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Review Article

The Role of the Brain-lymphatic Axis in Traumatic Brain Injury-associated Cognitive Impairment: From Glymphatic System Clearance Dysfunction to Peripheral Lymphatic Stasis

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Abstract

Traumatic brain injury (TBI)-associated cognitive impairment is highly prevalent, severely impacting patients' daily life and social functioning, with its mechanisms incompletely understood. Globally, TBI affects over 69 million people annually, and post-TBI cognitive impairment may last for years, or even a lifetime, imposing heavy burdens on patients' families. The brain-lymphatic axis (glymphatic + peripheral lymphatic systems, especially meningeal vessels) has gained attention: glymphatic dysfunction (dependent on astrocyte endfeet Aquaporin-4 polarization, key for clearing β-amyloid and other wastes) causes metabolic waste accumulation and neuroinflammation, while peripheral lymphatic stasis worsens cognitive decline. This review aims to summarize their roles, dissect mechanisms, and outline therapies. The review found that most current studies explore the glymphatic system and the peripheral lymphatic system in isolation, lacking understanding of their dynamic interplay (e.g., bidirectional inflammatory factor transmission, immune cell migration, synergistic dysfunction); longitudinal studies that track axis changes across TBI stages (acute, subacute, chronic) are scarce; diagnostic tools are insufficient (non-invasive biomarkers lack large-scale clinical validation, and imaging has limited clinical use); and existing therapeutic strategies mostly target single subsystems, with few combined interventions for the whole axis. In conclusion, this review highlights critical gaps in current knowledge and proposes integrated, axis-targeted approaches as a promising direction for future research and therapeutic development.

Introduction

Traumatic brain injury (TBI) has become a significant factor contributing to death and disability worldwide, and its secondary cognitive impairment has a serious impact on the quality of life of patients.[1] Previous studies have revealed that the pathological mechanisms of TBI are complex and diverse, and the brain-lymphatic axis (including the central nervous system glymphatic system and the peripheral lymphatic system) plays a crucial role in the pathological processes after TBI.[2,3] For example, dysfunction of the glymphatic system can lead to the accumulation of metabolic waste and neuroinflammation,[4] while peripheral lymphatic stasis can exacerbate cognitive decline.[5,6]

However, there are still many research gaps that urgently need to be filled in this field at present. On the one hand, most studies tend to view the glymphatic system and the peripheral lymphatic system in isolation, and there is still a lack of in-depth and comprehensive understanding of their dynamic interactions during the occurrence of TBI, such as the mechanisms by which they synergistically aggravate cognitive decline.[7,8] On the other hand, at the diagnostic level, there are still no highly sensitive and non-invasive biomarkers to accurately assess the dysfunction of the brain-lymphatic axis, making it difficult to effectively predict the progression of cognitive impairment.[9] Moreover, effective treatment strategies targeting the overall brain-lymphatic axis are relatively scarce, and most existing interventions focus on parts rather than the whole, resulting in limited overall efficacy.[10]

In view of these deficiencies, this review aims to synthesize the latest evidence and focus on key aspects such as the interaction between systems, biomarkers, and treatment strategies, so as to lay the foundation for improving the intervention measures for the

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long-term cognitive outcomes of TBI patients, with the expectation of filling the existing research gaps and providing support for the development of this field. By searching major academic databases including PubMed, Web of Science, and Embase with key terms like "TBI", "cognitive impairment", and "brain-lymphatic axis", we screened relevant studies from the recent decade (including basic studies, clinical studies, and reviews) for systematic synthesis.

Epidemiology and clinical characteristics of post-TBI cognitive impairment

Epidemiological data of post-TBI cognitive impairment

Epidemiological and clinical data on TBI-associated cognitive impairment (CTTI) after TBI show that it is complex and varies widely. Alawieh *et al*.[11] investigated cognitive decline after TBI. Their research indicates that the annual incidence of TBI reaches up to 69 million cases,[1] with a correspondingly high prevalence of subsequent CTTI. The severity and incidence of cognitive decline vary according to the severity of TBI. Königs *et al*.[12] examined the prediction of intelligence impairment based on post-traumatic amnesia (PTA). In the subacute recovery phase of severe TBI, full-scale intelligence quotient scores show a marked reduction, with an effect size of d = −1.07 (95% CI: −1.52 to −0.62, $P < 0.001$), persisting into the chronic phase (d = −0.78, 95% CI: −1.06 to −0.51, $P < 0.001$). Stålnacke *et al*.[13] tracked long-term functional impairments after TBI, showing that CTTI in severe TBI patients may persist for years or even a lifetime, imposing substantial burdens on daily life and social functioning. Ozono *et al*.[14] examined cognitive risk factors for mild TBI. With advancing age, the risk of CTTI increases significantly, especially in the presence of comorbidities such as hypertension and diabetes, which aggravate cognitive and functional deficits. Early identification and intervention for post-TBI CTTI, particularly in high-risk populations, are therefore essential for improving patient outcomes.

