РОЛЬ IL-6 В ИММУНОПАТОГЕНЕЗЕ УШИБА ГОЛОВНОГО МОЗГА РАЗЛИЧНОЙ СТЕПЕНИ ТЯЖЕСТИ

Норка А.О.[1, 2], Воробьев С.В.[3], Кузнецова Р.Н.[1, 2], Лапин С.В.[2], Коробова З.Р.[1, 2], Монашенко Д.Н.[3, 4], Тотолян Арег А.[1, 2]

[1] ФБУН «Санкт-Петербургский научно-исследовательский институт эпидемиологии и микробиологии имени Пастера», Санкт-Петербург, Россия
[2] ФГБОУ ВО «Первый Санкт-Петербургский государственный медицинский университет имени академика И.П. Павлова» Министерства здравоохранения РФ, Санкт-Петербург, Россия
[3] ФГБУ «Национальный медицинский исследовательский центр имени В.А. Алмазова» Министерства здравоохранения РФ, Санкт-Петербург, Россия
[4] СПбГБУЗ «Городская Больница № 26», Санкт-Петербург, Россия

Резюме. Иммунная система имеет ключевую роль в патогенезе черепно-мозговой травмы. Травматические повреждение головного мозга обуславливает высвобождение молекул «опасности» с последующем вовлечением клеток врожденного иммунного ответа, инициирующих развитие нейровоспаления. Возникающие нарушения в иммунной системе при черепно-мозговой травме являются проявлением защитной реакции организма, при этом исход черепно-мозговой травмы обусловлен не только тяжестью первичного поражения головного мозга, но и вторичными реакциями. Нейровоспаление – это иммунный ответ на поражение мозга, в ходе которого происходит высвобождение молекул, связанных с повреждением, дальнейшей активацией и пролиферацией клеток микроглии и астроглии, миграцией в зону повреждения Т-лимфоцитов, обладающих как протективным, так и деструктивным действием в отношении мозговой ткани. Управляющую роль в данных процессах играют цитокины – белки, продуцируемые резидентными клетками глии, опосредующие межклеточные взаимодействия при различных патологических состояниях. Уже на ранних стадиях развития в ответ на травму клетками микроглии синтезируются провоспалительные цитокины, которые дополнительно стимулируют активацию микроглии и блокируют процессы ремиелинзации. Показано, что после тяжелой травмы головного мозга высокие концентрации IL-6 в цереброспинальной жидкости демонстрируют прямую корреляцию со степенью тяжести и исходом заболевания. Целью данного исследования явилось изучение особенностей уровня IL-6 в цереброспинальной жидкости пациентов с ушибом головного мозга легкой, средней и тяжелой степени тяжести. Методом мультиплексного анализа по технологии xMAP определяли концентрацию IL-6 в цереброспинальной жидкости. Контролем служили образцы цереброспинальной жидкости пациентов с сотрясением головного мозга. Обнаружено достоверно повышенное содержание у всех пациентов с ушибом головного мозга: 19,59 пг/мл в группе с ушибом легкой степени тяжести, 103,6 пг/мл в группе с ушибом средней степени тяжести и 2225 пг/мл в группе с ушибом тяжелой степени тяжести против 2,58 пг/мл в контрольной группе. Установлена прямая корреляционная взаимосвязь с содержанием основного белка миелина в цере-

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:

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

Образец цитирования:

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броспинальной жидкости, что отражает степень воспаления и процессов нейродегенерации. Выявление особенностей содержания IL-6 у больных с ушибом головного мозга может свидетельствовать об его важной роли в течения заболевания. А также требует дополнительного более детального изучения, сопоставления с результатами содержания IL-6 в периферической крови.

