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Neuroinflammation in Traumatic Brain Injury-Related Delirium: Mechanisms and Clinical Significance

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Abstract: Traumatic brain injury (TBI) is one of the leading causes of neurological dysfunction and mortality, often accompanied by various neuropsychiatric complications. Among these, delirium occurs with a notably high incidence and significantly impairs rehabilitation and quality of life. Recent studies have identified neuroinflammation as a central pathological mechanism underlying the onset and progression of post-TBI delirium. This process is characterized by excessive release of inflammatory mediators, abnormal activation of glial cells, infiltration of peripheral immune cells, and activation of the complement system, ultimately leading to neurotransmitter imbalance and disruption of brain network function. Pro-inflammatory cytokines such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6), together with chemokines, play pivotal roles in amplifying inflammatory responses, while microglial polarization and blood–brain barrier disruption represent key events in central immune dysregulation. Despite growing evidence, the molecular signaling pathways and multicellular interactions mediating neuroinflammation-induced delirium remain incompletely understood. This review summarizes the mechanistic role of neuroinflammation in post-TBI delirium, aiming to provide a theoretical reference for its prevention and management.

Keywords: Neuroinflammation; Traumatic Brain Injury; Delirium; Inflammatory Mediators; Immune Response; Neuropsychiatric Complications.

1. Introduction

Traumatic brain injury (TBI) is one of the leading causes of trauma-related mortality and disability worldwide, posing a substantial burden on public health systems and socioeconomic resources. The rates of death and long-term disability following TBI remain high, particularly among young and middle-aged adults, thereby amplifying its societal impact [1]. Beyond the immediate life-threatening phase, TBI patients frequently experience persistent neurological dysfunction and neuropsychiatric complications. Among these, delirium is the most common and clinically significant acute neuropsychiatric disorder, characterized by abrupt fluctuations in consciousness and cognitive function. The occurrence of delirium can markedly prolong hospitalization and increase the risk of mortality [2-4]. Therefore, elucidating the pathophysiological mechanisms of TBI and their intrinsic relationship with delirium is of great importance for improving clinical outcomes and developing early intervention strategies.

The pathological evolution of TBI can be broadly divided into two stages: primary injury and secondary injury. The primary injury results from mechanical forces that cause cerebral contusions and diffuse axonal injury (DAI), leading to abnormalities in neuronal membrane permeability, disruption of the axonal cytoskeleton, and impairment of axoplasmic transport, thereby laying the foundation for subsequent neurological dysfunction [5]. The secondary injury develops progressively after the initial insult and encompasses a series of pathological processes, including excitotoxicity, calcium overload, mitochondrial dysfunction, oxidative stress, and inflammatory responses [6, 7]. These molecular and cellular events exacerbate neuronal damage through ionic imbalance and oxidative stress, ultimately triggering widespread neuroimmune activation [7, 8].

In the context of secondary injury, neuroinflammation is regarded as one of the key mechanisms driving the progression of brain damage. Following structural injury to brain tissue, resident immune cells and glial cells become activated, rapidly initiating a localized inflammatory response. Neuroinflammation is characterized by persistence, spatial propagation, and systemic crosstalk. Glial cells activated at the lesion site, together with their released mediators, can propagate along glial networks and induce responses in distant brain regions [9-12]. Concurrently, activation of the peripheral immune system and increased blood–brain barrier (BBB) permeability facilitate the infiltration of immune cells into the central nervous system [13]. An increasing body of evidence suggests that multisystem immune interactions, including the peripheral–central inflammatory axis and the gut–brain axis, may further amplify this inflammatory cascade [14]. These pathological processes not only contribute to neuronal injury and synaptic dysfunction but may also disrupt neurotransmitter metabolism and brain network homeostasis, thereby laying the foundation for subsequent neuropsychiatric complications such as delirium.

Delirium is highly prevalent after TBI and most commonly occurs within the first few days following injury [15, 16]. Persistent delirium not only prolongs ICU length of stay but is also associated with increased mortality and long-term cognitive impairment [12,13]. At the pathophysiological level, inflammatory responses may contribute to fluctuating cognition and impaired consciousness by altering neurotransmitter systems (such as cholinergic, glutamatergic, and dopaminergic pathways) and disrupting large-scale brain network connectivity [17]. Therefore, neuroinflammation is likely to represent a key pathological link in the occurrence and progression of delirium after TBI.