Clinical manifestations of post-TBI cognitive impairment

Clinical manifestations of post-TBI CTTI are diverse, primarily affecting multiple domains such as memory, executive function, attention, and information processing speed. Verhulst *et al*.[15] explored magnetic resonance imaging (MRI) correlates of cognitive functioning after brain injury. Studies show that TBI patients often experience profound short-term memory deficits during the acute phase, particularly within the first few days after injury. Impairments in executive functions, including planning, organization, and decision-making, are also common. Douglas *et al*.[16] evaluated the effectiveness of communication-focused interventions after TBI. These cognitive deficits affect not only daily living but also contribute to social difficulties and mental health issues such as anxiety and depression. Adams *et al*.[17] studied coping strategies of TBI survivors. Their findings revealed that long-term follow-up data indicate dynamic changes in cognitive function beyond the acute phase: in subacute and chronic stages, some patients may experience further decline, especially without timely rehabilitation or intervention. Such cognitive changes significantly impair quality of life and impose burdens on families and society. Establishing long-term follow-up mechanisms to monitor cognitive trajectories in TBI patients will facilitate personalized, supportive, and interventional strategies.

Pathophysiological basis of post-TBI cognitive impairment

The pathophysiological basis of post-TBI CTTI is complex and multifactorial, involving mechanisms such as neuronal injury, axonal damage, and alterations in synaptic plasticity. Criado-Marrero *et al*.[18] examined brain function in mice with brain injury. Following TBI, neurons may undergo acute injury, resulting in cell death and functional loss; axonal injury disrupts signal transmission, impairing overall neural network integrity. Montivero *et al*.[19] investigated neuroinflammation and oxidative stress after TBI. TBI also triggers sustained activation of neuroinflammatory and oxidative processes, which further damage neurons. Excessive release of pro-inflammatory cytokines after TBI contributes to dysfunction in neurons and glial cells, amplifying inflammatory responses and neural injury. Simultaneously, heightened oxidative stress is closely associated with neuronal apoptosis. Interventions for post-TBI CTTI must therefore combine strategies targeting neuroprotection, anti-inflammation, and antioxidation to improve cognitive outcomes and quality of life.

In-depth exploration of the epidemiology, clinical manifestations, and pathophysiological mechanisms of post-TBI CTTI provides essential theoretical and practical guidance for future clinical interventions and research in TBI patients.

Cerebral lymphatic axis: Physiological mechanisms of the glymphatic and peripheral lymphatic systems, and pathophysiology with bidirectional regulation after TBI

The cerebral lymphatic axis is a key functional network maintaining intracerebral homeostasis, consisting of the central glymphatic system and peripheral lymphatic system through synergistic interactions and bidirectional regulation.[3,20] Its core functions include clearing intracerebral metabolic wastes, maintaining immune balance, and stabilizing the internal environment. TBI can disrupt the structure and function of this axis, leading to the accumulation of metabolic wastes, amplification of neuroinflammation, and CTTI through glymphatic dysfunction, peripheral lymphatic stasis, and disturbed bidirectional regulation, thereby serving as a critical pathological basis for chronic neurological dysfunction after TBI.

Composition and physiological mechanisms of the cerebral lymphatic axis

Structure and core functions of the glymphatic system

The glymphatic system is a brain clearance network made mainly of periarterial cerebrospinal fluid (CSF) inflow channels, perivenous interstitial fluid (ISF) outflow channels, and Aquaporin-4 (AQP4) on astrocytes that link them. Its work depends on AQP4 being concentrated in astrocytic endfeet—this polarized AQP4 is needed for CSF–ISF exchange.[20] CSF first enters via periarterial spaces, moves through the parenchyma to clear metabolic waste, and then leaves through perivenous spaces, forming the pathway "periarterial inflow → parenchymal flow → perivenous outflow" (Fig. 1).[21]

Its physiological functions are mainly reflected in two aspects: first, it efficiently removes intracerebral metabolic wastes, including β-amyloid (Aβ) and tau proteins, which are closely associated with neurodegenerative diseases[22]; second, it is regulated by the sleep–wake cycle. During sleep, neuronal activity decreases and the interstitial space expands, significantly enhancing glymphatic clearance efficiency, whereas sleep deprivation suppresses its function and raises the risk of intracerebral toxin accumulation.[23] Current research methods include dynamic contrast-enhanced MRI, which evaluates CSF dynamics by tracking contrast agent distribution,[24] and two-photon microscopy combined with mouse

