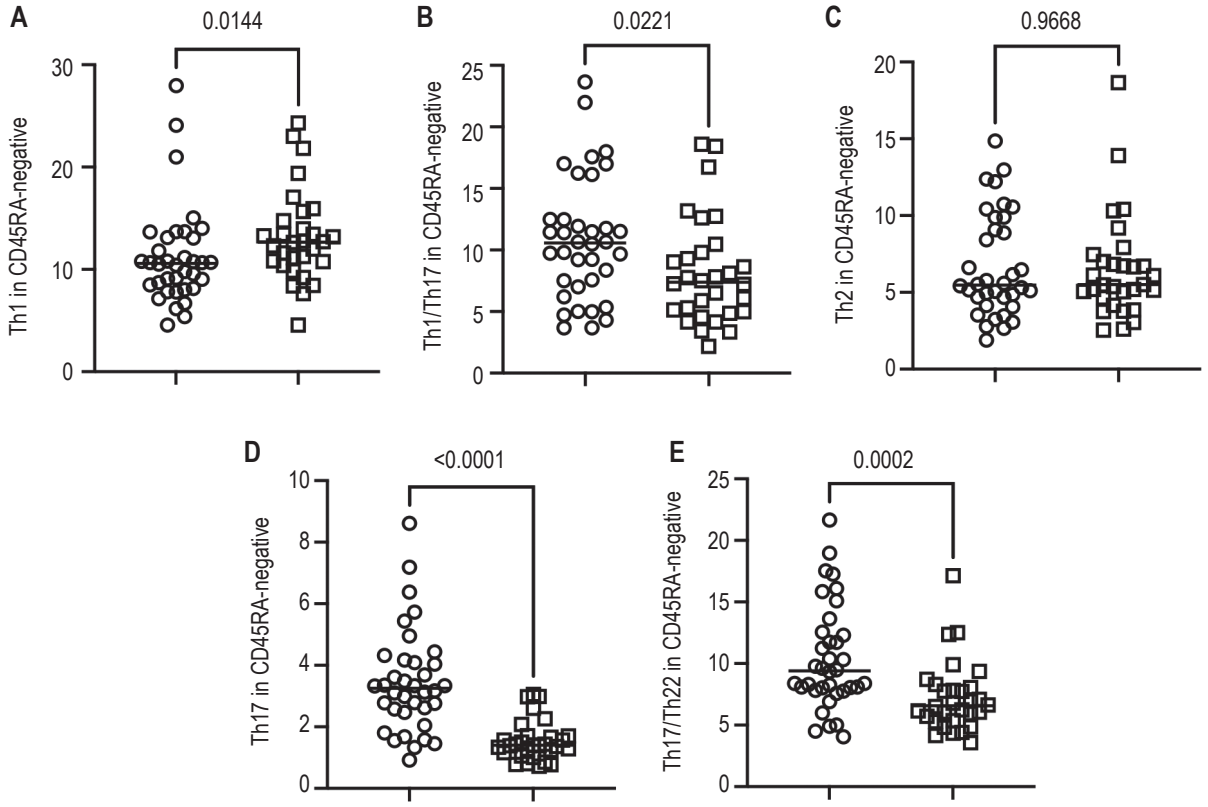

Figure 1. Comparative analysis of main subpopulation Th in brain contusion (n = 35, white circus) и healthy control (n = 52, white square)

Note. Dispersion charts A, B, C, D and E showing the percentages Th1 ($CXCR5^-CXCR3^+$ $CCR6^-CCR4^-$), Th1/Th17 ($CXCR5^-CXCR3^+CCR6^+CCR4^-$), Th2 ($CXCR5^-CXCR3^-CCR6^-CCR4^+$), Th17 ($CXCR5^-CXCR3vCCR6^+CCR4^+$) and Th17/Th22 ($CXCR5^-CXCR3^-CCR6^+CCR4^+$), accordingly in the peripheral blood of patients in brain contusion and healthy control group. The number indicates the percentage of the specified Th subpopulations amid general CD45RA−negative $CD3^+CD4^+$ cell population. Each dot represents either patient, and the horizontal bars show medians and quartile ranges – Me ($Q_{0.25}$-$Q_{0.75}$).

p values were $p < 0.05$. All of the statistical analysis of data was carried out with GraphPad Prizm 6 (GraphPad Software, USA).