In summary, the interaction between mechanical injury and secondary inflammatory responses following TBI leads to

profound structural and functional disruptions of the brain. Neuroinflammation not only amplifies tissue damage during the course of brain injury, but may also mediate the onset and persistence of delirium through neurotransmitter imbalance and disturbance of brain network function. This review will systematically summarize the mechanistic role and clinical significance of neuroinflammation in post-TBI delirium, with a particular focus on inflammatory signaling pathways, immune cell responses, and alterations in neural networks, in order to provide a theoretical basis and translational perspective for the prevention and management of delirium after TBI.

2. Pathophysiological Mechanisms of Neuroinflammation after Traumatic Brain Injury

2.1. Initiation of Neuroinflammation and Local Cellular Activation

Microglia are the principal resident immune cells of the central nervous system. Under physiological conditions, they exhibit a highly ramified, surveillant morphology and contribute to tissue homeostasis through immune surveillance and clearance of cellular debris. Upon injury, microglia rapidly shift from a resting to an activated state, characterized by enlarged cell bodies, retracted processes, and directed migration toward the lesion core within hours, making them one of the earliest cellular responders in the neuroinflammatory cascade [8, 18]. Microglial activation typically peaks within 24–72 hours after TBI and modulates the local inflammatory milieu through the release of cytokines, chemokines, and oxidative stress mediators.

Microglial responses exhibit pronounced functional heterogeneity. Traditionally, activated microglia have been classified into a pro-inflammatory M1 phenotype and an anti-inflammatory M2 phenotype based on their molecular and functional profiles [19]. M1 microglia amplify inflammatory responses and exacerbate neuronal injury through the release of mediators such as IL-1β, TNF-α, and CCL2, whereas M2 microglia secrete anti-inflammatory cytokines (e.g., IL-10) and neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and insulin-like growth factor-1 (IGF-1), thereby supporting tissue repair and neuroregeneration [20]. However, emerging evidence indicates that microglial activation states are better conceptualized as a dynamic continuum rather than a rigid M1/M2 dichotomy, with their functions tightly regulated by microenvironmental cues and metabolic programming [21]. In the acute phase of TBI, microglial responses are predominantly skewed toward a pro-inflammatory M1-like profile to clear necrotic tissue. Failure to transition in a timely manner toward a reparative M2-like or pro-resolving phenotype may result in sustained inflammation, chronic neurodegeneration, and cognitive impairment. Thus, promoting the shift from M1-dominant to M2-like microglial states may represent a promising strategy to modulate post-TBI neuroinflammation and facilitate neural repair.

Multiple damage-associated signals can drive microglial polarization toward a pro-inflammatory M1 phenotype. Following traumatic brain injury, mechanical impact and impaired cerebral perfusion trigger rapid release of damage-associated molecular patterns (DAMPs) from neurons, astrocytes, and vascular endothelial cells, including ATP, high mobility group box 1 (HMGB1), and mitochondrial DNA. These endogenous danger signals are recognized by pattern recognition receptors on microglia, particularly Toll-like receptors 2 and 4 (TLR2/4) and NOD-like receptors (NLRs) [8, 12, 22]. Upon binding DAMPs, membrane-bound TLR2/4 activate MyD88-dependent NF-κB and MAPK signaling pathways [23], leading to the transcription of a broad range of pro-inflammatory mediators, including TNF-α, IL-6, precursor forms of cytokines such as pro-IL-1β and pro-IL-18, as well as components of the inflammasome complex, such as NLRP3 [24].

Subsequently, cytosolic NOD-like receptors, such as NLRP3, sense intracellular stress signals including ionic imbalance, increased reactive oxygen species (ROS), and mitochondrial damage, thereby driving the assembly and activation of the NLRP3–ASC–caspase-1 inflammasome complex. Activated caspase-1 cleaves pro-IL-1β and pro-IL-18 into their mature, biologically active forms. In this process, the synthesis and secretion of TNF-α and IL-6 rely predominantly on TLR–NF-κB–mediated transcriptional activation, whereas the maturation and release of IL-1β and IL-18 require inflammasome-dependent caspase-1 cleavage [24]. Together, these coordinated signaling events markedly amplify the neuroinflammatory cascade following traumatic brain injury.

In addition to secreting cytokines, microglia exert phagocytic and metabolic regulatory functions. Their phagocytic activity contributes to the clearance of necrotic cells and metabolic debris, thereby exerting neuroprotective effects. However, sustained M1-like activation and excessive inflammasome activation have been implicated in post-TBI cognitive dysfunction and the development of delirium [25].