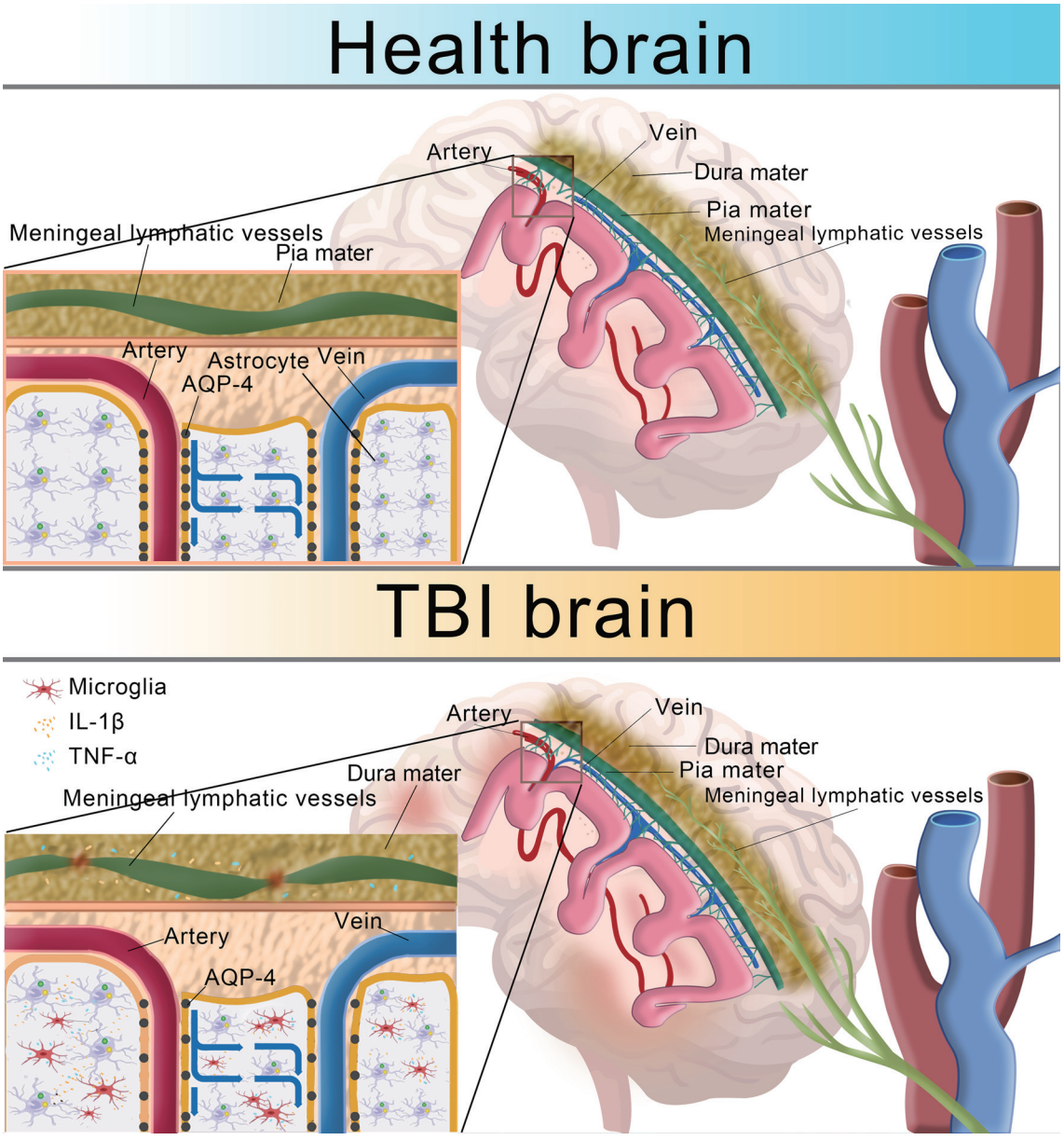

Fig. 1. In the healthy brain, the glymphatic system is composed of ISF, astrocytes, and meningeal lymphatic vessels. ISF originates in periarterial spaces, flows through brain tissue along these perivascular routes, converges in perivenous spaces, and subsequently drains back into the venous system. During this process, ISF carries abnormal proteins and metabolic wastes from brain tissue into meningeal lymphatic vessels, completing clearance. After TBI, however, the following pathological changes occur: (1) stagnation of lymphatic vessels, resulting in impaired clearance of metabolic wastes; (2) abnormal structural alterations of AQP-4, disrupted polarity of distribution, and impairment of ISF generation; (3) activation of microglia, excessive release of inflammatory factors, and the establishment of a pro-inflammatory microenvironment that drives a vicious cycle. AQP-4, Aquaporin-4; IL-1β, interleukin-1β; ISF, interstitial fluid; TBI, traumatic brain injury; TNF-α, tumor necrosis factor-alpha.

models, which allow in-depth analysis of glymphatic function in both healthy and pathological states.[25]

The glymphatic system is composed of specific structures and follows the pathway of "perivascular arterial inflow – parenchymal flow – perivascular venous outflow", with its core function being the clearance of metabolic wastes such as Aβ and tau and regulation by the sleep–wake cycle, and current research on it is mainly conducted through techniques including dynamic contrast-enhanced MRI and two-photon microscopy.

