Original article

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Features of peripheral and intrathecal content of immunological markers of inflammation in combatants with mild TBI depending on the chronicity of its course

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Aim: To investigate the levels of inflammatory mediators of the immune system in blood serum and cerebrospinal fluid (CSF) in combatants with mild traumatic brain injury (mTBI) at different time periods after its acquisition.

Materials and methods: IL-6, TNFα, IL-10 and TGFβ1 concentrations were measured according to the instructions of the «Human ELISA Kit» (Elabscience Bionovation Inc., USA) in 53 paired serum and CSF samples from patients with combat mTBI.

Results: In the general group of patients with mTBI, a significant increase in the peripheral content of IL-6, IL-10, TGFβ1 was found, compared with healthy donors (control). When studying these indicators depending on the duration of the post-traumatic period, a persistent increase in the level of IL-6 was shown in combination with significantly increased TGFβ1 concentration indicators and a tendency to an increased level of IL-10. At the same time, the analysis of the central content of inflammatory biomarkers did not reveal their significant changes at different times after TBI, with the exception of a tendency to a decrease in the presence of IL-6, the presence of which in paired analytes prevailed in CSF along with the prevalence of peripheral finding of TNFα, IL-10, TGFβ1.

Conclusions: Thus, the increased content of circulating pro-inflammatory IL-6 and TNFα in the intermediate and remote periods of the course of TBI and a significantly (approximately 6 times) increased level of pleiotropic TGFβ1 in combination with anti-inflammatory IL-10 indicate the persistent nature of inflammation, which indicates the possibility of induction of neurodegenerative processes in combatants with TBI. Such results confirm the feasibility of comprehensive monitoring of immunological markers of inflammation to identify potential directions for adequate pathogenetic therapy even in the context of significantly distant consequences of TBI.

Keywords: *combat mild TBI; inflammatory markers of the immune system; time periods of TBI*

Introduction

Traumatic brain injuries, which are widespread among young people, are often a factor in the development of long-term neurological deficits, cognitive impairments, and emotional disorders. These consequences pose important medical and socio-economic challenges associated with high mortality and disability of patients, as well as with the triggering value of post-traumatic neuroinflammation in the occurrence of neurodegenerative processes, which subsequently lead to an increased risk of developing Alzheimer's and Parkinson's diseases, chronic traumatic encephalopathy, etc. [1–7]. Currently, TBI is a global health problem worldwide, exacerbated by inadequate monitoring and the lack of effective diagnostic methods and pathogenetic treatment at various stages of the post-traumatic period, which can cause complications of the disease due to the initiation of complex biochemical cascades and immunological processes leading to secondary neuroinflammation [8–12].

Moreover, the issue of TBI-related consequences is becoming increasingly urgent in the context of a full-scale war of aggression in Ukraine with a violation of the world charter of the sovereignty of democratic states due to the Russian invasion. This applies both to direct participants in hostilities using modern destructive weapons, and to the civilian population, which is permanently exposed to stochastic terrorist bombing.

In the overall structure of brain injuries, mine-explosive injuries are detected in 70% of victims, and at least 80% of them are diagnosed as mild injuries [13, 14]. The most common type of mTBI among military personnel is concussion and mild brain contusion, and such injuries, most often caused by an explosion, are considered "signature wounds" of the wars in Iraq and Afghanistan [15–18]. Currently, there are quite limited objective indicators for identifying individuals with a high risk of developing neuropsychiatric disorders and adverse consequences and complications [18], in particular, among military personnel and veterans of

modern wars against the background of the staggering spread of TBI [19].

It is known that TBI is accompanied by an immediate immune system response. Innate immunity helps to reduce the progression of pathogens by activating the healing processes and remodeling of nerve tissue damage while also preparing the body for an adaptive immune response, which is based on the activation of T and B lymphocytes, the excess of which has the ability to stimulate neuroinflammation [11]. Previous studies have documented a reversible increase in the levels of inflammatory cytokines IL-6, TNFα and IL-10 within 24 hours after the explosion during training [20], and as a result of the acute phase reaction in combatants with severe TBI [21]. The cytokines promote the induction of the first phase of inflammation, which is aimed at neuroprotection and restoration of homeostasis and nervous tissue integrity [22, 23].