2.2. Cellular Crosstalk and Amplification of Inflammatory Signaling

Astrocytes are among the most abundant glial cell types in the central nervous system (CNS), widely distributed throughout the brain and spinal cord. They perform multiple essential physiological functions. Through their extensive processes, astrocytes closely interact with neurons, blood vessels, and other glial cells, thereby providing structural support and metabolic regulation. They play key roles in maintaining ionic homeostasis, including potassium buffering, as well as in the uptake and clearance of neurotransmitters. In addition, astrocytes contribute to the formation and maintenance of the blood–brain barrier (BBB), limiting the entry of exogenous substances and pathogens into the CNS [26].

Upon microglial activation, astrocytes rapidly enter a reactive state as well. This reactive astrocytosis is characterized by upregulation of astrocytic markers such as glial fibrillary acidic protein (GFAP) [27], glutamine synthetase, and S100β, along with cellular hypertrophy and proliferation, ultimately contributing to the formation of a glial scar in the subacute phase after injury. Similar to microglia, astrocytes also express pattern recognition receptors, including Toll-like receptors (TLRs). Damage-associated molecular patterns released from injured tissue activate pattern recognition receptors on astrocytes, leading to NF-κB signaling and the production of pro-inflammatory cytokines (such as TNF-α), chemokines, and inflammatory mediators including cyclooxygenase-2 (COX-2) and matrix metalloproteinase-9 (MMP-9) [28]. Through NF-κB–dependent pathways, reactive astrocytes also contribute to

cellular swelling and cytotoxic edema, which represent key mechanisms underlying increased intracranial pressure after TBI [29]. Despite these potentially deleterious effects, astrocytes can, via NF-κB-associated signaling, upregulate neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), thereby supporting neuroprotection and tissue repair [30]. Physiologically, reactive astrocytes help to restrict the spread of necrotic tissue, isolate inflammatory foci, maintain ionic homeostasis, and provide structural support for the reconstruction of the blood–brain barrier [31]. However, excessively activated astrocytes may chronically release IL-1β, TNF-α, and reactive oxygen species, leading to neuronal apoptosis and synaptic abnormalities, thereby acting as key drivers of chronic neuroinflammation [28,30]. Thus, astrocytes exert both neuroprotective and neurotoxic effects in TBI, depending on the context and degree of their activation [32].

Bidirectional signaling between astrocytes and microglia is one of the core mechanisms underlying amplification of inflammation after TBI. Microglia-derived IL-1α, TNF, and C1q can induce the transformation of astrocytes into a neurotoxic A1-like pro-inflammatory phenotype [33]. In turn, astrocytes may modulate microglial activity by secreting factors such as granulocyte–macrophage colony-stimulating factor (GM-CSF) and IL-6, thereby potentially establishing a feed-forward amplification loop, although direct experimental evidence for this mechanism in the specific context of TBI remains relatively limited [34].

Overall, astrocytes are not merely passive responders after TBI but serve as critical hubs integrating immune and metabolic signals. Their coordinated interactions with microglia shape both the spatial extent and temporal persistence of neuroinflammation. Precise modulation of glial activation states, as well as targeted interference with inflammatory signaling and intercellular crosstalk, may offer promising therapeutic strategies to limit chronic neuroinflammation and promote neurological recovery following TBI.

2.3. Disruption of the Blood–Brain Barrier and Peripheral Immune Cell Infiltration

The blood–brain barrier (BBB) is a key structural and functional interface that maintains central nervous system (CNS) homeostasis. It is primarily composed of brain microvascular endothelial cells, the basement membrane, pericytes, and the end feet of astrocytes. BBB permeability is largely regulated by the expression and integrity of tight junction proteins on endothelial cells. Following traumatic brain injury, mechanical impact and inflammatory signaling lead to disruption or downregulation of tight junction proteins such as claudin-5, resulting in widened interendothelial gaps, increased permeability, and the extravasation of plasma components and peripheral inflammatory mediators into the brain parenchyma, thereby contributing to vasogenic edema [35]. This structural breakdown exposes the cerebral microenvironment to circulating immune stimuli and provides a pathological basis for the sustained amplification of neuroinflammation.