Role of the peripheral lymphatic system and its synergy with the glymphatic system

The peripheral lymphatic system, particularly meningeal lymphatic vessels, is an essential component of the cerebral lymphatic axis, forming functional coupling with the glymphatic system:

Metabolic wastes (e.g., Aβ, tau) collected by the glymphatic system enter meningeal lymphatic vessels through perivenous spaces and are subsequently transported to cervical lymph nodes.[26] The peripheral lymphatic system completes final elimination, form-

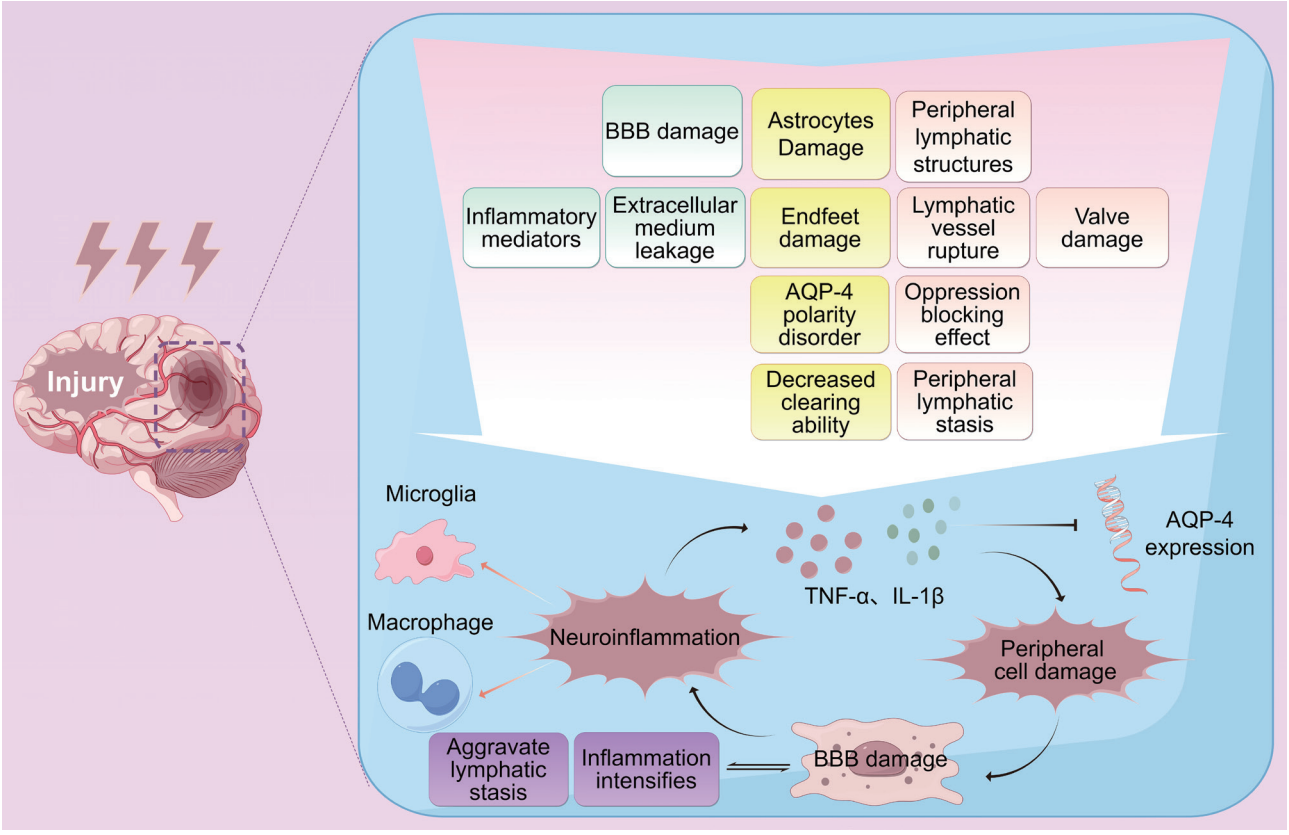

Fig. 2. The figure shows the pathophysiological processes following traumatic brain injury (TBI) involving interactions at the molecular, cellular, and tissue levels. Direct injuries caused by TBI include blood–brain barrier (BBB) disruption accompanied by leakage of inflammatory mediators, damage to astrocytic endfeet leading to Aquaporin-4 (AQP4) polarity disorder, and decreased metabolic waste clearance capacity, as well as peripheral lymphatic structural damage (lymphatic vessel rupture, valve damage, and peripheral lymphatic stasis). These injuries result in the release of a large number of inflammatory factors, forming a vicious cycle, which further recruits peripheral lymphocytes, activates microglia, and exacerbates neuroinflammation. Meanwhile, neuroinflammation inhibits the expression of AQP4, further leading to dysfunction of the glymphatic system. This figure was designed using figdraw.com. IL-1β, interleukin-1β; TNF-α, tumor necrosis factor-alpha.

ing a hierarchical pathway of "glymphatic collection – meningeal lymphatic transport – peripheral lymphatic elimination" (Fig. 1).[27]

Under physiological conditions, the glymphatic system restricts peripheral immune cell infiltration by maintaining blood–brain barrier (BBB) integrity,[28] while meningeal lymphatic vessels drain intracerebral quiescent microglia and soluble immune mediators to the periphery, preventing excessive neuroinflammation. Conversely, the peripheral lymphatic system can deliver anti-inflammatory signals (e.g., regulatory T cells) into the brain through circulation, contributing to local inflammation resolution.[29]

In response to minor brain insults, the glymphatic system accelerates waste clearance to limit damage,[30] while the peripheral lymphatic system enhances the drainage of inflammatory mediators.[31] Together, the two systems maintain intracerebral homeostasis and protect cognitive function.