Accordingly, the study of neuroinflammation and its associated immune biomarkers is of growing importance [23, 24]. Evidence suggests that uncontrolled or insufficiently effective regulation of the balance of pro- and anti-inflammatory activity of mediators of the immunological response may be the cause of the formation of long-term symptoms of CNS damage due to TBI [25–28] with the development of autoimmune processes and the subsequent formation of neurodegenerative pathology.

It is noteworthy that most of the literature on the pathogenesis of neuroinflammation focuses on studying the mechanisms of its development, which are activated in patients with severe TBI in the most acute period (the first hours, days, weeks) [14, 21, 29, 30]. At the same time, studies of immunological markers in the chronic course of combat mTBI are not sufficiently presented.

Taking this into account, the aim of the work was to study the levels of inflammatory mediators of the immune system in the serum and CSF in combatants with mTBI at different time periods after its acquisition.

Materials and methods

Study participants

The study was performed using 53 paired serum and CSF samples obtained from male patients aged 36.03±1.40 years, who were treated in the neurosurgical department of the P. V. Voloshyn Institute of Neurology, Psychiatry and Narcology of the National Academy of Medical Sciences of Ukraine during 2024 years.

Inclusion criteria

Patients who suffered mTBI in the form of concussion and mild brain contusion during active hostilities in Ukraine.

Exclusion criteria

Severe TBI, the presence of multiple trauma and chronic somatic diseases.

Group characteristics

Depending on the duration of the post-traumatic period, the combatants were divided into three groups: I (acute period) – 1.22±0.19 months; II (interim period) – 6.39±0.74 months; III (remote period) – 13.43±1.13 months. The control group, limited to serum samples only for ethical and medical reasons, consisted of 8 practically healthy male donors aged 37.38±2.40 years. All patients with TBI, regardless of the time after its acquisition, were included in the general comparison group – TBI.

Study design

Peripheral blood with a volume of up to 8 ml was obtained by puncture from the cubital vein with subsequent centrifugation (4000 revolutions per minute, within 10 minutes), serum collection (120 μl into separate Eppendorf tubes) and storage at -80°C until quantitative ELISA.

CSF samples were obtained with patient consent during neurosurgical intervention by lumbar puncture with subsequent storage of the required number of its samples (120 μl) at -80°C. The process from serum and CSF sample collection to storage lasted no more than 3 hours. Serum and CSF samples were used with one freeze-thaw cycle.

The concentrations of immune system mediators were measured spectrophotometrically with recording of values on a microplate enzyme immunoassay analyzer GBG Stat Fax 2010 (USA) with a wavelength of 450 nm according to the instructions and protocols of the manufacturer of «Human ELISA Kit» from «Elabscience Bionovation Inc.» (USA), «…which are used for their determination in blood serum and other biological fluids of the body (plasma, CSF, tissue homogenates, supernatants of cell structures, etc.)». The concentrations of pro-inflammatory cytokines IL-6 and TNFα and anti-inflammatory IL-10 and TGFβ1 were determined. The sensitivity of the analyses was: IL-6 – 0.94 pg/ml, IL-10 – 0.94 pg/ml, TNFα – 4.69 pg/ml, TGFβ1 – 18.75 pg/ml; detection range: IL-6 – 1.56–100 pg/ml, IL-10 – 1.56–100 pg/ml, TNFα – 7.81–500 pg/ml, TGFβ1 – 31.25–2000 pg/ml. Since the «Human ELISA Kit» is intended for research purposes only and cannot be used for clinical diagnosis or any other related procedures, reference values for cytokine levels in peripheral blood and CSF are not provided in this test system.

