NEUROINFLAMMATION IN ACUTE TRAUMATIC BRAIN INJURY

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ABSTRACT

Neuroinflammation is an inflammatory process that occurs in the central nervous system (CNS), including the brain and spinal cord. It can be triggered by various conditions such as traumatic injuries, infections, neurodegenerative diseases (e.g., Alzheimer's or Parkinson's), autoimmune disorders, or metabolic stress. In cases of acute traumatic brain injury, neuroinflammation is caused by the primary injury and can exacerbate the evolving tissue pathology. The cells involved in the primary brain injury initiate a series of pathological reactions that involve a response from the immune system. It is this immune response that initiates neuroinflammation and leads to pathological consequences over time.

The immune response varies depending on the injury mechanism, the location of immune cells in the brain, as well as the affected individual. Understanding the signals that initiate neuroinflammation and the context in which they arise can be crucial for understanding the contributions of immune cells in both pathology and regeneration. This article aims to review a number of factors that could influence the behavior of immune cells following acute traumatic brain injuries and the role of Interleukin-6 in neuroinflammation.

Key words: neuroinflammation, traumatic brain injury, Interleukin-6

1. Introduction

Traumatic brain injury (TBI) is one of the most severe types of injuries in terms of both case mortality and long-term implications for survivors. The treatment of TBI can be complex and costly. Based on clinical evaluation, acute traumatic brain injury is most commonly classified as mild, moderate, or severe according to the Glasgow Coma Scale (GCS). These categories have been shown to be predictive of the patient's long-term outcome, although other measures and models have also been tested (1).

1. Epidemiology

In 2014, the United States Centers for Disease Control and Prevention (CDC) documented 2.53 million emergency department (ED) visits related to traumatic brain injuries (TBI). There were approximately 288,000 hospitalizations related to TBI and 56,800 deaths associated with TBI. These data include both adults and children. Persons aged 75 years and older had the highest rate of ED visits associated with TBI (1,682 per 100,000 people), followed by young children aged 0 to 4 years (1,618.6 per 100,000 people), and lastly adolescents and young adults aged 15 to 24 years (1,010.1 per 100,000 people). According to the CDC’s 2014 data, the most common causes of TBI-related deaths, in descending order, were intentional self-harm (32.5%), unintentional falls (28.1%), and motor vehicle collisions (18.7%) (2).

In Europe, across all age groups, studies on the severity of traumatic brain injuries (TBI) reported the lowest incidence

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rate as 47.3 per 100,000 population per year, and the highest as 849 per 100,000 population per year. Reported mortality rates ranged between 3.3 and 28.10 per 100,000 population per year (1).

Worldwide, the incidence of traumatic brain injuries (TBI) may continue to increase due to the widespread use of vehicles in low- and middle-income countries and an increase in falls among elderly individuals in high-income countries (3).

2. Primary and secondary injury

Traumatic brain injury (TBI) is unique compared to other neurological conditions because it is caused by a biomechanical event, known as the primary injury, and therefore affects individuals regardless of age, sex, and/or baseline health status. The secondary injury, initiated by the primary mechanical insult, is driven by a series of positive feedback cascades, including neuroinflammation, cell death, excitotoxicity, blood-brain barrier (BBB) dysfunction, and mitochondrial dysfunction, all of which exacerbate neuronal dysfunction and tissue loss (4). It has long been established that neuroinflammation plays a major role in secondary injury. Indeed, it has been argued that in many cases, TBI-induced neuroinflammation is more detrimental to pathological progression than the primary injury itself (5).

3. Blood-brain barrier disruption

In a landmark paper in neuroimmunology, Davalos et al. (2005) observed that microglia adopt a more reactive morphology within minutes after a laser-induced injury in the mouse cortex (6). Additionally, in 2006, Farkas et al. demonstrated that mechanical forces induced by acute traumatic brain injury generate changes in the membranes of affected neurons (7). In 2018, Kathryn L. Wofford et al. observed increased neuronal permeability in the cortex, subcortical white matter, and hippocampus of the porcine animal model used. Together, these findings suggest that microglia represent a highly sensitive cell population and that generalizations about microglial functionality are difficult, as these cells can alter their reactivity and function depending on the brain region and species, as well as the mechanism of neuronal injury induction and the severity of the injury.