Pathophysiological mechanisms of the cerebral lymphatic axis after TBI

Direct damage and dysfunction of the glymphatic system

TBI can directly impair the structure and function of the glymphatic system through mechanical forces. TBI damages astrocytic endfeet, causing the loss of AQP4 polarization and its redistribution on the cell membrane, which disrupts CSF–ISF exchange and reduces metabolic waste clearance (Figs. 1 and 2).[32,33] TBI damages the BBB, letting inflammatory mediators and extracellular matrix components leak out, which then further harms the barrier.[34] This not only aggravates intracerebral inflammation but also further obstructs glymphatic pathways, forming a vicious cycle of "BBB disruption – glymphatic stasis – inflammation exacerbation".[35]

Interaction between neuroinflammation and glymphatic function

Activated microglia after TBI release pro-inflammatory cytokines (e.g., interleukin-1β, tumor necrosis factor-alpha), which downregulate AQP4 expression and inhibit its function, thereby reducing glymphatic clearance efficiency.[36] Simultaneously, the inflammatory microenvironment impairs microglial phagocytosis, weakening their ability to clear intracerebral wastes. This dual effect promotes waste accumulation, which in turn activates neuroinflammation, forming a positive feedback loop of "inflammation–glymphatic inhibition" (Fig. 2).[4]

Peripheral lymphatic stasis and disordered bidirectional regulation with the glymphatic system

TBI can induce stasis in the peripheral lymphatic system, particu-

larly in cervical lymphatics, disrupting the synergy of the cerebral lymphatic axis. Mechanical forces from TBI, especially blunt impact or whiplash, can directly injure peripheral lymphatic vessels, particularly cervical ones anatomically connected to meningeal lymphatics.[7] Such trauma may rupture lymphatic endothelium, impair valvular function that prevents backflow, or compress vessels due to edema or hematoma, thereby blocking lymphatic drainage and impeding the clearance of intracerebral wastes to the periphery. Glymphatic dysfunction hinders clearance of intracerebral interleukin-1β, tumor necrosis factor-alpha, and other mediators, while peripheral lymphatic stasis impairs their peripheral degradation, resulting in dual accumulation of inflammatory factors in both the central nervous system and systemic circulation.[37,38] Moreover, peripheral cytokines released from stagnant lymphoid tissues may re-enter the brain through a compromised BBB, amplifying neuroinflammation and further suppressing glymphatic function.[39,40] The pro-inflammatory niche induced by TBI recruits peripheral immune cells (e.g., pro-inflammatory macrophages), but lymphatic stasis traps them within meninges and perivascular spaces, where they directly damage neurons via cytotoxic factors.[29] Meanwhile, activated intracerebral microglia fail to be drained by meningeal lymphatic vessels, persisting in the inflammatory microenvironment and worsening glymphatic clearance impairment (Fig. 2).

In short, TBI can cause glymphatic system injury and peripheral lymphatic stasis, forming a vicious cycle with neuroinflammation, impairing the synergy of the cerebral lymphatic axis, and hindering waste clearance and inflammation regulation.

Impact of cerebral lymphatic axis dysfunction on post-TBI cognitive function

Dysfunction of the cerebral lymphatic axis constitutes a core mechanism underlying cognitive decline after TBI: the combined impairment of the glymphatic and peripheral lymphatic systems compromises the clearance of toxic proteins such as Aβ and tau,[26] whose accumulation disrupts synaptic plasticity and induces neuronal death.[41] Furthermore, persistent neuroinflammation together with peripheral systemic inflammation can impair neurovascular coupling through the compromised BBB, thereby reducing cerebral blood flow and further suppressing glymphatic activity, which aggravates the accumulation of metabolic wastes.[33]

This vicious cycle of "waste accumulation – inflammation amplification – neuronal damage" ultimately results in marked deficits in cognitive domains such as memory, executive function, and attention, and may even accelerate the onset of neurodegenerative diseases such as chronic traumatic encephalopathy.

Diagnostic techniques for the brain-lymphatic axis in post-TBI cognitive impairment

Neuropsychological assessment of post-traumatic cognitive decline

Neuropsychological assessment is a critical tool for the clinical diagnosis of post-traumatic CTTI. Various tests evaluate cognitive abilities from multiple dimensions. In Hicks *et al*.,[42] the Wechsler Adult Reading Test was used to assess premorbid intelligence quotient, while the Digit Symbol Coding Test, Digit Span Backward Test, Rey Auditory Verbal Learning Test, and Trail Making Test Part B evaluated processing speed, working memory, memory, and executive function, respectively. Additionally, Segev *et al*.[43] investigated variability in the duration of PTA after TBI and found that prolonged PTA in pediatric patients worsens cognitive deficits in attention and executive function. In summary, neuropsychological assessment after TBI effectively detects cognitive decline, providing a critical reference for clinical diagnosis and treatment.

