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MOLECULAR FACTORS IN THE DEVELOPMENT OF NEUROINFLAMMATION IN TRAUMATIC BRAIN INJURY

S. A. Sharifbaev
E. A.Vasilevsky,
O. T. Dadabaev,
N. G. Kamalov
Andijan State Medical Institute Andijan, Uzbekistan

ABSTRACT

Traumatic brain injury is one of the main causes of both acute and long-term morbidity in the human population. A large number of preclinical and clinical studies do not provide a full description and understanding of the pathophysiological processes occurring during traumatic brain injury and the neuroinflammation it initiates. The neuroinflammatory reaction is a very complex interaction between cells of the innate and adaptive immune systems. The innate immune system is activated by nonspecific danger signals released from damaged cells and tissues, which in turn leads to neutrophil filtration, activation of microglia and astrocytes, release of complement, as well as histamine release by mast cells. We have presented a review of biomarkers and their role in predicting outcomes in traumatic brain injury. Among the biomarkers considered in this article, the most specific for traumatic brain injury and neuroinflammation are interleukin-6, interleukin-8, interleukin-10, and matrix metalloproteinases. Data on other indicators considered in the article are insufficient to use them as specific biomarkers for traumatic brain injury. For a more objective assessment of the patient's condition, several biomarkers should be determined in combination, as the complex of indicators allows a more complete assessment of the condition of the patient with traumatic brain injury.

Keywords: Traumatic brain injury, biomarkers, neuroinflammation

INTRODUCTION

Basic Concepts. Traumatic brain injury is a change in brain function or other signs of brain pathology caused by an external force [11]. Traumatic brain injury may include focal intracranial hemorrhage, epidural and subdural hematomas, hypoxemia, hypotension, edema, axonal damage, neuronal death, gliosis, and blood-brain barrier disruption [23]. The initial mechanical damage initiates pathological biochemical processes, so-called "secondary damage," which contributes to the development of neuroinflammation [23].

In the modern world, traumatic brain injury is one of the socially significant diseases. There are several classification systems for traumatic brain injury, but the most commonly used are classifications by clinical severity or by physical mechanism of impact. According to K.E. Saatman et al. [18], symptomatic, etiological, pathoanatomical, mechanistic (biological mechanism of injury) and prognostic classifications of traumatic brain injury are distinguished [18].

Neuroinflammation in Traumatic Brain Injury. Neuroinflammation arising from traumatic brain injury is a summation of interactions of various components of the body's immune and nervous systems. It occurs after the action of a damaging factor and can continue for a long period (up to several decades) [20].

After exposure to an external factor in trauma, primary brain damage occurs with disruption of the integrity of nerve and glial cells, blood vessels [20]. Further, the primary damage causes biochemical cascades [20], leading to secondary damage in the brain [23].

Secondary disorders include: excitotoxicity, oxidative stress, mitochondrial dysfunction, blood-brain barrier damage, and neuroinflammation [20].

In excitotoxicity, damaged neurons secrete the neurotransmitter glutamate into the extracellular space, activating amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors and N-methyl-d-aspartate. Receptor activation ensures the entry of sodium and calcium ions into the cells. Due to the increase in calcium concentration in neurons, activation of intracellular enzymes occurs: protein phosphatases, phospholipases and endonucleases, which ensure the cleavage of cell structures (proteins, membrane phospholipids, deoxyribonucleic acid (DNA) strands) and lead to neuronal death by necrosis and apoptosis [20, 8]. Also, an increase in calcium level in the cell ensures a change in the membrane potential of mitochondria, leading to disruption of biochemical processes occurring in mitochondria and release into the intracellular space of substances that trigger apoptosis [20, 8].