Furthermore, rapid mechanical changes related to cerebral stress—specific to traumatic brain injury (TBI)—can cause membrane disruptions and passive release of chemotactic signals and immune activators that are traditionally sequestered within the intracellular space. In addition, resulting necrosis may facilitate the activation of immune cells within the brain (8).

Regulation of post-traumatic blood-brain barrier dysfunction would play an active role in reducing morbidity and mortality caused by traumatic brain injuries. This aspect is particularly relevant in patients with premorbid conditions (such as chronic smoking), which have harmful effects on blood-brain barrier function and immune responses (9).

4. Interleukin 6 – Physiology and pathology

Interleukin-6 (IL-6) is a typical example of a cytokine characterized by functional redundancy and pleiotropy. Under normal healthy conditions, the serum level of IL-6 is less than 4 pg/ml; however, when stress factors such as infections or tissue injuries occur, IL-6 is promptly produced by monocytes and macrophages in response to pattern recognition receptor

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stimulation by pathogen-associated molecular patterns or damage-associated molecular patterns. As a result, serum IL-6 levels rise to several tens to hundreds of pg/ml, depending on the infection or injury (10).

IL-6 binds to its specific receptor IL-6 receptor (IL-6R), and the IL-6/IL-6R complex associates with and activates the signal transducer gp130, which is common to cytokines in the IL-6 family. IL-6 then activates hepatocytes, competent immune cells, and hematologic cells, inducing acute-phase, immune, and hematologic responses. These responses are essential for the elimination of infectious agents and tissue healing, making IL-6 a major cytokine involved in host defense.

After the complete removal of the stress factor, IL-6 synthesis ceases, and the serum concentration of IL-6 returns to normal. However, excessive IL-6 expression during infections or tissue injury can lead to severe and fatal acute complications or to persistent IL-6 production in chronic inflammatory diseases (11).

In chronic inflammatory diseases, such as rheumatoid arthritis (RA), serum IL-6 concentration is usually elevated, ranging from tens to several hundreds of pg/ml, whereas in acute and severe inflammatory diseases, such as fatal complications of septic shock, its level can rise from a few ng/ml up to µg/ml (12). At these levels, IL-6 can stimulate nearly all cells expressing gp130 (13), since IL-6 associates with the soluble IL-6R receptor in serum and can activate gp130 even if the target cells do not express the transmembrane IL-6R. This state of "hyper-IL-6" leads to multiple organ failure. Therefore, strict control of IL-6 expression is very important for the host organism.

5. IL-6 and neuroinflammation

IL-6 is a cytokine widely involved in inflammation, playing an important role in triggering the hepatic acute-phase response, influencing the differentiation of lymphocytes and monocytes, as well as neuroinflammation (14). It has also been observed that IL-6 induces malaise, fatigue, changes in sleep, and appetite (15).

Particularly in the context of neuroinflammation, IL-6 has varied effects. In the absence of IL-6 (in genetically modified mice), the glial cell response is reduced, which limits the damage caused by traumatic brain injury (TBI) (14). However, if IL-6 is overexpressed, equally harmful neurodegeneration occurs (16). IL-6 contributes to oligodendrocyte differentiation, neuronal tissue growth, and peripheral nervous system regeneration. Thus, the role of IL-6 in neuroinflammation is variable, and two cellular signaling pathways help explain its dual effects (17).

In its regenerative role, IL-6 uses classic signaling. IL-6 binds to its membrane-bound receptor, causing dimerization of the gp130 protein and activation of intracellular signals. This type of signaling has been associated with neuroprotective mechanisms and enhanced nerve regeneration after trauma and spinal cord injuries. However, in neuronal cells, membrane IL-6 receptors are present only on microglia, although messenger RNA for IL-6 receptors is also found in microglia, astrocytes, and neurons. The presence of messenger RNA may help explain the contradictory role of IL-6 in inflammatory processes.

As a modulator of inflammation, IL-6 uses trans-signaling. Soluble IL-6 receptors bind IL-6 to activate gp130 on distant cells, including neurons, neuronal cells, endothelial cells, and oligodendrocytes. Cells involved in

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neuroinflammation possess gp130 but not membrane IL-6 receptors, which is why they require the IL-6/soluble receptor complex to promote inflammation (17). These different signaling mechanisms offer niche therapeutic opportunities to reduce neuroinflammation. In the case of TBI (traumatic brain injury) and PTSD (post-traumatic stress disorder), elevated IL-6 levels may open new treatment avenues, considering these findings on IL-6 signaling (18).

