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CYTOKINE PROFILE IN CHILDREN AFTER TRAUMATIC BRAIN INJURY.

Associate Professor of the Department of Neurology, ASMI,

M.I. Abdullaeva.

Abstract: The cytokine profile following traumatic brain injury (TBI) in children represents a critical marker of neuroinflammatory processes and a significant factor influencing clinical outcomes. Neuroinflammation, characterized by activation of microglia and astrocytes, leads to the release of pro-inflammatory cytokines (IL-1β, TNF-α, IL-6) and anti-inflammatory cytokines (IL-10, TGF-β), which regulate neural tissue damage and repair. Current studies indicate that the dynamics of cytokine levels in peripheral blood and cerebrospinal fluid are closely associated with TBI severity, the extent of secondary injury, and long-term cognitive and behavioral impairments in pediatric patients. Developmental features of the immature brain and immune system result in age-dependent variations in cytokine responses, which have clinical significance for early diagnosis, prognosis, and individualized neuroprotective therapy. The literature highlights the need for comprehensive monitoring of cytokines and the investigation of their temporal profiles to optimize treatment strategies for children with TBI.

Keywords: Traumatic brain injury, children, cytokines, neuroinflammation, IL-1β, TNF-α, IL-6, neuroprotection, secondary brain injury, pediatric neurology

Introduction. Traumatic brain injury (TBI) in children is a significant medical and social problem due to its high prevalence, complex pathophysiology, and long-term impact on neurodevelopment and cognitive function [1,2]. Pediatric TBI differs from adult TBI in several critical aspects, including the ongoing development of the central nervous system (CNS), incomplete myelination, high neuroplasticity, and an immature immune system, all of which influence both the primary response to injury and secondary pathophysiological cascades [3,4].

A key mechanism mediating secondary brain injury is neuroinflammation, with cytokines playing a central role. Cytokines, small signaling proteins released by immune and glial cells, regulate neural tissue responses to injury, including cell survival, apoptosis, synaptic plasticity, and tissue repair [5]. After TBI, activated microglia and astrocytes release pro-inflammatory cytokines (IL-1β, TNF-α, IL-6) that amplify local inflammation and may exacerbate neuronal damage, as well as anti-inflammatory cytokines (IL-10, TGF-β) that contribute to tissue repair and immune modulation [6,7].

In pediatric patients, the cytokine response shows significant age-dependent variability. The immature immune system, combined with ongoing brain development, can lead to either exaggerated inflammatory reactions or insufficient neuroprotective responses, affecting recovery trajectories [8]. Peripheral measurements of cytokines in blood and cerebrospinal fluid have been proposed as potential biomarkers for injury severity, secondary complications, and long-term cognitive and behavioral outcomes [9,10].

Despite growing interest, the pediatric cytokine profile following TBI remains incompletely characterized. Variations in study design, timing of sample collection, and age-related physiological differences contribute to inconsistent findings. Comprehensive analysis of cytokine dynamics is essential for identifying critical windows for therapeutic intervention and optimizing neuroprotective strategies in children [11,12].

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Understanding the cytokine profile in pediatric TBI is fundamental not only for elucidating mechanisms of secondary brain injury but also for improving early diagnostics, prognosis, and individualized treatment approaches [13].

Pathophysiology of Pediatric TBI. Primary injury in pediatric TBI occurs immediately upon impact and includes contusions, hematomas, and diffuse axonal injury (DAI). These mechanical lesions initiate immediate neurological deficits [14].

Secondary injury develops over minutes to days post-trauma and involves a cascade of biochemical and cellular processes, including:

- Ionic imbalance (Na^+, K^+, Ca^{2+})

- Glutamate-mediated excitotoxicity

- Mitochondrial dysfunction and ATP depletion

- Oxidative stress and lipid peroxidation

- Neuroinflammatory responses [15,16]

Secondary mechanisms largely determine the severity and duration of clinical symptoms and long-term neurodevelopmental outcomes in children [17].

Cytokines and Neuroinflammation in Pediatric TBI. Cytokines are key mediators of neuroinflammation. Pediatric studies indicate that pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6 are rapidly elevated after TBI and correlate with injury severity and adverse outcomes [18,19]. These molecules can exacerbate neuronal apoptosis, disrupt synaptic function, and compromise the blood–brain barrier (BBB) [20].

Anti-inflammatory cytokines (IL-10, TGF-β) are released to modulate the inflammatory response, promote tissue repair, and limit secondary damage [21]. The balance between pro- and anti-inflammatory cytokines is crucial for neuroprotection, and dysregulation may contribute to prolonged inflammation and neurodegeneration [22].

In children, age-dependent differences in cytokine production are significant. Neonates and younger children often display exaggerated pro-inflammatory responses, whereas older children may exhibit more balanced cytokine profiles [23].

Biomarkers in Pediatric TBI. Peripheral and cerebrospinal fluid (CSF) cytokine measurements have been proposed as biomarkers to assess injury severity, predict secondary complications, and evaluate recovery potential [24]. Promising biomarkers include:

- GFAP (Glial Fibrillary Acidic Protein)

- UCH-L1 (Ubiquitin C-terminal Hydrolase L1)

- S100B

- NFL (Neurofilament Light Chain)

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- Inflammatory markers: IL-6, IL-1β, TNF-α, NLRP3-related proteins [25,26]

Combined biomarker panels, such as GFAP + UCH-L1, have demonstrated higher sensitivity for detecting structural brain injury, but temporal profiles and pediatric thresholds require further validation [27].

Neuroimaging and Correlation with Cytokines. Advanced neuroimaging techniques, including MRI and DTI, allow detection of diffuse axonal injury and microstructural white matter changes [28]. Elevated pro-inflammatory cytokine levels often correlate with the extent of white matter injury and clinical outcomes, providing complementary information for prognosis and therapeutic planning [29].

Therapeutic Implications. Current pediatric TBI management focuses on symptomatic care, intracranial pressure control, and prevention of secondary complications [30]. Emerging strategies target neuroinflammation and cytokine modulation, including:

- Anti-inflammatory agents

- Antioxidants

- Mitochondrial function modulators

- Rehabilitation and neuroadaptive approaches [31,32]

Age-specific pharmacokinetics and brain development considerations are critical in designing effective neuroprotective therapies for children.

Knowledge Gaps and Future Directions. Key gaps include:

- Limited longitudinal pediatric cohort studies

- Incomplete characterization of cytokine temporal dynamics

- Insufficient data on long-term outcomes following repeated mild TBIs

- Need for multicenter studies integrating clinical, neuroimaging, and biomarker data

- Exploration of genetic and epigenetic modifiers of cytokine response and outcomes [33,34]

Conclusion. The cytokine profile in pediatric TBI reflects a complex interplay of neuroinflammatory, excitotoxic, metabolic, and vascular mechanisms. Age-dependent differences in immune and neural development necessitate dedicated pediatric strategies for monitoring, prognosis, and neuroprotection. Integrating cytokine biomarkers with neuroimaging and clinical data may improve early diagnosis, individualized therapy, and long-term outcomes in children with TBI.

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