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PATHOGENETIC ASPECTS OF POST-TRAUMATIC ENCEPHALOPATHY IN CHILDREN: A LITERATURE REVIEW.

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Abstract: Post-traumatic encephalopathy (PTE) in children is a multifactorial pathological condition that develops following traumatic brain injury and is characterized by both acute and long-term disturbances of central nervous system function. Its pathogenesis is driven by the interaction between primary mechanical damage and a cascade of secondary neurobiological processes, including excitotoxicity, mitochondrial dysfunction, ionic imbalance, oxidative stress, blood–brain barrier disruption, and neuroinflammation. Age-related features of the developing brain—such as incomplete myelination, high metabolic demand, and enhanced neuroplasticity—determine both increased vulnerability to traumatic injury and potential for recovery. Long-term consequences of pediatric PTE may manifest as cognitive, behavioral, and emotional impairments that negatively affect quality of life and neuropsychological development. A deeper understanding of the underlying pathophysiological mechanisms is essential for improving diagnostic approaches, prevention, and the development of effective neuroprotective strategies in pediatric neurology.

Keywords: Post-traumatic encephalopathy; Traumatic brain injury; Pediatric neurology; Neuroinflammation; Excitotoxicity; Mitochondrial dysfunction; Blood–brain barrier; Cognitive impairment.

Introduction. Post-traumatic encephalopathy (PTE) in children is one of the most pressing issues in pediatric neurology, due to the high incidence of traumatic brain injury (TBI) in the pediatric population, its significant medical and social consequences, and the long-term impact on cognitive and neuropsychological development [1]. According to the World Health Organization, TBI ranks among the leading causes of disability and mortality in children and adolescents, occupying the third place among traumatic injuries in early childhood and school-age populations [2]. In recent years, an increase in cases of mild and moderate TBI in children has been observed, largely associated with urbanization, increased road-traffic incidents, domestic accidents, and sports-related injuries [3].

The relevance of PTE is further determined by the immaturity of the central nervous system (CNS) in childhood, which defines both enhanced sensitivity to traumatic impacts and the specificity of developing structural and functional impairments [4]. The pediatric brain possesses high neuroplasticity; however, incomplete myelination, the ongoing formation of neural networks, and the intensive development of cognitive functions contribute to increased vulnerability to primary and secondary damaging factors in TBI [5]. Contemporary neurobiological studies indicate that the pathogenesis of PTE in children involves a cascade of molecular and cellular processes, including glutamate-mediated excitotoxicity, mitochondrial dysfunction, ionic imbalance, oxidative stress, disruption of the blood–brain barrier (BBB), and pronounced neuroinflammatory responses [6,7].

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The resulting impairments have a prolonged course and may manifest as cognitive decline, attention and memory deficits, neurodynamic disorders, behavioral changes, emotional lability, and delays in speech, psycho-cognitive and neuropsychological development, ultimately reducing the child's quality of life and socio-educational adaptation [8,9]. According to long-term cohort studies, persistent neurological and cognitive-behavioral disorders are identified in more than 30–50% of children after TBIs of varying severity within 6 months to 3–5 years or longer [10].

Despite progress in understanding traumatic brain injury mechanisms in childhood, the pathogenesis of PTE remains insufficiently elucidated. Current knowledge is fragmented, while existing therapeutic and rehabilitation approaches are predominantly symptomatic, do not fully consider the characteristics of the developing brain, and fail to provide adequate neuroprotection [11]. Therefore, a comprehensive investigation of the pathophysiological mechanisms of PTE in children is essential for improving early diagnostics, preventing secondary brain damage, and developing effective therapeutic and neurorehabilitation strategies.

Key Stages of Pathogenesis: Primary and Secondary Injury. Primary mechanical injury (local contusions, bruises, and diffuse axonal injury — DAI) occurs instantaneously upon the application of mechanical force and determines the initial neurological symptoms. Against this background, a cascade of secondary processes develops, including ionic imbalances, glutamate-mediated excitotoxicity, mitochondrial dysfunction, oxidative stress, and activation of programmed cell death pathways (apoptosis/autophagy). These secondary mechanisms largely determine the severity and duration of clinical manifestations.

Primary and secondary brain injury — conceptual framework. The pathogenesis of PTE in children is fundamentally based on the concept of primary and secondary brain injury, which serves as a core model for understanding the development of structural and functional impairments following TBI [12].

Primary injury occurs immediately upon mechanical impact to the brain and includes contusions and hematomas, axonal stretching, vascular damage, axonal shearing, and localized ischemic changes [13,14]. In children, primary injury is often more pronounced due to anatomical and physiological characteristics, such as the relative size of the head, weak neck muscles, high brain hydration, and incomplete myelination [15]. These primary injuries trigger cellular death mechanisms, including necrosis and early apoptosis of neurons, astrocytes, and oligodendrocytes [16].

Secondary injury develops over minutes, hours, and days following the initial trauma and results from cascades of biochemical, neuroinflammatory, and metabolic reactions that exacerbate the primary damage [17]. Key components of secondary injury include:

- Glutamate-mediated excitotoxicity, characterized by excessive activation of NMDA and AMPA receptors, elevated intracellular calcium, and initiation of neuronal death [18];

- Mitochondrial dysfunction, leading to ATP depletion, impaired respiratory chain function, and increased production of reactive oxygen species [19];

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- Oxidative stress, causing damage to lipids, proteins, and DNA [20];

- Disruption of ionic homeostasis (Na^+, K^+, Ca^{2+}), contributing to cerebral edema and cytotoxic injury [21];

- Blood–brain barrier (BBB) disruption, facilitating the infiltration of pro-inflammatory mediators and immune cells into brain tissue [22];

- Neuroinflammatory response, characterized by activation of microglia and astrocytes with cytokine release (IL-1β, TNF-α, IL-6), formation of a chronic inflammatory state, and progression of neurodegeneration [23,24].