Statistical analysis

Statistical analysis of the results was performed using the Microsoft Office Excel program using Student's t-test to assess differences between comparison groups.

Results

Determination of concentrations of inflammatory mediators of the immune system in the generalized group of patients with combat TBI revealed a significant increase, compared with controls, in the peripheral content of pro-inflammatory IL-6, anti-inflammatory IL-10 and TGFβ1 (***Table 1***). When studying these indicators depending on the duration of the post-traumatic period, it was shown that the increased level of IL-6 production was preserved in combination with significantly increased, relative to healthy donors, serum TGFβ1 concentrations and a tendency to an increased level of IL-10 at all stages of the course of TBI.

This article contains some figures that are displayed in color online but in black and white in the print edition.

At the same time, analysis of the content of inflammatory markers in CSF did not reveal significant differences at different times after TBI, with the exception of a tendency to decrease the concentration of IL-6 depending on the increase in the duration of the post-traumatic period. When comparing the ratio of peripheral and central inflammatory cytokine content in paired biological analytes, it was found that in the process of chronicity of TBI consequences in combatants, only the content of IL-6 prevails in CSF along with the prevalence of peripheral TNFα, IL-10 and TGFβ1 (***Fig. 1***).

The obtained results do not contradict the literature data on the content of immune system mediators in patients with TBI, taking into account the severity and time periods of its course. Thus, when studying the concentrations of IL-6, IL10, TNFα, TGFβ1, their multidirectional correlation was revealed with a particularly significant (28 times) predominance of IL-6 content in CSF compared to serum, which demonstrated its important role in the initiation of the acute phase [21, 30], and in our study, the quantitative features of the representation of inflammatory cytokines in the brain and blood reflect the consequences of chronic neuroinflammation.

Table 1. Levels of pro- and anti-inflammatory cytokines in the serum and CSF in patients with combat mTBI at different periods after its receipt

Cytokines (pg/ml)	Analytes	Groups				
		Control	mTBI	I (acute period, 1.22±0.19 months)	II (interim period, 6.39±0.74 months)	III (remote period, 13.43±1.13 months)
IL-6	serum	0.20±0.03	0.30±0.04**	0.32±0.05**	0.26±0.05	0.32±0.07
	CSF	—	1.06±0.19	1.68±0.54	0.81±0.09#	0.76±0.16#
IL-10	serum	0.04±0.01	0.38±0.14***	0.35±0.26	0.46±0.24*	0.34±0.26
	CSF	—	0.19±0.04	0.27±0.10	0.14±0.05	0.14±0.05
TNFα	serum	15.93±3.54	65.04±31.02*	5.37±3.01**	51.39±26.45#	149.44±94.40
	CSF	—	6.95±0.85	6.00±1.36	5.94±1.00	9.17±1.91
TGFβ1	serum	242.80±81.70	1374.78±230.13*****	1471.90±41.11****	1450.50±447.80***	1179.50±345.80***
	CSF	—	88.31±12.78	82.30±16.10	104.70±30.60	77.60±18.10

Notes. * p ≤ 0.1; ** p ≤ 0.05; *** p ≤ 0.02; **** p ≤ 0.01; ***** p ≤ 0.001: compared to control; # p ≤ 0.1: compared to group I