Imaging techniques for evaluating brain-lymphatic axis function

Imaging techniques are essential for assessing the physiological and pathological state of the brain-lymphatic axis. Near-infrared fluorescence imaging has been applied to determine whether manual lymphatic drainage enhances lymphatic contractility. Tan *et al*.[44] evaluated lymphatic contractile function and confirmed that this technique detected an average increase in apparent lymphatic flow velocity of 23%, 25%, and 28% in the affected limb, unaffected limb, and healthy control group, respectively, after manual lymphatic drainage treatment, along with shortened lymphatic propulsion cycles.

MRI and positron emission tomography (PET) are also used to visualize brain ISF, CSF, and lymphatic outflow. Lee *et al*.[45] investigated brain lymphatic imaging. In rodent and human brains, contrast-enhanced MRI with intrathecal injection, combined with *ex vivo* fluorescence microscopy and *in vivo* two-photon imaging, demonstrated the CSF-to-lymphatic outflow pathway.

Optical coherence tomography is another method suitable for imaging meningeal lymphatics, allowing non-invasive identification of lymphatic drainage patterns. Semyachkina-Glushkovskaya *et al*.[46] applied optical coherence tomography to monitor meningeal lymphatic vessels, describing its use in measuring the depth and size of mouse meningeal lymphatics.

Together, these imaging techniques provide direct insights into brain-lymphatic axis function, offering important references for disease diagnosis and treatment.

Biomarker research for evaluating brain-lymphatic axis function

Current research primarily focuses on using glymphatic system-related indices, such as the diffusion tensor imaging (DTI)-derived along-the-perivascular-space (ALPS) index, to predict glymphatic activity. Brain function and biomarkers were assessed with PET/MRI in the study by Okazawa *et al*.[47] In Alzheimer's disease research, higher DTI-ALPS values line up with more brain amyloid, lower Mini-Mental State Examination scores, and smaller hippocampal volume. Because the link with amyloid is stronger than with other markers, researchers think glymphatic failure might occur early in Alzheimer's disease.

In TBI, especially in mild-to-moderate chronic cases, the DTI-ALPS index is an important measure. Tomizawa *et al*.[48] studied the lymphatic system in multiple sclerosis and found that patients with secondary progressive multiple sclerosis had much lower ALPS indices than those with relapsing-remitting multiple sclerosis, which links glymphatic problems to multiple sclerosis progression. Therefore, the ALPS index could be used as a diagnostic biomarker for secondary progressive multiple sclerosis.

ALPS index changes can show how TBI has harmed the glymphatic system and may reflect how severe CTTI is after the injury.[9,49] These results point to new ways to diagnose and track diseases caused by glymphatic dysfunction.

Potential strategies targeting the brain-lymphatic axis as a therapeutic target

Interventions to improve glymphatic system function

In studies of the brain-lymphatic axis, the glymphatic system is

Table 1. A summary of core therapeutic strategies targeting the brain-lymphatic axis for Traumatic brain injury-associated cognitive impairment, including therapeutic categories, specific interventions, and core mechanisms

Therapeutic category	Specific interventions	Core mechanism
Glymphatic system function improvement	AQP4 regulation (e.g., VEGF-C intervention): 2. Sleep optimization (lateral position, improved sleep quality)	1. Regulates AQP4 expression/distribution, promotes cerebrospinal fluid (CSF)-interstitial fluid (ISF) exchange, and enhances metabolic waste clearance.[49] 2. Increases cerebral blood flow and CSF-ISF exchange efficiency during sleep; lateral position further improves glymphatic clearance activity.[50]
Peripheral lymphatic drainage enhancement	Lymphatic massage: 2. VEGF-C therapy	1. Physically stimulates peripheral lymph flow, reduces lymphatic stasis, and alleviates edema and pain.[52] 2. Stimulates proliferation/migration of lymphatic endothelial cells, increases lymphatic vessel density, and improves drainage and immune surveillance functions.[53,54]
Multi-target combined therapy	Anti-inflammatory drugs (e.g., macromolecular dexamethasone prodrug) + Glymphatic enhancement strategies (e.g., AQP4 regulation/sleep optimization)	Simultaneously reduces neuroinflammation (decreases secondary neuronal damage), optimizes cerebral fluid homeostasis, and synergistically promotes metabolic waste clearance
Surgical intervention	Cisternostomy (including basal cisternostomy)	Open the brain cisterns and expose them to atmospheric pressure, then utilize the Virchow-Robin spaces (perivascular spaces) to promote the reflux of CSF from the swollen brain tissue into the cisterns, thereby reducing intracranial pressure (ICP)[55,56]

AQP4, Aquaporin-4; VEGF-C, vascular endothelial growth factor-C.