Ключевые слова: черепно-мозговая травма, биомаркер, провоспалительные цитокины, нейровоспаление, IL-6, основной белок миелина, мультиплексный анализ

ROLE OF IL-6 IN THE IMMUNOPATHOGENESIS OF MILD, MODERATE AND SEVERE TBI

Norka A.O.[a, b], Vorobyev S.V.[c], Kuznetsova R.N.[a, b], Lapin S.V.[b], Korobova Z.R.[a, b], Monashenko D.N.[c, d], Totolian Areg A.[a, b]

[a] *Saint Petersburg Pasteur Institute, St. Petersburg, Russian Federation*
[b] *First St. Petersburg State I. Pavlov Medical University, St. Petersburg, Russian Federation*
[c] *V. Almazov National Medical Research Centre, St. Petersburg, Russian Federation*
[d] *St. Petersburg City Hospital No. 26, St. Petersburg, Russian Federation*

Abstract. Traumatic brain injury (TBI) results in a significant inflammatory burden that increase the production of inflammatory mediators and biomarkers. The immune system plays a key role in the pathogenesis of traumatic brain injury. Neuroinflammatory mediators released from resident glia (activated microglia and astrocytes) inside the brain recruit immune cells where cytokines are small soluble proteins that confer instructions and mediate communication among immune and non-immune cells. Interleukin-6 (IL-6) is a proinflammatory cytokine known to be elevated after trauma, and a major contributor to the inflammatory response following TBI. Previous studies have investigated associations between IL-6 and outcome following TBI, but to date, studies have been inconsistent in their conclusions. The purpose of the current study was to assessment of cerebrospinal fluid (CSF) interleukin-6 (IL-6) and MBP levels in patients with TBI. Samples of cerebrospinal fluid of 85 patients with TBI were examined. Concentrations IL-6 were measured via xMAP multiplexing technology. The control was the course of CSF in patients with concussion. An increased content was found in all patients with traumatic brain injury: 19.59 pg/mL in the group with mild traumatic brain injury; 103.6 pg/mL in the group with moderate traumatic brain injury; and 2225 pg/mL in the group with severe traumatic brain injury load versus 2.58 pg/mL in the control group. A direct correlation was found with the presence of basic myelin proteins in the cerebrospinal fluid, which indicates the degree of damage and neurodegeneration processes. Identification of the features of IL-6 content in patients with brain injury may indicate its important role in the course of disease. It also requires additional more detailed study, including comparison with IL-6 content in peripheral blood.

Keywords: traumatic brain injury, biomarker, inflammatory cytokines neuroinflammation, IL-6, myelin basic protein, multiplex analysis

Introduction

Traumatic brain injury (TBI) is defined as intracranial injury when a direct and indirect external mechanical force transmitted to the head or body results in structure of the brain damage and dysfunction, change in its functioning [5]. Extensive progress has been made in understanding the immunopathogenesis over the last 10 years. Many of the issues that TBI patients face are thought to be mediated by the immune system. TBI results in a significant inflammatory burden that increases the production of inflammatory mediators and biomarkers. It is a disease with a wide variety of injury mechanisms and tissue pathologies.

The clinical presentation and prognosis TBI depend on both the type and severity of the exposure termed the "primary injury" which leads to primary structural and functional brain damage of varying degrees and prevalence at the molecular, subcellular, cellular, tissue and organ levels with abnormalities of the central regulation of body system. When the brain is injured, it can cause disturbance of cerebral circulation, fluid circulation, hypothalamic-pituitary-adrenal system and blood-brain barrier (BBB) [3]. Following the primary injury extensive and lasting damage is sustained through a complex cascade of events referred to as "secondary injury". Secondary injury includes BBB-disturbance, excitotoxicity, mitochondrial dysfunction, oxidative stress and neuroinflammation [10]. Thus, the pathogenesis of brain injury may be divided into two injury-mechanisms: primary and secondary [12].

There is increasing interest in the role the immune system in TBI pathogenesis because neuroinflammation caused by detrimental or beneficial outcomes. In addition, neuroinflammation leads to appear CSF Myelin basic protein (MBP). MBP is a constituent of the sheath, is essential for normal myelination and axonal signal conduction, and mediates adhesion

between cytoplasmic surfaces of individual myelin layers. Brain injury contributes to increased MBP in blood and CSF. Neuroinflammation instigated by TBI is a complex immune process resulting from a mechanical compression insult and depending on the degree of the insult and leads to axon damage occurs due to direct cytotoxic intercellular interaction or due to the synthesis of pro-inflammatory cytokines and chemokines [2].