In traumatic brain injury, activated microglia cells intensively produce reactive oxygen species and nitric oxide [23]. In addition, reactive oxygen species production is caused by oxyhemoglobin, methemoglobin, and bradykinin [8]. Bradykinin causes reactive oxygen species production indirectly through arachidonic acid, which activates NADPH oxidase-2. Reactive oxygen species provide a cascade of reactions leading to oxidation of cell proteins, lipids, nucleic acids, altering their structure and functions, thereby ensuring even greater disruption and death of brain cells.

As a result of mechanical damage and the resulting brain edema, the blood-brain barrier is disrupted [12], as matrix metalloproteinase-9 is activated, which destroys intercellular contacts, ensuring an increase in the permeability of the blood-brain barrier [20], which leads to the penetration into the focus of immune system cells: neutrophils, leukocytes, monocytes and circulating blood factors [20, 12], exacerbating brain edema [20].

After brain damage, intracellular endogenous molecular fragments associated with damage [23] and pathogen-associated molecular fragments [12] are released. Binding of damage-associated molecular fragments with Toll-like receptors leads to microglia activation with its further transformation into M1 or M2 type [13]. Although there are data on the presence of a mixed phenotype [8]. Type M1 is pro-inflammatory, type M2 is anti-inflammatory [12, 14]. Differentiation of the microglia transformation pathway (M1 or M2 type) is determined by the presence of lipopolysaccharide and interferon, interleukin-4 and interleukin-13 [20, 8]. After differentiation, microglia begins to secrete cytokines and other factors: M1 – interleukin-1ß, tumor necrosis factor-α, interleukin-12, transforming growth factor-ß, reactive oxygen species [13], M2 – interleukin-10 [20, 13]. This explains the protective and damaging effects of microglia on the brain. In addition, under the influence of secreted substances, there is an increase in blood-brain barrier permeability, leading to even greater brain tissue damage.

Also, activated microglia expresses NADPH oxidase-2, providing reactive oxygen species production [19, 17].

Astrocytes have a dual effect on the brain after traumatic brain injury. They protect healthy brain tissues from the effects of toxins of damaged brain substance, forming a glial scar [23, 20]. But at the same time, they also secrete chemokines, cytokines, reactive oxygen species, metalloproteinase-9, causing inflammation and increased blood-brain barrier permeability [23, 5]. In addition, the glial scar can both promote and hinder regeneration of damaged tissue [20, 5].

The processes occurring during neuroinflammation are characterized by changes in the levels of certain substances in biological fluids depending on the volume of damage, the number of cells involved in inflammation, and other factors; these substances can be considered as biomarkers of neuroinflammation and traumatic brain injury.

Biomarkers of Traumatic Brain Injury and Neuroinflammation. After traumatic brain injury, activation of various cellular elements occurs, and as a consequence, enhanced production of chemokines, cytokines, and other factors with both pro-inflammatory and anti-inflammatory properties. Based on changes in the concentration of these substances in biological fluids, predictions and conclusions about the patient's condition can be made, i.e., they can be used as biomarkers.

Interleukin-1ß. It is a pro-inflammatory cytokine of the interleukin-1 family, secreted by activated microglia and macrophage cells [3] and regulates the production of other cytokines, induces fever, stimulates phagocytosis and cell apoptosis [15]. Active secretion of interleukin-1ß after traumatic brain injury contributes to increased excitability and excitotoxicity through glutamatergic and GABAergic mechanisms and changes in calcium ion concentration, which potentially can lead to the development of epilepsy [2]. Another source also confirms the relationship between elevated levels of interleukin-1ß in cerebrospinal fluid/serum with an increased risk of developing post-traumatic epilepsy [3]. In the article by T. Rodney et al. [15], contradictory results were described: according to one study conducted in a group of 32 people (women and men with severe traumatic brain injury), a lower level of interleukin-1ß in cerebrospinal fluid during the 5 days after injury meant more favorable neurological outcomes during the 6 months after injury; according to another study, the level of interleukin-1ß showed no significant differences in blood when assessed in men during the 48 hours after severe traumatic brain injury compared to the control group (people without traumatic brain injury), as well as deceased patients [15]. Thus, it is impossible to make unambiguous conclusions about the correlation between the level of interleukin-1ß and the development of unfavorable neurological consequences, but studies confirming this relationship exist.