Once BBB integrity is compromised, peripheral immune cells can extensively infiltrate the brain parenchyma. After TBI, monocytes, neutrophils, and T lymphocytes accumulate around the lesion site, where they release pro-inflammatory cytokines and chemokines that further activate microglia and astrocytes. Infiltrating monocytes can differentiate into macrophages to assist in the clearance of necrotic tissue, whereas activated Th1 and Th17 cells enhance neurotoxic responses and exacerbate neuronal injury through the production of pro-inflammatory mediators [13, 36]. In turn, elevated levels of cytokines and oxidative stress further suppress the expression of tight junction proteins in endothelial cells and disrupt interactions between pericytes and the basement membrane, thereby aggravating BBB breakdown and promoting sustained permeability.

Thus, BBB disruption is not only a consequence of post-TBI neuroinflammation but also a major driver of its persistence and spread. Therapeutic strategies aimed at inhibiting endothelial apoptosis, preserving tight junction integrity, and limiting aberrant infiltration of peripheral immune cells have emerged as promising approaches to attenuate the propagation of neuroinflammation and prevent secondary brain injury.

2.4. Activation of the Complement System

The complement system exerts dual effects in post-TBI neuroinflammation. On the one hand, activation of components such as C1q, C3, and C5 promotes neutrophil infiltration, disruption of the blood–brain barrier, and neuronal injury. On the other hand, appropriately regulated complement activation contributes to debris clearance and tissue repair. Following TBI, both neurons and glial cells can synthesize complement components, and receptors for C3a and C5a are widely expressed within the brain [37]. Experimental and clinical studies have demonstrated marked deposition of C1q, C3b, and the membrane attack complex (MAC) in perilesional areas, while pharmacological or genetic inhibition of C3/C5 activation attenuates inflammation and cerebral edema [38, 39]. Notably, complement-mediated synaptic pruning by microglia has been implicated as a key mechanism by which acute neuroinflammation transitions into chronic neurodegeneration [40].

3. Mechanistic Links between Neuroinflammation and Delirium

3.1. Effects of Inflammatory Mediators on Neurotransmitter Systems

Neuroinflammation plays a pivotal role in the development of delirium following traumatic brain injury (TBI), with disruption of neurotransmitter systems by inflammatory mediators representing an early and direct pathological mechanism. Pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6 can affect the synthesis, release, and reuptake of key neurotransmitters—including acetylcholine, glutamate, γ-aminobutyric acid (GABA), and dopamine—through multiple pathways, thereby disturbing neurochemical homeostasis [41].

The cholinergic system is frequently implicated in the cognitive consequences of traumatic brain injury. Within this system, IL-1β and TNF-α can suppress the expression of choline acetyltransferase (ChAT) and reduce acetylcholine synthesis, thereby attenuating cholinergic neurotransmission in cortical and hippocampal regions [42]. Cholinergic deficiency is considered one of the core neurochemical mechanisms underlying delirium [43], and similar alterations have been observed in patients with non-traumatic delirium [44].

Within the glutamatergic system, inflammatory mediators promote glutamate release while inhibiting its uptake by excitatory amino acid transporters (EAATs), leading to extracellular glutamate accumulation and excitotoxicity [45]. Excessive activation of N-methyl-D-aspartate (NMDA) receptors results in calcium overload, further amplifying neuronal injury [46]. Meanwhile, the γ-aminobutyric acid (GABA) ergic system is also affected by inflammation and structural injury, characterized by downregulation of GABA transporters (GATs) and remodeling of GABA receptor subunits, leading to impaired inhibitory neurotransmission and further disruption of the excitatory–inhibitory balance [47]. In addition, inflammatory signaling can modulate dopamine synthesis and receptor function, altering activity within prefrontal–striatal circuits and contributing to attentional deficits and fluctuations in cognitive function [48]. The combined imbalance across these neurotransmitter systems compromises coordinated neuronal network activity and constitutes a major neurochemical basis for the development of delirium.

3.2. Inflammation-Mediated Neuronal Injury and Synaptic Dysfunction

Persistent neuroinflammation not only alters the neurochemical milieu but also induces structural and functional damage to neurons and synapses through cytotoxic mechanisms. Pro-inflammatory cytokines and reactive oxygen species (ROS) impair mitochondrial function, inhibit ATP production, and trigger neuronal apoptosis, a process further amplified by sustained activation of microglia and astrocytes [49].

Under inflammatory [50-52] conditions, the expression of synaptic proteins (such as postsynaptic density protein 95 (PSD-95) and Synaptophysin) is downregulated, accompanied by reduced dendritic spine density and diminished postsynaptic receptor responsiveness, ultimately leading to impaired synaptic plasticity and disrupted signal transmission [50]. Astrocyte-derived IL-6 and TGF-β interfere with synaptic remodeling, while complement-mediated excessive synaptic pruning by microglia further weakens neuronal circuit connectivity [40], [51]. This cascade—from inflammation-induced mitochondrial dysfunction to loss of synaptic plasticity and network disconnection—provides the structural basis for the development of delirium.