Already at the early stages of development in response to damage microglial cells synthesize IL-1β, IFNγ, IL-6, IL-12, IL-18, which can subsequently induce the synthesis of GM-CSF and CCL2 by astrocytes, additionally stimulating microglial activation and blocking remyelination processes [4, 6]. Elevated levels of many cytokines have been noted in peripheral blood plasma and cerebrospinal fluid (CSF), but the clinical results of their determination are often contradictory [12]. It has been shown that after TBI high concentrations CSF IL-6 directly correlate with the severity and outcome [7]. IL-6 together with TGFβ stimulates the maturation clones of T-lymphocytes into of Th17 and suppresses the development of Treg, which provides aggravating the course of the disease [8].

One of the factors in the development of the inflammatory process induced by trauma and accompanied by a structural impairment of the brain and BBB permeability is immune dysfunction the main regulators of which are cytokines and their synthesis have provided by resident neuronal and glial cells of the brain that secrete pro- and anti-inflammatory cytokines [1]. In addition, the source of cytokines in the CNS is the cells of the immune system recruited to the focus of inflammation due to a violation of the BBB [4]. The inflammatory process that occurs during traumatic damage to brain tissues accompanied by hypersecretion of proinflammatory and inhibitory cytokines is essential during and after TBI. Canonically, a shift in cytokine profile towards anti-inflammatory mediator predominance can increase neuroprotection and regeneration of the CNS after injury [7, 11]. However, the role of IL-6 in TBI pathogenesis remains insufficiently studied and literature reviews are often contradictory, debatable and require further study.

The purpose of the current study was to assessment of CSF Interleukin-6 (IL-6) and MBP levels in patients with TBI.

Materials and methods

Informed consent was obtained from patients for sample collection. The study included 85 TBI patients (aged 18-55 years (mean: 42.3±11.3). Cerebrospinal fluid (CSF) samples were obtained from patients with the diagnosis of TBI at the time of the patient's admission to the hospital. Control CSF samples were obtained from twenty-five age-matched controls who underwent lumbar puncture.

According to the international classification, TBI is classified as mild, moderate or severe, typically based on the Glasgow Coma Scale (GCS) score:

1 group – control (n = 25);

2 group – mild brain injury (n = 30);

3 group – moderate brain injury (n = 31);

4 group – severe brain injury (n = 24);

CSF was obtained by lumbar puncture. All samples were collected in tubes and they were centrifuged (1100 g, 10 min, room temperature), aliquoted into several portions and frozen at -80 °C until assayed.

The CSF IL-6 (pg/mL) level were measured using Luminex xMAP technology for multiplexed quantification. The samples were analyzed using the "Milliplex MAP" (Millipore) (USA) with magnetic microspheres "Milliplex Mag" (USA), according to the manufacturer's instructions. Registration and analysis of data on the device "Luminex MAGPIX" (Luminex) (USA). All samples were assayed in duplicate wells and the mean of the ensuing results was used.

Statistical analysis of the data was performed on commercially available software (GraphPad Prism 5.00 for Mac). The nonparametric Mann–Whitney U test was used for analysis of data. A P value less than 0.05 was considered to be statistically significant. Data is presented as the median (Me) and interquartile range ($Q_{0.25}$-$Q_{0.75}$). Spearman's correlation coefficient was used for assesses how well the relationship between MBP and IL-6.

Results and discussion

In order to investigate the cytokine level patients with brain injury of varying severity underwent lumbar puncture according to indications. A comparative analysis was carried out with samples of the cerebrospinal fluid of patients with concussion, which was due to the absence of structural changes in them, on the one hand, as well as the difficulties of collecting cerebrospinal fluid (CSF) from apparently healthy individuals, as a group that does not have indications for this medical manipulation, on the other hand.

Our study was showed that TBI patients had a significantly higher CSF level of IL-6 as compared to the 1st group (Control) (Table 1).

IL-6 in all groups with TBI: 19.59 pg/mL (8.4-46.5) at p = 0.0117 in the 2nd group (Mild TBI), 103.6 pg/mL (27.4-138.7) at p < 0.0001 in the 3rd group (Moderate TBI) and 2225 pg/mL (872.3-3739) in the 4th group (Severe TBI) at p < 0.0001 as compared to the 1st group (2.58 pg / mL (1.1-3.7)).