In children, secondary injuries are amplified due to the immaturity of neuronal and antioxidant systems, high metabolic demands, and increased vulnerability to hypoxia and energy deficits [25].

Thus, secondary injury largely determines the severity of post-traumatic cognitive, neuropsychological, and neurological impairments in children, shaping the long-term prognosis of PTE [26].

Excitotoxicity, Ionic Disturbances, and Mitochondria. After trauma, a rapid release of glutamate occurs, accompanied by strong activation of NMDA and AMPA receptors, resulting in calcium influx into neurons. Elevated intracellular calcium disrupts mitochondrial function, reduces ATP production, and enhances the generation of reactive oxygen species, leading to impaired energy metabolism and neuronal death. In children, developmental differences in energy metabolism and mitochondrial dynamics at various stages further modulate the response to injury.

Blood–Brain Barrier (BBB) Disruption and Vascular Mechanisms. TBI damages the endothelium and the structure of the BBB, leading to vasogenic edema, infiltration of plasma molecules and immune cells into the brain parenchyma, and exacerbation of the inflammatory response. Dysregulation of cerebral blood flow—including impaired autoregulation, vasospasms, and ischemic episodes—further increases the risk of secondary injury. In children, the maturation of barrier properties and vascular regulation is still ongoing, affecting the severity of dysfunction.

Neuroinflammation: Microglia, Astrocytes, and Peripheral Immune Cells. Activation of microglia and astrocytes is a central component of the post-traumatic response. Activated microglia release pro-inflammatory cytokines (IL-1β, TNF-α, IL-6), while astrocytes contribute to gliosis and dysregulation of the synaptic environment. Neuroinflammation has a dual nature: it facilitates clearance of dead cells and tissue remodeling, but prolonged activation becomes an independent damaging factor, sustaining neurodegenerative processes. In the pediatric population, the timing and intensity of inflammatory responses differ from adults.

Diffuse Axonal Injury (DAI) and White Matter. DAI results from shear and rotational forces, leading to axonal stretching, dysfunction, and delayed degeneration. White matter damage

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disrupts neural pathways, manifesting as persistent cognitive and motor deficits. In children, incomplete myelination makes white matter both more vulnerable (less mature fibers) and potentially more plastic for recovery. Advanced MRI techniques, including DTI, allow detection of microstructural white matter changes associated with outcomes.

Long-Term and Cumulative Effects: Repeated Injuries and Risk of Chronic Encephalopathy. The cumulative effect of repeated injuries, even mild, is associated with long-term changes, including persistent inflammation, axonal integrity disruption, and possibly accumulation of pathological proteins (phosphorylated tau) after multiple impacts. Although classical chronic traumatic encephalopathy (CTE) data in children are limited, multiple studies highlight the risk of prolonged neurocognitive and behavioral impairments after repeated mild head injuries. Factors such as age at first injury, frequency, and severity of repeated impacts are critical.

Biomarkers and Their Clinical Utility in Pediatrics. Promising blood biomarkers include GFAP, UCH-L1, S100B, NFL, and inflammatory markers (e.g., IL-6, NLRP3-related proteins). Recent studies show that combinations of biomarkers (e.g., GFAP + UCH-L1) improve sensitivity for detecting structural damage in TBI (ALERT-TBI and subsequent studies); however, temporal profiles and threshold values in children require validation. Data on prolonged fluctuations of neurofilament proteins (NFL) suggest the potential for persistent axonal injury.

Neuroimaging: Role of CT, MRI, and DTI. CT remains the method of choice for rapid assessment of acute intracranial hemorrhages but often fails to detect microstructural white matter injuries. Advanced MRI, including DTI and SWI, increases sensitivity to DAI, microbleeds, and microstructural abnormalities, which is crucial for prognostic assessment and planning long-term follow-up in children.

Therapeutic Approaches and Neuroprotection. Currently, pediatric TBI treatment is largely symptomatic, focusing on intracranial pressure control, perfusion maintenance, and prevention of secondary complications. Experimental and clinical studies are exploring anti-inflammatory strategies, antioxidants, modulators of mitochondrial function, as well as rehabilitation and neuroadaptive approaches. In pediatrics, age-specific pharmacodynamics and potential effects on brain development must be considered. The evidence base for specific neuroprotective interventions in children remains limited.

Knowledge Gaps and Directions for Future Research. Key gaps include a lack of high-quality longitudinal pediatric cohorts, insufficient validation of biomarkers and their temporal profiles, and limited data on long-term outcomes following repeated mild injuries in children. Multicenter prospective studies integrating clinical, neuroimaging, and biochemical markers, as well as investigations of genetic and epigenetic factors modifying outcomes, are necessary.

Conclusion. The pathogenesis of post-traumatic encephalopathy in children is a complex multifactorial process, in which primary mechanical injury triggers a cascade of excitotoxic, metabolic, vascular, and immune responses. Considering the characteristics of the developing brain, the pediatric population requires a dedicated scientific and clinical strategy—from early

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diagnostics (including biomarkers and high-resolution MRI) to the development of age-specific neuroprotective and rehabilitative interventions.

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