Interleukin-6. Production of interleukin-6 by activated microglia and astrocytes increases during neuroinflammation, and experiments on rats showed that interleukin-6 performs a neuroprotective function [15]. Interleukin-6 functions by forming a complex with membrane-bound or soluble proteins, leading to activation of the signal along the JAK/STAT pathway [3]. Interleukin-6 is produced ubiquitously in the body, so its concentration in serum should be

determined with caution, as damage outside the central nervous system can also cause an increase in this biomarker [3], which does not allow objective assessment of this indicator in combined injury. In the study by D.B. Yang et al. [22], serum concentrations of several cytokines, including interleukin-6 in serum, were determined in patients with severe traumatic brain injury. Compared to the control group, the levels of these determined substances were significantly elevated [22]. In the work by M.J. Feng et al. [6], it was shown that a higher level of serum interleukin-6 in patients with severe traumatic brain injury is associated with an increased level of mortality (in the first 30 days) and an increase in the risk of developing post-traumatic complications.

Interleukin-8. Interleukin-8 is produced by various immune cells (monocytes, macrophages, and other tissue cells) and has chemoattractant properties. It attracts neutrophils to the inflammation focus, mediating the inflammatory process [15]. According to T. Rodney et al. [15], elevated interleukin-8 levels in plasma during the 24 hours after severe traumatic brain injury correlate with mortality: "an increase in plasma interleukin-8 levels during the 10 hours after traumatic brain injury accurately predicted mortality during the next month" [15]. Higher levels of interleukin-8 both in cerebrospinal fluid and in plasma blood in patients with moderate or severe traumatic brain injury, obtained 6–24 hours after injury, correlate with poor outcomes, represented in the extended Glasgow Outcome Scale from 1 to 4 points 6 months after injury [15]. In the review by T. Bogoslovsky et al. [2], the relationship between serum interleukin-8 levels and hourly values of intracranial pressure and cerebral perfusion pressure in patients with severe traumatic brain injury (n = 24, hospitalization at Glasgow Coma Scale < 9) is shown. Thus, an increase in interleukin-8 levels can predict intracranial hypertension and cerebral hypoperfusion before their clinical manifestation [2]. The concentration of interleukin-8 6 hours after severe traumatic brain injury is peak, its value is 3.5 times higher than that in healthy people of the control group. In the blood of deceased patients, the interleukin-8 concentration was more than 2 times higher than in surviving patients [4]. Based on the data of the studies, it can be concluded that elevated interleukin-8 levels in serum correlate with mortality, extended Glasgow Outcome Scale scores, development of intracranial pressure and cerebral perfusion pressure, and also allow predicting secondary brain damage in traumatic brain injury.

Interleukin-10. Interleukin-10 is a potent anti-inflammatory cytokine capable of reducing the synthesis of pro-inflammatory cytokines such as tumor necrosis factor-α, interleukin-6, and interleukin-1, and suppressing cytokine receptor activation [15]. An increase in interleukin-10 levels in serum in the first day after injury correlates with the severity of traumatic brain injury and mortality rate [15]. However, the review article by T. Rodney et al. [15] shows that interleukin-10 levels had no significant differences in patients with favorable and unfavorable outcomes. The study by A.P. Di Battista et al. [4] confirms an increase in interleukin-10 levels 6, 12, and 24 hours after traumatic brain injury in patients with unfavorable consequences and in patients with fatal outcome. "Interleukin-10 was the most reliable predictor of death among all analyzed cytokines (peak, 6 hours; odds ratio – 2.82; 95% confidence interval 1.63–4.87)" [4]. In the study by L. Lagerstedt et al. [9], the association of several markers with

computed tomography results in patients with mild traumatic brain injury was determined. Data analysis showed that interleukin-10 can be an interesting and clinically useful diagnostic tool capable of distinguishing positive and negative computed tomography results in patients with mild traumatic brain injury and can compete with S100B – the most studied protein for traumatic brain injury diagnosis. "The specificity of S100B at 100% sensitivity was 18% (95% confidence interval 10.8–25.2), while interleukin-10 achieved a specificity of 27% (95% confidence interval 18.9–35.1)" [9]. According to the presented data, we can consider the relationship between interleukin-10 levels and unfavorable outcomes of traumatic brain injury and mortality.