3.3. Neuroinflammation and Aberrant Brain Network Function

In patients with TBI, functional neuroimaging studies have demonstrated reduced connectivity within the default mode network (DMN) and the frontoparietal executive control network. Concurrently, electroencephalography (EEG) studies indicate a shift in the post-injury background activity toward increased low-frequency (δ/θ) power and decreased high-frequency (α/β) power, along with reduced local and global synchrony [52-54]. Similar alterations in large-scale network connectivity and electrophysiological patterns have been observed in patients with delirium [55, 56]. Although many of these studies do not directly quantify inflammatory biomarkers, accumulating evidence suggests that neuroinflammation may contribute to such network dysfunction by disrupting neuronal synchrony and modulating neuron–glia interactions, thereby participating in the pathophysiological basis of delirium [57].

4. Clinical Implications and Future Perspectives

Delirium is a common acute neuropsychiatric complication following traumatic brain injury (TBI), characterized by abrupt fluctuations in consciousness and cognitive function. Its occurrence is closely associated with increased mortality, prolonged hospitalization, and long-term cognitive impairment. Current evidence indicates that neuroinflammation plays a pivotal role in the onset and progression of post-TBI delirium. The release of pro-inflammatory cytokines, aberrant activation of glial cells, disruption of the blood–brain barrier, and complement-mediated immune responses collectively contribute to amplification of inflammation and neuronal dysfunction. These mechanistic insights provide an important foundation for clinical risk stratification, early detection, and the development of targeted intervention strategies.

Dynamic monitoring of inflammatory biomarkers holds potential clinical value. Elevated levels of IL-1β, IL-6, TNF-α, and related mediators in the serum or cerebrospinal fluid of TBI patients may reflect central immune activation, and their temporal profiles may be associated with an increased risk of delirium [58]. Integrating these markers with neuroimaging and neurophysiological parameters to construct multidimensional predictive models could facilitate early identification of high-risk patients and enable individualized monitoring and intervention.

Therapeutic strategies targeting neuroinflammation may offer a promising approach to reducing the incidence of delirium after TBI. Emerging evidence from human studies and clinical trials has focused on interventions modulating microglia-associated pro-inflammatory pathways and the complement cascade. Interleukin-1 receptor antagonists have been shown to modify cytokine profiles in cerebrospinal fluid and extracellular brain tissue and to be safe in patients with severe TBI [59]. Complement inhibitors, such as C1 esterase inhibitor (C1-INH), have entered randomized controlled trials in TBI populations to evaluate their effects on neuroinflammatory responses and clinical outcomes [60]. In contrast, clinical evidence directly targeting astrocyte reactivity remains limited, highlighting this area as a potential avenue for future translational research. In parallel, pharmacological interventions targeting inflammation-induced disturbances in neurotransmitter systems—particularly imbalances within the cholinergic, glutamatergic, and GABAergic pathways—may help alleviate cognitive fluctuations and impairments of consciousness in patients with post-TBI delirium.

Temporal dynamics of neuroinflammation also offer new perspectives for comprehensive management. Tailoring the use of sedative agents, early rehabilitation strategies, and nutritional support in accordance with the peak and duration of inflammatory responses may help attenuate the severity of delirium and improve long-term outcomes. Incorporating assessment of inflammatory status into multidisciplinary care pathways could provide an objective basis for the longitudinal management of patients with TBI.

Future research should further elucidate the causal relationship between neuroinflammation and delirium, as well as the key molecular pathways involved. Current evidence is largely derived from animal models and small clinical cohorts, with a paucity of large-scale, prospective human data. Multicenter clinical studies integrating multi-

omics approaches hold promise for delineating the distinct roles of various cell types and signaling networks within the inflammatory cascade.

At the translational level, further exploration is needed to evaluate the therapeutic potential of anti-inflammatory agents, immunomodulators, and neuroprotective drugs in the prevention and management of post-TBI delirium, ideally through well-designed randomized controlled trials to establish their efficacy and safety. Overall, advancing our understanding of the role of neuroinflammation in post-TBI delirium and promoting the translation of mechanistic insights into targeted clinical interventions will provide new avenues and an evidence-based foundation for improving patient outcomes.

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