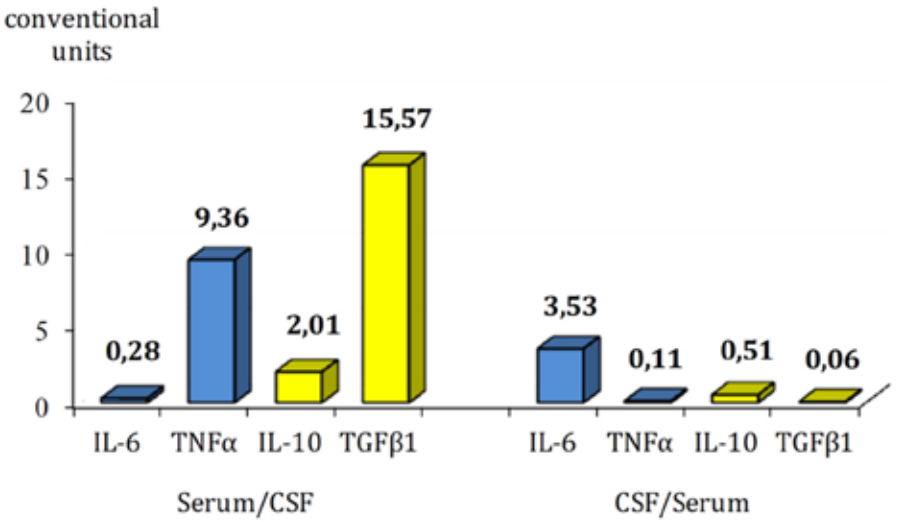

Fig. 1. Relation between peripheral and central inflammatory cytokine levels in the serum and CSF in patients with combat TBI

Conclusion

The moderately elevated serum IL-6 level is consistent with the idea that it can escape from the injured brain into the bloodstream. It is believed that this is the main mechanism for activating peripheral metabolism, endocrine and immune responses, i.e., its production in the periphery is stimulated [31] with simultaneous induction of the synthesis of anti-inflammatory IL-10 and TGFβ1 to provide a regulatory immunosuppressive effect [30]. This likely demonstrates a physiological normalization of the balance of pro- and anti-inflammatory cytokines as a mechanism for restraining the intensity of the secondary phase of neuroinflammation, which in the process of chronic mTBI is aimed at slowing down or preventing complications, which in the case of uncontrolled hyperadaptive immune response leads to "secondary injury", which can contribute to further strengthening of neuropsychiatric symptoms in much later periods.

Given that IL-6 plays a key role in both the acute and chronic phase of the response, and persistent neuroinflammation is associated with a poor prognosis [26, 32], our long-term findings after mTBI suggest the persistence of chronic inflammatory processes with a predominance of their activity in the periphery. This likely reflects the consequences of secondary neuroinflammation with changes in systemic immunity, which may be associated with disruption of the vascular network of the CNS barrier structures, leading to the leakage of detritus (a product of tissue breakdown) and inflammatory mediators with the development of complications such as systemic inflammatory response syndrome (SIRS) [11, 33–35], which in turn may complicate the consequences of the primary injury and local inflammatory reaction. According to the increase in the post-traumatic period, the body compensates for SIRS by increasing the peripheral level of inflammatory mediators, which, along with the activation of anti-inflammatory cytokines, contributes to the normalization of their balance and outlines directions for selective immunomodulatory therapeutic interventions at much later stages of the course of TBI.

In the context of the current study, the results obtained are organically combined with the literature and our previous data on the features of immune reactivity at different times after mTBI in combatants, which indicate chronic inflammation in the remote periods of its course, which is capable of initiating the formation of autoimmune processes with subsequent induction of neurodegenerative pathology. This concerns the increase in serum concentrations of immunoglobulins of the main classes, especially IgG, which reflected the formation and long-term maintenance of the humoral component of adaptive immunity in the remote periods of mTBI, as well as the modulation of the eliminating (detoxification) function of the immune system in the form of an increase in the number of small, most pathogenic, soluble antigen-antibody complexes along with the suppression of the formation of large and medium-sized conglomerates that stimulate the activity of micro- and macrophage systems of nonspecific natural resistance of the organism [36]. In addition, a slight increase in the content of circulating pro-inflammatory cytokines IL-6 and TNFα in the intermediate and long-term observation periods, along with a significantly (approximately 6 times) increased level of pleiotropic TGFβ1 in serum, confirms the persistent character of inflammation, which does not exclude its role in stimulating neurodegenerative processes in patients with mTBI.