recognized as a critical pathway for clearing brain ISF and metabolic waste. AQP4, a key water channel protein in the glymphatic system, plays an essential role in maintaining brain fluid homeostasis through regulation of its expression and distribution.[50] Lan *et al*.[51] linked AQP4 dysfunction to the pathogenesis of several neurodegenerative diseases. For example, reduced AQP4 expression in Alzheimer's disease brain tissue impairs clearance and promotes Aβ accumulation, highlighting AQP4 as a promising therapeutic target. Chu *et al*.[52] studied vascular endothelial growth factor-C (VEGF-C), showing that it promotes AQP4 expression, enhances glymphatic function, reduces brain edema, and alleviates inflammatory responses—providing novel therapeutic insights for improving post-TBI cognition (Table 1).[49,50,52–56]

Sleep is another critical factor in glymphatic activation. Yan *et al*.[57] studied the link between lymphatic dysfunction and mood disorders. In their findings, during sleep, cerebral blood flow and CSF–ISF exchange efficiency increase markedly, facilitating waste clearance. Vasciaveo *et al*.[58] studied the effect of sleep fragmentation on the lymphatic system and showed that sleep deprivation impairs AQP4 function, disrupts glymphatic dynamics, and exacerbates neurotoxic protein accumulation, linking it to neurodegenerative disease risk (Table 1).

Thus, optimizing sleep quality and applying positional therapy (e.g., side-position sleep) can enhance glymphatic activity. These strategies improve CSF circulation and metabolic waste clearance, playing a proactive role in TBI rehabilitation.

Therapeutic approaches to enhance peripheral lymphatic drainage

Enhancing peripheral lymphatic drainage is essential for treating conditions such as lymphedema and mass lesions. Lymphatic massage, a non-invasive therapeutic technique, mechanically stimulates lymphatic flow to reduce stasis. Hitscherich *et al*.[53] suggested opportunities for osteopathic manipulative medicine within the lymphatic continuum. Their clinical evidence demonstrated its effectiveness in increasing peripheral lymphatic velocity, reducing edema, and alleviating pain. Combined with conventional physical therapy, lymphatic massage yields significant benefits, particularly in postoperative recovery (Table 1).

Advances in lymphatic system biology have identified the VEGF-C signaling pathway as a key target for promoting lymphangiogenesis. VEGF-C stimulates the proliferation and migration of lymphatic endothelial cells, thereby enhancing vessel growth and drainage efficiency.[54] Böhmer *et al*.[55] studied leukocyte-mediated regulation of lymphangiogenesis, showing that VEGF-C not only increases lymphatic vessel density but also improves functional capacity for fluid clearance and immune surveillance. Liao *et al*.[56] studied mechanisms related to TBI. After intracisternal magna injection of VEGF-C in TBI rats, VEGF-C upregulated lymphatic-specific proteins, improved the function and structure of meningeal lymphatic vessels, promoted CSF drainage and brain edema absorption, reduced neuroinflammation, decreased reactive oxygen species production, and improved neurological function and prognosis (Table 1).

This finding provides a novel pharmacological target for lymphatic-related disorders; in post-TBI recovery, enhancing lymphatic drainage may reduce brain edema and improve cognitive function.

Multitarget combinatorial therapy strategies

As noted above, neuroinflammation exacerbates CTTI after brain injury. Inflammation plays a central role in post-TBI recovery, making anti-inflammatory therapy fundamental for limiting secondary neuronal damage and preserving glymphatic function. Wei *et al*.[59] studied a macromolecular dexamethasone prodrug for TBI-induced neuroinflammation. Combinatorial strategies integrating anti-inflammatory agents (e.g., glucocorticoids) with glymphatic-enhancing interventions demonstrated synergistic effects in improving post-traumatic cognition (Table 1).

Such multitarget therapies mitigate inflammation-driven secondary injury and accelerate recovery by optimizing brain fluid homeostasis.

Surgical interventions: CSF diversion

Surgical strategies targeting the brain-lymphatic axis have emerged as potential interventions for post-TBI CTTI, particularly when glymphatic or peripheral lymphatic dysfunction is severe or unresponsive to conservative measures. Cherian *et al*.[60] studied the surgical treatment of TBI and introduced the emerging surgical procedure of cisternostomy—this procedure reduces intracranial pressure by opening the brain cisterns to atmospheric pressure and utilizing the Virchow–Robin spaces (perivascular spaces) to facilitate the backflow of CSF from the swollen brain tissue to the cisterns, with new evidence supporting this surgical method. Han *et al*.[61] conducted a retrospective analysis of 41 patients aged 18–70 with severe TBI who underwent surgery between January 2019 and March 2023 (excluding those with severe multiple injuries, preoperative intracranial pressure > 60 mmHg, and other such conditions). They concluded that basal cisternostomy is significantly effective in reducing intracranial pressure and improving prognosis in patients with severe TBI without the need for bone flap removal, but it requires further verification through larger-scale, multi-center randomized trials (Table 1). These approaches aim to restore fluid homeostasis, promote waste clearance, and reduce neuroinflammation through mechanical or structural modification of drainage pathways.