6. IL-6 and TBI

IL-6 appears to play an essential role in the inflammatory and healing processes associated with traumatic brain injury (TBI). In military personnel, serum IL-6 levels were significantly higher compared to those of civilians in the control group (19). This study also showed a decrease in serum IL-6 levels 8 hours after concussion, suggesting that IL-6 triggers acute inflammatory responses to protect and help the brain heal after TBI.

Supporting the role of IL-6 in TBI, post-mortem brain tissue samples from TBI victims showed increased levels of IL-6 messenger RNA (20).

IL-6 could also be used to determine the severity of TBI; a study on military personnel demonstrated higher blood IL-6 levels in patients with more severe TBI. Although IL-6 levels are clearly elevated in TBI, they may also be useful in predicting clinical outcomes. Several studies support a positive correlation between increased IL-6 and more severe effects of TBI. A study on 62 patients with acute brain injuries noted elevated IL-6 values at the time of brain death diagnosis (21). The same study showed a positive correlation between increased IL-6 levels upon admission and mortality rate.

Similarly, Singhal and colleagues associated high IL-6 levels with poorer clinical outcomes in TBI patients (22). IL-6 also correlates with an increased risk of elevated intracranial pressure (ICP), which can lead to hypoxic areas in the brain due to poor perfusion, herniation, and death (23). This study showed that patients with ICP > 25 mmHg had significantly higher IL-6 levels during the first 17 hours after admission compared to patients with ICP < 20 mmHg.

Table 1 Studies regarding IL-6 and TBI

Study objective	Author, year	Number of patients	Outcome
High IL-6 levels in military personnel relates to multiple brain injuries and post-traumatic stress disorder	Rodney et al. (2020)	repetitive TBI (≥2 TBIs) n=44 1-2 TBIs n=29 control (no history of TBI) n=33	Repetitive TBIs are associated with greater levels of inflammatory cytokines, most notably, elevations in IL-6 compared to those who had either 1-2 TBIs or no history of TBI PTSD is also correlated with higher levels of IL-6

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Acute CSF IL-6 trajectories after TBI – neuroinflammation, polytrauma and outcome	Kumar et al. (2015)	114 adults with severe closed-head TBI control 15 healthy adults	CSF IL-6 levels are highly sensitive to brain injury and CNS levels increase dramatically post-TBI; elevated levels are associated with unfavorable global outcomes
Serum IL-6 – a candidate biomarker for intracranial pressure elevation following isolated TBI	Hergenroeder et al. (2010)	patients with ICP ≤20 mmHg n=14 patients with ICP ≥25 mmHg n=14 healthy volunteers n=14	Sustained increases in IL-6 levels in TBI patients irrespective of their ICP status Patients who experienced ICP levels ≥25 mmHg had significantly higher levels of IL-6 levels withing the first 17 hours of injury
IL-6 is associated with acute concussion in military combat personnel	Edwards et al. (2020)	Military personnel who sustained concussion n=45 Healthy control participants in the same deployment environment, no history of concussion n=49	Significant elevation of IL-6 levels in concussed military personnel less than 8h following injury
Plasma cytokines IL-6 association with ARDS syndrome in patients with severe TBI	Aisiku et al. (2016)	200 TBI patients enrolled in study	Plasma IL-6 proinflammatory marker was associated with development of ARDS in patients with severe TBI
Inflammation biomarker IL-6 may improve the diagnostic and prognostic accuracy of currently authorized traumatic brain injury tools	Tsitsipanis et al. (2023)	109 adult patients with TBI 20 adult healthy controls	Elevated levels of IL-6 were found in patients with TBI, higher levels associated with more severe TBI