In order to investigate the diagnostic values of the IL-6 for TBI we performed receiver operating characteristic (ROC) curve analysis. Using ROC curves, sensitivity and specificity were calculated for each possible threshold value. The ROC characteristic significant increased were IL-6 (Figure 1): sensitivity – 87.5%; specificity -100%; AUC = 0.906; Cutoff = 11.4 pg/mL, p = 0.0117 for the 2nd group (Mild TBI); sensitivity – 94%; specificity -100%; AUC = 0.941; Cutoff = 17.33 pg/mL, p < 0.0001 for the 3rd group (Moderate TBI); sensitivity -100%; specificity – 87.5%; AUC = 0.961; Cutoff = 241 pg/mL, p < 0.0001 for the 4th group (Severe TBI). The AUC of IL-6 all greater than 0.7 which indicated that they represented a high diagnostic value.

Additionally, to identify IL-6 characteristics of TBI with different severity we performed receiver operating characteristic (ROC) curve analysis. The optimal cut-off for CSF IL-6 application in the 3rd group was 46.14 pg/mL; the sensitivity and specificity were 69% and 75%, respectively (Figure 2).

The optimal cut-off for CSF IL-6 application in the 4th group was 240.9 pg/mL; the sensitivity and specificity were 100% and 88%, respectively. The 4th group appeared to have the best discriminatory ability with an AUC of 0.981.

In this paper, we report the optimal cut-off for CSF IL-6 the 2nd group was 11.4 pg/mL.

Spearman's test showed there was clinically relevant correlation between IL-6 and MBP level (Figure 3) in TBI patients ($r = 0.465$; $p = 0.017$). These findings reflect the degree of inflammation and the process of neurodegeneration.

TBI activates microglia, the endogenous brain immune cells and a major source of pro-inflammatory cytokines in the central nervous system. In recent years, the functions and role of IL-6 have been actively studied in the in the pathogenesis of inflammation from brain injury.

Some studies have identified associations between IL-6 levels and outcome following TBI. Inflammation in the context of TBI can be contributed to CNS damage, including astrogliosis and disruption of the BBB. Obviously, neuroinflammation contribute to breakdown of the BBB and infiltration of immune cells. So, in the study by Monsour M. [9] an increase in IL-6 is considered as an unfavorable marker of outcomes. According to our results, an increased concentration of IL-6 was found in all patients with TBI and had significantly significant informative indicators ($p < 0,05$).

TABLE 1. CEREBROSPINAL FLUID LEVELS OF CYTOKINES (PG/ML) IN PATIENTS WITH TBI, Me ($Q_{0.25}$-$Q_{0.75}$)

Cytokines	Cerebrospinal fluid levels of cytokines (pg/mL)				Statistically significant (p)
	Concussion (1st group)	Mild TBI (2nd group)	Moderate TBI (3rd group)	Severe TBI (4th group)	
	n = 25	n = 30	n = 31	n = 24	
IL-6	2.5 (1.1-3.7)	19.59 (8.4-46.5)	103.6 (27.4-138.7)	2225.0 (872.3-3739.0)	$p_{1-2} = 0.011$ $p_{1-3} < 0.0001$ $p_{1-4} < 0.0001$

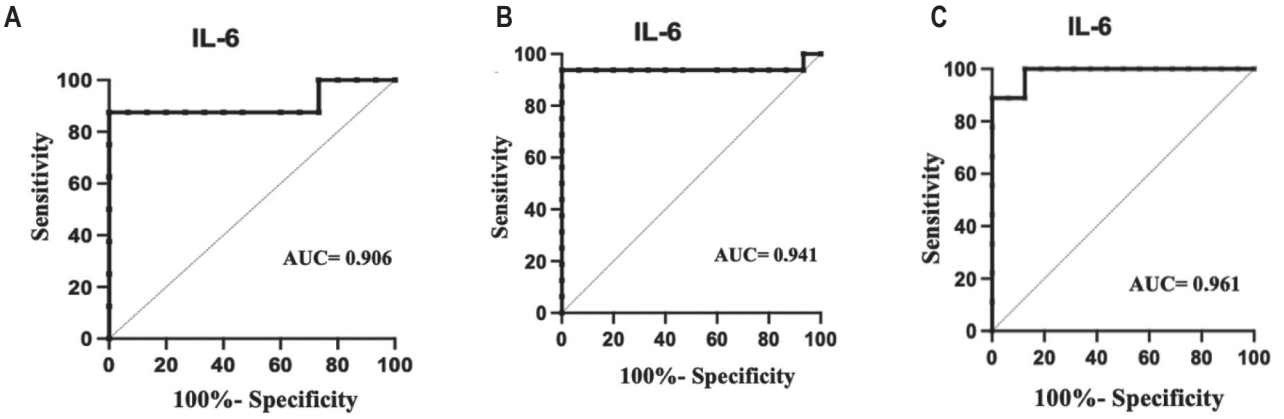

Figure 1. ROC curves and AUC of CSF IL-6: mild TBI (A), moderate TBI (B) and severe TBI (C) compared to control