It is known that activation of TGFβ1 production can be a consequence of both beneficial and harmful effects of neuroinflammation in order to suppress proinflammatory reactions and enhance tissue repair of reactive astrocytes and microglia [37]. Astrocytes are the main source of endogenous TGFβ1 production in the CNS, providing metabolic and structural support for neurons and participating in the regulation of brain homeostasis, synaptic plasticity and blood-brain barrier (BBB) integrity [38–40]. In addition, astrocytes play a crucial role in responses to the pathological effects of disease and brain injury [38–42]. TGFβ, among other inflammatory cytokines, is a key regulator and signaling factor in the transformation of normal astrocytes into reactive phenotypes [40, 43, 44]. As TGFβ1 is a pleiotropic cytokine, its excess may contribute to neuronal dysfunction and cognitive impairment in TBI [45–47], as well as to the inhibition of microglial proliferation, astrocyte activity, and glial scar formation [41, 43, 48]. Reactive astrogliosis is thought to be a protective mechanism aimed at limiting damage, controlling inflammation, and restoring homeostasis [38, 49, 50]. However, like peripheral inflammation, astrogliosis can become maladaptive and contribute to secondary damage to neural tissues [51]. As a result of studying these aspects of reactivity, neurotoxic (A1) and neuroprotective (A2) astrocytes have been identified [52]. The importance of considering the context-dependent modulation of their reactivity by TGFβ1 signaling is emphasized. It is noteworthy that TGFβ1 promotes the development of macrophages and their polarization into an M-2-like pool, which is associated with neuroprotection, migration, and angiogenesis [53].

Thus, when studying the content of inflammatory mediators of the immune response in patients with combat mTBI, a total increase in their level in the peripheral blood serum was found, which corresponds to the literature data on the important role of the immune system in the course of TBI and the formation of its long-term consequences and complications [26, 29, 33, 54]. Modern scientific studies have obtained numerous data indicating the global role of the immune system both in the mechanisms of acute response and in the chronic course of TBI, which emphasizes the need to modulate neuroinflammation in the process of forming secondary trauma due to its uncontrolled development. At the same time, there is a lack of consensus on the methodology of TBI research in connection with the measurement of inflammatory cytokines in peripheral blood, which does not provide accurate differentiation of the causes of inflammation in patients who suffer multiple trauma during combat operations [32]. In view of this, studies of both peripheral and central content of immune response mediators are of particular importance, which is one of the virtues of this work.

Thus, the results of our study indicate the feasibility of comprehensive monitoring of central and peripheral inflammatory cytokine content to determine potential directions of adequate pathogenetic therapy even in

conditions of significantly distant consequences of mTBI in order to substantiate the possibility of returning servicemen to direct participation in combat operations, which is extremely relevant during war.

Against the background of the high modernity of the actual study, which was carried out using biological materials from participants and veterans of active hostilities in Ukraine, unfortunately, a certain drawback can be noted in the form of a relatively small size of the comparison groups and a limited spectrum of inflammatory cytokines, and the inability of determining neurotrophic factors (BDNF, VEGF, PDGF) in order to study the mechanisms of neuroplasticity in the process of structural and functional recovery of the CNS in patients with TBI. This is objectively related to limited funding for scientific research in a medical institution under the conditions of Russia's full-scale aggressive attack on Ukraine.

In the direction of future research, it seems appropriate to include clinical and immunological comparisons of the course of TBI, taking into account the neurosurgical treatment of comorbid pathology associated with mechanical damage during combat TBI.

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Disclosures

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

The work was carried out in accordance with the main provisions of the Declaration of Helsinki of the World Medical Association on the ethical principles of conducting scientific research involving human subjects, the Council of Europe Convention on Human Rights and Biomedicine. The study was approved by the Biomedical Ethics Committee of the SI «P. V. Voloshyn Institute of Neurology, Psychiatry and Narcology of the NAMS of Ukraine», which did not reveal any violations of ethical or legal standards during the study (Minutes No.12-a dated 27.12.2024).

Informed consent

Informed consent to participate in the study was obtained from all participants.

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