Tumor Necrosis Factor-α. In the brain, tumor necrosis factor-α normally participates in many processes, but in trauma, its concentration increases and causes disease progression, inflammation, and other processes [15]. The mechanism of action of tumor necrosis factor-α at the cellular level is due to its activation of TNF-R1 (p55) and TNF-R2 (p75) receptors. Launching further cascade reactions leads to cell death by apoptosis [3]. In traumatic brain injury, the tumor necrosis factor-α value is higher than in the control group [22]. The peak is observed in the first hours after injury [3]. The level of tumor necrosis factor-α in patients with severe traumatic brain injury correlates with mortality [6] and multiple organ failure [3]. Elevated tumor necrosis factor-α levels 6 and 12 hours after injury were associated with unfavorable neurological outcomes in patients [4]. In the study of postmortem samples from males, a relationship between tumor necrosis factor-α levels and elevated intracranial pressure was found, but no significant relationship with injury severity was established [15]. The correlation of tumor necrosis factor-α levels with the risk of developing intracranial pressure is confirmed by data from the article by M.M. Banoei et al. [3]. Therefore, an increase in tumor necrosis factor-α concentration in the inflammation focus leads to activation of neuronal death processes and neurodegeneration, as well as correlates with injury severity and mortality.

C-Reactive Protein. The level of C-reactive protein increases in severe traumatic brain injury [22, 6], with this indicator being higher in patients with fatal outcome and in patients with unfavorable events after injury [6]. In the study by R.P. Anada et al. [1], to assess the degrees of injury severity, along with the Glasgow Coma Scale, the level of C-reactive protein was determined, which was higher in patients with mild, moderate, and severe traumatic brain injury compared to the control group. At the same time, depending on the severity, the level of C-reactive protein differed, which allows it to be used for more objective diagnosis of patients with traumatic brain injury [1]. However, C-reactive protein is not a marker specific only to traumatic brain injury, so in the presence of other injuries or pathologies causing changes in C-reactive protein levels, the assessment of the obtained results will not be objective [1].

Tissue Inhibitor of Metalloproteinases-1. Experiments on mice showed a neuroprotective role of tissue inhibitor of metalloproteinases-1, while patient data with severe traumatic brain injury indicate a relationship with injury severity [3] and mortality [3, 7]. In most cases, higher mortality within 30 days was observed at tissue inhibitor of metalloproteinases-1 levels above

220 ng/ml [3]. Thus, the role of tissue inhibitor of metalloproteinases-1 in traumatic brain injury is not fully studied to establish its relationship with traumatic brain injury severity and mortality.

Transforming Growth Factor-ß. In traumatic brain injury, disruption of the blood-brain barrier occurs, making it possible for fibrinogen to enter the brain. This, in turn, leads to activation of serum transforming growth factor-ß [3]. Activated transforming growth factor-ß has autoinduction in astrocytes, i.e., ensures its own synthesis [3]. In addition, transforming growth factor-ß is released by activated M1-type (pro-inflammatory) microglia [13]. It can be concluded that transforming growth factor-ß, being a possible marker of fatal outcome and the occurrence of post-traumatic epilepsy [3], requires further study at the present time. Although there are no data on the relationship between clinical outcome and transforming growth factor-ß level in humans, in mice under head trauma conditions, a higher ratio of transforming growth factor-ß level in cerebrospinal fluid and serum was determined, indicating an increased risk of developing post-traumatic epilepsy [8].