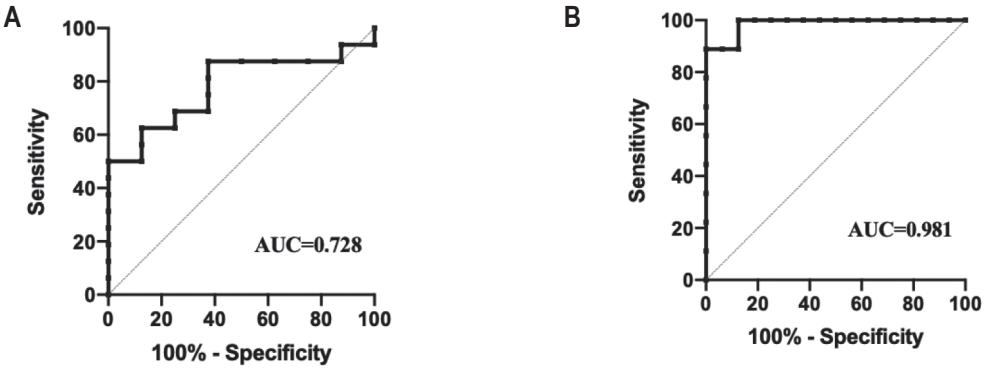

Figure 2. ROC curve and AUC of CSF IL-6: mild TBI (A) and moderate TBI (B) compared to severe TBI

The use of ROC analysis data allows for differential diagnosis of brain contusion based on the assessment CSF IL-6 showed that IL-6 ≥ 11.4 pg/mL – Mild TBI, CSF IL-6 ≥ 46.14 pg/mL – Moderate TBI, CSF IL-6 ≥ 240.9 pg/mL – Severe TBI (Figure 4).

Also, based on the fact that IL-6 is a pro-inflammatory cytokine and can influence the degree and risk of demyelination, a correlation analysis was performed between IL-6 and MBP level. Thus, MBP is a specific structural component of neuronal membranes, which is necessary for myelination of oligodendrocytes and maintenance of myelin structure. The detection of MBP in the CSF is a sensitive marker of myelin degradation. In healthy people, this indicator is not determined. Myelin degradation in addition to TBI is possible with neuroinfectious and demyelinating diseases. Additionally, the level of IL-6 was positively correlated with the level of MBP ($r = 0.465$; $p = 0.017$).

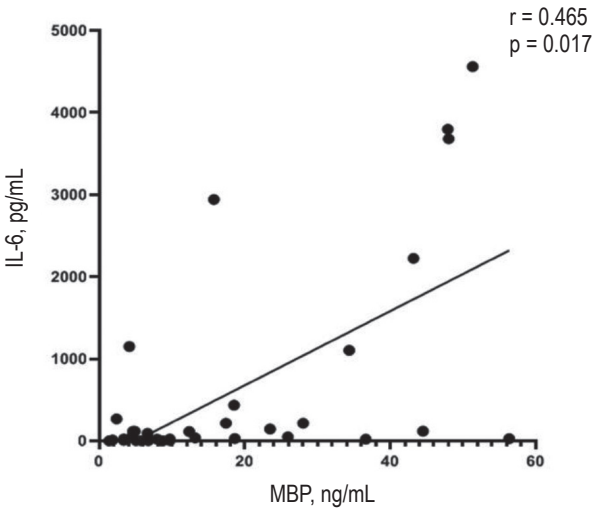

Figure 3. Correlation between the concentration of myelin basic protein (ng/mL) and IL-6 (pg/mL)

Note. r, Spearman's correlation coefficient; MBP, myelin basic protein.