Future research directions and challenges

Studies on dynamic changes of the brain–lymphatic Axis in TBI

Investigating the dynamic changes of the brain–lymphatic axis after TBI is increasingly important. The functions of the glymphatic and peripheral lymphatic systems may vary considerably across different stages following TBI. Peters *et al*.[33] found that, during the acute phase, glymphatic dysfunction leads to reduced clearance of brain metabolic waste, which is closely linked to acute neuroinflammation. Gao *et al*.[31] pointed out that in the subacute phase, as inflammation subsides, glymphatic clearance may gradually recover, while the peripheral lymphatic system begins to play a critical role in removing infiltrated immune cells and damaged brain components, thereby reducing the risk of secondary injury. Zhuo *et al*.[62] emphasized that chronic-phase studies should focus on long-term neural recovery, with evidence suggesting a positive correlation between improved glymphatic function and cognitive restoration. Longitudinal investigations of glymphatic and peripheral lymphatic activity at multiple time points are therefore essential for elucidating post-TBI recovery mechanisms.

The application of multimodal imaging techniques provides a new perspective on brain–lymphatic axis dynamics in TBI. PET–MRI, which integrates metabolic and anatomical imaging, enables simultaneous evaluation of brain metabolic activity and structural alterations, offering a novel tool for studying glymphatic function.[63,64] This approach allows real-time monitoring of glymphatic flow and peripheral lymphatic engagement; therefore, it may reveal the functional status of the brain–lymphatic axis at different post-TBI stages. Such advances highlight the potential of more precise assessment tools to inform personalized treatment strategies.

Development of individualized treatment strategies

Individualized treatment plans are central to managing TBI. Recent biomarker work—especially measuring metabolic waste in CSF—has made these markers useful for judging injury severity and forecasting recovery. Oeckl *et al*.[65] confirmed that CSF biomarkers work for diagnosis. Levels of neuron-specific proteins in CSF, like neurofilament light chain and phosphorylated neurofilament heavy chain, show how severe the injury is and how recovery may go, helping clinicians pick precise therapies. Monitoring these biomarkers lets clinicians follow patients over time, adjust treatment, and improve outcomes.

Genetic factors are now seen as important for predicting treatment outcomes. Variations in the AQP4 gene, which affect brain–lymphatic axis function, may change how patients respond to therapy.[66] Studying these genetic markers could show each patient's recovery potential after TBI, open new paths for personalized care, and highlight the need to use genetic data in clinical practice for better treatment plans.

Challenges in translational medicine

In translational medicine, animal studies are still key to exploring TBI mechanisms and treatments. However, current models differ in important ways from human TBI, which limits their clinical value.[67] Some drugs work in animals but fail in trials, likely because the models do not fully match human physiology and pathology.[68] For this reason, animal models must be improved to better reflect human disease and increase translational success.

Designing better clinical trials is another major challenge in translational medicine. In TBI trials, choosing the right endpoints is vital because measures must show true treatment effects while accounting for patient differences and clinical complexity.[69] Many traditional trials focus on "hard" outcomes like survival and functional recovery, yet they often leave out "soft" outcomes such as quality of life and mental health. Future studies should therefore prioritize these softer measures and include patient perspectives in trial design to make translational medicine more effective and adaptable.

Limitations

This review has certain limitations. Firstly, the included clinical research are relatively limited, and caution should be exercised when generalizing the relevant conclusions to the human TBI patient population, which requires further verification. Secondly, although existing studies have explored TBI-related disease heterogeneity (such as disease severity and age of onset), the number of such studies is relatively small, and their connection with the brain–lymphatic axis is not close. Therefore, this review only briefly mentions relevant content when necessary, without in-depth collation and commentary.

Conclusions

Existing studies have confirmed that the brain-lymphatic axis plays a core role in the occurrence and progression of traumatic brain injury-associated cognitive impairment. Dysfunction in the glymphatic system's metabolic waste clearance and abnormal regulation of neuroinflammation by the peripheral lymphatic system are key pathological links driving post-TBI cognitive decline. This review identifies four critical research gaps in the field: most studies investigate the glymphatic system and peripheral lymphatic system in isolation; longitudinal tracking across TBI's acute, subacute, and chronic phases is scarce; clinical diagnostic tools (non-invasive biomarkers and imaging technologies) have inherent limitations; and multi-target combined interventions are insufficient. These gaps limit the comprehensive understanding of the brain-lymphatic axis' role and hinder the translation of basic research to clinical practice. Therefore, targeted addressing of these gaps is crucial for advancing the field, providing a more systematic

theoretical support for elucidating the pathological mechanisms of post-TBI cognitive decline and ultimately contributing to improving TBI patients' long-term outcomes.

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Conflict of interest

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Author contributions

Drafting of the Chinese manuscript (SD), translation of the draft (XL), literature search (YZ), full-text screening (KT, CZ), data analysis and organization (JQ, JW), project design, and quality control (JS). All authors have approved the final version and publication of the manuscript.

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