Substance P. Substance P is a protein containing 11 amino acids [21, 10], belonging to the tachykinin family [3, 21, 10]. In the human body, substance P can be found in the central and peripheral nervous system and intestinal neurons [21, 10]. In the brain, substance P is located in nuclei and in capsaicin-sensitive sensory neurons [10]. Mostly – in the gray matter of the brain [21]. It is assumed that substance P, bound to the endothelial wall of brain vessels, ensures an increase in blood-brain barrier permeability and the development of vasogenic edema [10]. Substance P binds predominantly to the NK1 receptor [3, 10], having a greater affinity for this receptor than for NK2 and NK3 [21, 10], and enhances transcription of matrix ribonucleic acids of interleukin-12, interleukin-10, interleukin-6, and interleukin-8 [3]. Substance P increases expression of intercellular adhesion molecule-1, which increases blood-brain barrier permeability for leukocytes. In addition, substance P causes activation of microglia, astrocytes [3] and mast cells [21] with their further secretion of various factors. In traumatic brain injury, the substance P concentration in serum is elevated and correlates with injury severity and mortality level [3, 10]. The substance P level in serum of patients exceeding 299 µg/ml is associated with higher 30-day mortality [3], as well as with an increase in the risk of developing brain edema, motor and cognitive dysfunctions [10]. When using an NK1 receptor antagonist in laboratory animals, a decrease in blood-brain barrier permeability, brain edema, and cognitive dysfunctions was observed [10]. The data of the studies suggest that a high level of substance P leads to an increase in blood-brain barrier permeability and activation of synthesis of some cytokines, leading to enhancement of neuroinflammation and brain edema.

Monocyte Chemoattractant Protein-1. It belongs to chemokines, in traumatic brain injury it is produced by astrocytes [7]. The role of monocyte chemoattractant protein-1 in neuroinflammation is to attract monocytes and macrophages to the injury site [7]. The study by J.R. Huie et al. [7] showed that monocyte chemoattractant protein-1 has high sensitivity and specificity in traumatic brain injury. In patients with severe and moderate degrees of

traumatic brain injury severity, the level of monocyte chemoattractant protein-1 is elevated [4]. Monocyte chemoattractant protein-1 can be used as a prognostic marker, as its level is elevated in the first day in patients with unfavorable outcome [4]. In the study of mild traumatic brain injury, when comparing positive and negative computed tomography results in patients with marker levels, at 100% sensitivity, specificity was 7%, which was lower than the indicator for interleukin-10 (at 100% sensitivity, specificity was 31%) [9]. That is, the concentration of monocyte chemoattractant protein-1 correlates with traumatic brain injury severity and allows predicting the outcome of injury.

Macrophage Migration Inhibitory Factor. Macrophage migration inhibitory factor is a well-known pro-inflammatory cytokine. D.B. Yang et al. [22] sought to demonstrate the relationship between macrophage migration inhibitory factor concentration in blood serum with inflammation, degree of injury severity, complications after traumatic brain injury, and prognosis. Compared to the control, concentrations of macrophage migration inhibitory factor and several other markers in serum were significantly increased in patients who suffered traumatic brain injury [22]. Macrophage migration inhibitory factor concentrations correlated with the number of leukocytes, C-reactive protein concentration, interleukin-6, tumor necrosis factor-α, and Glasgow Coma Scale [22]. Elevated macrophage migration inhibitory factor concentrations were also associated with the severity of the injury received. But the role of macrophage migration inhibitory factor in relation to prognosis remains unclear [22]. In addition, it cannot be said with accuracy that changes in macrophage migration inhibitory factor concentration have prognostic value for determining 6-month unfavorable outcome of intracranial injury [22]. Thus, although the macrophage migration inhibitory factor concentration in blood correlates with injury severity, number of leukocytes, and concentration of other inflammation components, it does not allow assessing the prognosis of traumatic brain injury.