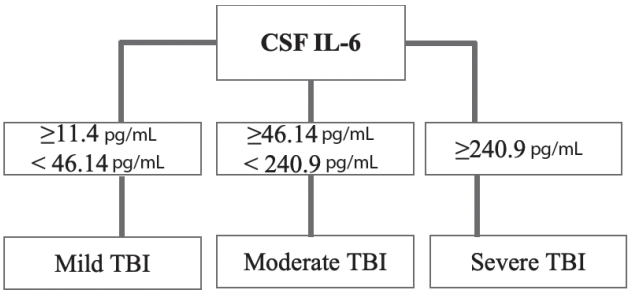

Figure 4. Algorithm in differential diagnosis of brain injury

Conclusion

Thus, TBI is a reaction of the whole organism to CNS injury. It causes a violation of homeostasis and is accompanied by a complex of morphofunctional changes not only in the area of damage, but throughout the brain, and then in other organs and systems. The inflammatory process that occurs during traumatic damage to brain tissues, accompanied by hypersecretion of pro-inflammatory cytokines (IL-6), is essential during and after TBI.

All of these results suggest the important role of IL-6 in TBI immunopathogenesis, as a cytokine that supports neuroinflammation and which is involved in white matter damage.

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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; врач-невролог медицинского центра ФБУН «Санкт-Петербургский научно-исследовательский институт эпидемиологии и микробиологии имени Пастера», 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, 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» Министерства здравоохранения РФ; врач — аллерголог-иммунолог Медицинского центра ФБУН «Санкт-Петербургский научно-исследовательский институт эпидемиологии и микробиологии имени Пастера», Санкт-Петербург, Россия*

Лапин С.В. *— к.м.н., заведующий лабораторией аутоиммунной диагностики ФГБОУ ВО «Первый Санкт-Петербургский государственный медицинский университет имени академика И.П. Павлова» Министерства здравоохранения РФ, Санкт-Петербург, Россия*

Коробова З.Р. *— младший научный сотрудник лаборатории молекулярной иммунологии ФБУН «Санкт-Петербургский научно-исследовательский институт эпидемиологии и микробиологии имени Пастера»; старший лаборант кафедры иммунологии ФГБОУ ВО «Первый Санкт-Петербургский государственный медицинский университет имени академика И.П. Павлова» Министерства здравоохранения РФ, Санкт-Петербург, Россия*

Монашенко Д.Н. *— к.м.н., врач-нейрохирург, заведующий 1 НХО СПбГБУЗ «Городская больница № 26»; доцент кафедры нейрохирургии ФГБУ «Национальный медицинский исследовательский центр имени В.А. Алмазова» Министерства здравоохранения РФ, Санкт-Петербург, Россия*

Тотолян Арег А. *— д.м.н., профессор, академик РАН, директор, ФБУН «Санкт-Петербургский научно-исследовательский институт эпидемиологии и микробиологии имени Пастера»; заведующий кафедрой иммунологии ФГБОУ ВО «Первый Санкт-Петербургский государственный медицинский университет имени академика И.П. Павлова» Министерства здравоохранения РФ, Санкт-Петербург, Россия*

Authors:

Norka A.O., *Senior Laboratory Assistant, Department of Immunology, First St. Petersburg State I. Pavlov Medical University; Neurologist, Medical Centre, St. Petersburg Pasteur Institute, 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*

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 Institute, St. Petersburg, Russian Federation*

Lapin S.V., *PhD (Medicine), Head, Laboratory of Autoimmune Diagnostics, First St. Petersburg State I. Pavlov Medical University, St. Petersburg, Russian Federation*

Korobova Z.R., *Junior Research Associate, Laboratory of Molecular Immunology, Saint Petersburg Pasteur Institute; Senior Assistant, Department of Immunology, First St. Petersburg State I. Pavlov Medical University, St. Petersburg, Russian Federation*

Monashenko D.N., *PhD (Medicine), Neurosurgeon, St. Petersburg City Hospital No. 26; Associate Professor, Department of Neurosurgery, V. Almazov National Medical Research Centre, St. Petersburg, Russian Federation*

Totolian Areg A., *PhD, MD (Medicine), Professor, Full Member, Russian Academy of Science, Director, Saint Petersburg Pasteur Institute; Head, Department of Immunology, First St. Petersburg State I. Pavlov Medical University, St. Petersburg, Russian Federation*

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