Results and discussion

In the analysis of the CD45RA-negative population of $CD3^+CD4^+$-cells in patients with brain contusion immediately after admission compared with a control group based on the expression of chemokine receptors (CXCR5, CXCR3, CCR6, CCR4). This allowed us to define the phenotype of Th1/Th17 ($CXCR5^-CXCR3^+CCR6^+CCR4^-$) and Th17 ($CXCR5^-CXCR3^-CCR6^+CCR4^-$), Th1 ($CXCR5^-CXCR3^+CCR6^-CCR4^-$) and Th2 ($CXCR5^-CXCR3^-CCR6^-CCR4^+$), Th17/Th22 ($CXCR5^-CXCR3^-CCR6^+CCR4^+$)-cells. The results demonstrate in Figure 1. The clinical significance of T-helpers (Th) with the $CD3^+CD4^+$ phenotype is shown in a very wide range of diseases, when their content can be a significant marker for determining the severity of pathological conditions and assessing the effectiveness of the therapy used. Changes in the subpopulation composition of Th among $CD3^+CD4^+$-cells in patients with brain contusion were identified, which makes it possible to raise the question of the need to determine these cells subpopulations in clinical practice.

The comparison of these different Th subsets between patients and control group indicated significantly lower Th1 ($p < 0.05$) and significantly higher Th17 ($p < 0.0001$), Th1/Th17 ($p < 0.05$), Th17/Th22 ($p < 0.001$) with patients of brain contusion if compared with healthy controls. Also, we didn't observe significant changes in the number of Th2-cells with patients of MS-TBI if compared with healthy controls.

Among the cells of adaptive immunity, T-helpers play a leading role in the development of inflammation in response to traumatic brain injury. The revealed changes in the CD45RA-negative $CD3^+CD4^+$-cell population in patients with TBI allowed to raise the

question of the significance of determining these cells subpopulations, which may be a predictor of the course of TBI in the acute period. T-cells play a leading role in the neuroplasticity of the brain. It was shown for the first time that in patients with TBI in the peripheral blood against the background of a decrease in Th1 ($CXCR5^-CXCR3^+CCR6^-CCR4^-$), there is an increase in the relative amount of Th17 ($CXCR5^-CXCR3^-CCR6^+CCR4^-$), Th1/Th17 ($CXCR5^-CXCR3^+CCR6^+CCR4^-$), Th17/Th22 ($CXCR5^-CXCR3^-CCR6^+CCR4^+$). It is known that type Th1 play a role in learning and memory processes by limiting the activation of meningeal myeloid cells and promoting the expression of neutrophic factor [6]. As for T-helper 17 (Th17) – are capable of secreting a broad span of cytokines such as interleukin-17A (IL-17A), IL-21, IL-22, IL-25, IL-26, TNFα and chemokines. It should be noted that it is under the influence of IL-17 and IL-22, the receptors for which are present on the endothelial cells that make up the blood-brain barrier, that the structure of tight junctions is disrupted. In addition, most of the cytokines secreted by Th17 have pro-inflammatory activity. Their role in the pathogenesis of various autoimmune diseases has been noted. Given that myelination of nerve fibers plays an important role in ensuring motor activity and neuroplasticity, damage to myelin can negatively affect recovery after TBI, causing the development of cognitive and other disorders, contributing to the formation of cerebral atrophy. A number of authors are inclined to believe that Th17-type cells are not so much pro-inflammatory as act as modulators of the immune response [1]. The role of Th17 in human organ transplantation and autoimmune disease [2]. The revealed increase in the relative amount of Th1 among $CD3^+CD4^+$-cells consistent with the severity of the injury, since Th1 are responsible for chronic inflammation, thereby providing assistance to tissue macrophages and cytotoxic T-cells, and synthesizing a number of cytokines (IFNγ, IL-2, TNFα, TNFβ), having a pro-inflammatory nature [11]. Head trauma affects cellular immunity, thereby leading to a decrease or increase in certain subpopulations of T-cells among the CD45RA-negative population of $CD3^+CD4^+$-cells. It is known that with a brain injury, the activation of cells that are involved in inflammatory processes occurs, together with cells that are involved in reparative processes. Possibly these variations can be a prognostic factor for the formation of the clinical picture of post-traumatic neurodegeneration in the long-term period, which requires an improvement in treatment algorithms with the possible inclusion of an assessment of the immune status and rehabilitation of patients with brain contusion to improve management tactics.