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Neurological symptoms and their association with inflammatory biomarkers in the chronic phase following TBIs	Li et al. (2022)	72 TBI patients followed 6 months to 2 years post TBI	IL-6 was positively associated with presence of sleep disturbance (p=0.021)
IL-6 levels after fatal traumatic brain injury	Ondruschka et al. (2018)	95 adult cadavers postmortem interval up to 6 days Fatal TBI n=46 Non-fatal TBI control n=49	IL-6 proved to be interesting postmortem biomarker to provide specific information on the injury pattern and the survival time of traumatic fatalities
Do patients with TBIs have a differential cytokine response to exercise compared to healthy subjects	Timmerman et al. (2015)	8 patients post TBI 8 healthy controls	Patients recovering from TBI have blunted IL-6 response following a peak exercise test compared to non-TBI controls – possible impaired hypothalamic-pituitary-adrenal axis function

Persistently elevated levels of proinflammatory cytokines, including plasma IL-6, have been linked to poorer cognitive recovery 12 months after TBI. Arand and collaborators found that plasma IL-6 levels were eight times higher in patients who did not survive TBI compared to survivors. Furthermore, the researchers discovered that IL-6 was increased 45-fold at 12 hours after admission in deceased patients, but only 13-fold at 6 hours after admission in survivors (24).

Another study showed that patients with an average serum IL-6 level of 85.2 ± 51.6 had a favorable outcome, while levels of 162.3 ± 141.1 were associated with unfavorable clinical outcomes (25). These correlations between elevated IL-6 and negative clinical outcomes may be related to the dual function of IL-6. If IL-6 is extremely high in the early phases or does not decrease after acute inflammation, it may contribute to harmful chronic inflammation (26).

Many studies measure serum IL-6 in the blood after TBI, but IL-6 does not normally cross the blood-brain barrier (BBB), and therefore may not always be present in serum. As mentioned earlier, TBI affects the BBB and makes it more permeable (27). Thus, serum IL-6 levels after TBI may be more relevant for assessing BBB damage than for the direct severity of TBI.

Although there is strong evidence that elevated IL-6 helps determine the severity and progression of TBI, direct measurement of IL-6 in the brain reduces the risk that polytrauma influences the

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measurements or that IL-6 levels are falsely low due to an intact BBB.

Regardless of the measurement method, IL-6 clearly plays a role in TBI pathology.

7. Inflammation following maxillo-facial surgery

The management of patients suffering from a fracture of one or more facial bones begins with a proper initial assessment, appropriate surgery for reduction and stabilization of the fractures, and postoperative care that allows the patient to recover pre-injury morphology and function as quickly as possible while minimizing the negative effects of the intervention. For patients undergoing surgery for facial trauma, there is a high rate of pre- and postoperative pain, facial edema that worsens during the first three days, as well as functional limitations in mouth opening, chewing, eyelid opening, etc. (depending on the facial skeletal region involved) (28). As a result of tissue incision, skeletonization, and traction forces applied for fracture reduction, facial edema is one of the constant features in surgical interventions for facial trauma.

If maxillofacial injuries remain undiagnosed or untreated, the patient will be left with significant functional and aesthetic sequelae that are difficult to treat later. Initial management of these injuries can be carried out simultaneously with the management of other life-threatening injuries, and a successful outcome can be achieved. The traditional approach of waiting "until the edema completely subsides" before properly addressing definitive correction of bone or soft tissue problems has been shown to produce insufficient and structurally and functionally disabling results. After the first or, at most, the second week post-injury, the bone healing process and scar formation typically progress very rapidly. This is especially true for children, who normally have a very high metabolic rate. A displaced facial fracture that is not properly corrected during the initial "golden" period will require major manipulations and even refracturing to adequately reduce the segments into the correct position, resulting in a less satisfactory outcome than acute management. Similar considerations regarding the skin and soft tissues are also important. Once scar tissue has formed, restoring a normal or near-normal appearance becomes very difficult (29).

8. Conclusions

The neuroinflammatory response following acute traumatic brain injury plays a dual role: it contributes to the worsening prognosis of progressive brain injury; however, the neuroinflammatory response can also promote functional recovery immediately after the injury. Neuroinflammation in the context of acquired traumatic injuries of the central nervous system highlights the complexity and multifactorial nature of the neuroimmune response. Recent advances in understanding the metabolic and phenotypic regulation of neuroimmune cells, the complex interactions between different cell types, and the development of innovative therapeutic strategies have brought new perspectives on potential interventions to mitigate neuroinflammatory processes. Diverse research approaches, from single-cell omics analysis to the integration of artificial intelligence, offer promising pathways for uncovering the intricate pathophysiological dimensions of neuroinflammation.

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