Matrix Metalloproteinases. Matrix metalloproteinases are a family of calcium-dependent zinc-containing endopeptidases that perform various physiological and pathological functions, including degradation of the extracellular matrix, regulation of cytokines, chemokines, cleavage of surface receptors, and others [16]. They are subdivided into categories depending on the substrate: collagenases (matrix metalloproteinases-1, -8, and -13), elastases (matrix metalloproteinases-7, -12), gelatinases (matrix metalloproteinases-2, -9), stromelysins (matrix metalloproteinases-3, -10, -11), and membrane-type matrix metalloproteinases (matrix metalloproteinases-14, -15, -16, -17, membrane-type matrix metalloproteinases) [3]. During the first 7 days after traumatic brain injury, metalloproteinase levels increase in serum and brain extracellular fluid [3]. Levels of various metalloproteinases in some cases can serve as an inflammation biomarker. Activation of matrix metalloproteinases alters extracellular matrix proteins and contributes to changes in blood-brain barrier permeability and neurovascular system dysfunction [5]. Analysis of brain extracellular fluid in patients with severe traumatic brain injury showed that first, the expression of matrix metalloproteinases-8, -9 increases, then matrix metalloproteinases-2, -3, and finally matrix metalloproteinase-7 [16]. Expression of neutrophil collagenase, matrix metalloproteinase-8, increased with

increasing intracranial pressure [16]. Its concentration was higher in patients with fatal outcome after traumatic brain injury [16]. As a result of primary brain damage, matrix metalloproteinase-9 is activated, which increases blood-brain barrier permeability [20]. Experiments on laboratory mice knockout for matrix metalloproteinase-9 and mice receiving matrix metalloproteinase-9 inhibitors demonstrate less functional impairment and cellular degeneration after traumatic brain injury [3]. Quantitative determination of metalloproteinases in patients with traumatic brain injury revealed increased expression of matrix metalloproteinase-9 within 72 hours after injury [16]. In patients with severe traumatic brain injury, plasma concentrations of matrix metalloproteinase-9 and cellular fibronectin 6, 12, 24, and 48 hours after injury correlated with mortality [2]. But it is not possible to definitively determine whether matrix metalloproteinase-9 is a neuroprotective or damaging agent [16]. It is assumed that post-traumatic inflammatory cytokines, including interleukin-1α, interleukin-2, and tumor necrosis factor-α, enhance transcription of matrix metalloproteinases-8 and -9 in the central nervous system [3]. In the article by V. Dinet et al. [5], it is shown that levels of matrix metalloproteinases-9 and -2 sharply increase after traumatic brain injury in rodents [5]. Activity of matrix metalloproteinase-3 increases after traumatic brain injury. Possibly, it participates in synaptic remodeling [5]. This means that in traumatic brain injury, expression levels of different types of matrix metalloproteinases change. The most studied is matrix metalloproteinase-9. An increase in its expression after traumatic brain injury contributes to increased blood-brain barrier permeability and is associated with fatal outcome.

CONCLUSION

Traumatic brain injury is one of the most common diseases in the world and is characterized by diverse manifestations and consequences. Most processes occurring in traumatic brain injury are interconnected, they complement and enhance each other's action. Unfavorable consequences and complications of intracranial injuries are associated with secondary damage and development of neuroinflammation. Neuroinflammatory reaction processes are mediated by activation of cellular elements (glial cells, immune system cells) and secretion of various substances (cytokines, chemokines, etc.). The mechanisms of neuroinflammation development are very complex – events develop one after another, forming cascade reactions that sometimes close in a vicious circle. Therefore, studying and understanding the processes occurring in the body after traumatic brain injury, which substance levels change in biological fluids, and identifying the most specific ones is very important. Identification of biomarkers helps to assess injury severity and risks of distant consequences, as well as increases the effectiveness of therapy for patients with traumatic brain injury and neuroinflammation.

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