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Авторы:

Норка А.О. *— старший лаборант кафедры иммунологии ФГБОУ ВО «Первый Санкт-Петербургский государственный медицинский университет имени академика И.П. Павлова» Министерства здравоохранения РФ; ординатор кафедры неанотологии с курсами неврологии и акушерства-гинекологии ФП и ДПО ФГБОУ ВО «Санкт-Петербургский государственный педиатрический медицинский университет» Министерства здравоохранения РФ, Санкт-Петербург, Россия*

Воробьев С.В. *— д.м.н., главный научный сотрудник научно-исследовательской лаборатории неврологии и нейрореабилитации ФГБУ «Национальный медицинский исследовательский центр имени В.А. Алмазова» Министерства здравоохранения РФ; профессор кафедры клинической лабораторной диагностики ФГБОУ ВО «Санкт-Петербургский государственный педиатрический медицинский университет» Министерства здравоохранения РФ, Санкт-Петербург, Россия*

Кузнецова Р.Н. *— к.м.н., доцент кафедры иммунологии ФГБОУ ВО «Первый Санкт-Петербургский государственный медицинский университет имени академика И.П. Павлова»; врач аллерголог-иммунолог Медицинского центра ФБУН «Санкт-Петербургский научно-исследовательский институт эпидемиологии и микробиологии имени Пастера», Санкт-Петербург, Россия*

Серебрякова М.К. *— аспирант, научный сотрудник отдела иммунологии ФГБНУ «Институт экспериментальной медицины», Санкт-Петербург, Россия*

Кудрявцев И.В. *— к.б.н., старший научный сотрудник отдела иммунологии ФГБНУ «Институт экспериментальной медицины»; доцент кафедры иммунологии ФГБОУ ВО «Первый Санкт-Петербургский государственный медицинский университет имени академика И.П. Павлова» Министерства здравоохранения РФ, Санкт-Петербург, Россия*

Коваленко С.Н. *— преподаватель кафедры нейрохирургии ФГБВОУ ВО «Военно-медицинская академия имени С.М. Кирова» Министерства обороны РФ, Санкт-Петербург, Россия*

Authors:

Norka A.O., *Senior Laboratory Assistant, Department of Immunology, First St. Petersburg State I. Pavlov Medical University; Resident, Department of Neonatology with Courses of Neurology and Obstetrics-Gynecology, Faculty of Continuing Education and Professional Training, St. Petersburg State Pediatric Medical University, St. Petersburg, Russian Federation*

Vorobyev S.V., *PhD, MD (Medicine), Chief Research Associate, Research Laboratory of Neurology and Neurorehabilitation, V. Almazov National Medical Research Centre, St. Petersburg, Russian Federation; Professor, Department of Clinical Laboratory Diagnostics, State Pediatric Medical University, St. Petersburg, Russian Federation*

Kuznetsova R.N., *PhD (Medicine), Associate Professor, Department of Immunology, First St. Petersburg State I. Pavlov Medical University; Allergist-Immunologist, Medical Centre, St. Petersburg Pasteur Research Institute of Epidemiology and Microbiology, St. Petersburg, Russian Federation*

Serebriakova M.K., *Postgraduate Student, Research Associate, Department of Immunology, Institute of Experimental Medicine, St. Petersburg, Russian Federation*

Kudryavtsev I.V., *PhD (Biology), Senior Research Associate, Department of Immunology, Institute of Experimental Medicine; Associate Professor, Department of Immunology, First St. Petersburg State I. Pavlov Medical University, St. Petersburg, Russian Federation*

Kovalenko S.N., *Lecturer, Department of Neurosurgery, S Kirov Military Medical Academy, St. Petersburg, Russian Federation*

Поступила 04.05.2021
Отправлена на доработку 11.05.2021
Принята к печати 13.05.2021

Received 04.05.2021
Revision received 11.05.2021
Accepted 13.05.2021