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Indian Journal of Clinical Anatomy and Physiology

Journal homepage: <https://www.ijcap.org/>

Review Article

The role of the lymphatic system in brain clearance mechanisms implications for neurodegenerative disorders

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ARTICLE INFO

Article history:

Received 02-11-2024

Accepted 10-12-2024

Available online 15-01-2025

Keywords:

Neurodegenerative disorders

Cerebrospinal fluid

Lymphatic system

ABSTRACT

The lymphatic system, traditionally associated with immune surveillance and fluid homeostasis, has emerged as a pivotal player in maintaining brain health. Recent discoveries highlight the brain's unique clearance mechanisms, particularly the glymphatic system and meningeal lymphatic vessels, in removing metabolic waste and facilitating neuroimmune communication. Dysfunction in these pathways has been implicated in the pathogenesis of neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis (MS). This review explores the anatomy and physiology of the lymphatic system in the brain, its role in waste clearance, and its implications for neurodegenerative disorders, drawing on recent advances in imaging and molecular research.

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1. Introduction

The brain was long considered an immune-privileged organ due to the blood-brain barrier (BBB) and the absence of conventional lymphatic vessels. However, studies over the last decade have revolutionized this understanding. Researchers have identified functional lymphatic vessels in the meninges and a glymphatic system a network facilitating cerebrospinal fluid (CSF) and interstitial fluid (ISF) exchange for waste clearance.^{1,2} These discoveries have redefined our understanding of brain homeostasis and its disruptions in neurodegenerative diseases. This article reviews the lymphatic and glymphatic systems, their roles in brain clearance mechanisms, and their implications for neurodegenerative disorders.



Figure 1: Neurodegenerative disease grants

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This figure can serve as Fig.no. 1 to introduce or visualize the concept of brain signaling or neurodegenerative changes, particularly in disorders like Alzheimer's disease or Type-3 diabetes mellitus.^{3,4} It visually complements discussions about the role of disrupted neuronal signaling, oxidative stress, or metabolic disturbances in the progression of neurodegenerative diseases.

2. Anatomy and Physiology of Brain Lymphatic Pathways

The pathway of the glymphatic system is a highly organized fluid transport system and has been well described in animal models. The glymphatic fluid exchange and drainage system dependent on astrocytes including the entire perivascular space (PVS) network surrounding the arteries, arterioles, capillaries, venules, and veins in the brain parenchyma. PVS is a network of low-resistance tubes formed by astrocyte foot processes surrounding the arteries, arterioles, capillaries, venules, and veins in the brain parenchyma. PVS is constructed as a coaxial system in which the inner cylinder is the cerebral vascular wall, and the outer cylinder is the glial boundary that wraps around blood vessels or the ends of astrocytes that penetrate arterioles. The flow of cerebrospinal fluid (CSF) into and out of the glymphatic system has been described in detail. At the beginning of the pericapillary pathway, cerebrospinal fluid from the subarachnoid space flows into the brain through the perivascular space of the great pia meningeal artery. As the vascular tree branches, cerebrospinal fluid enters the brain parenchyma through the perivascular space in the artery. Then from the perivascular space, CSF passes through the glial basement membrane and astrocyte terminal processes, wrapping the cerebrovascular system.⁵ Furthermore, in brain interstitial fluid, fluid is dispersed by the movement of polarized net fluid toward veins and the space around nerves. Eventually, CSF is expelled along the schwannomas, meningeal lymphatics, and arachnoid granulations of cranial and spinal nerves.⁶ Thus, it can be inferred that under certain conditions, waste products produced by brain tissue can be removed along with cerebrospinal fluid through these pathways.

2.1. The glymphatic system

The glymphatic system, named for its dependence on glial cells, is a brain-wide pathway that facilitates the clearance of solutes, including amyloid- β and tau proteins.

This image provides a detailed anatomical depiction of the blood-brain barrier (BBB), illustrating its structure and functionality in regulating the transport of molecules between the blood and the central nervous system (CNS). The figure highlights endothelial cells, tight junctions, and the supportive roles of astrocytes and pericytes in maintaining BBB integrity. Figure 2 emphasizes the critical role of the BBB in neuroprotection and its

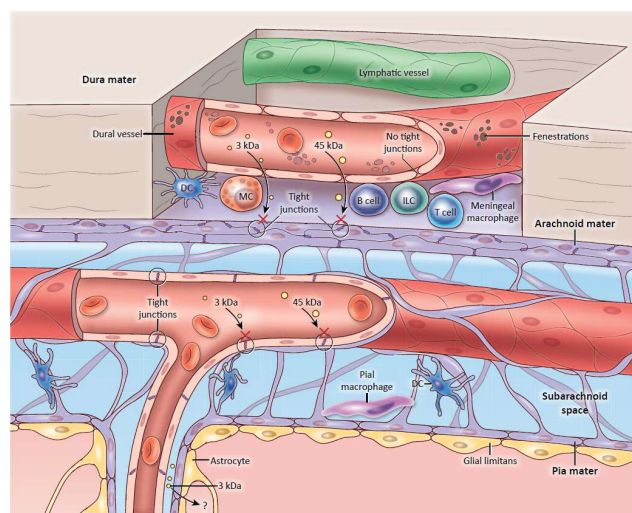


Figure 2: Schematic illustration of the structural composition of the meninges⁷ (Image Source: https://www.researchgate.net/figure/Schematic-illustration-of-the-structural-composition-of-the-meninges_fig2_336473671)

potential disruption in diseases like Alzheimer's and fungal infections. It showcases how pathogens or therapeutic agents interact with the BBB, affecting disease progression or treatment strategies. This visualization can effectively support discussions about challenges in drug delivery to the CNS and the development of nanotechnological approaches for overcoming these barriers.⁸

1. Perivascular pathways: CSF enters the brain parenchyma via para-arterial routes, driven by arterial pulsatility and aquaporin-4 (AQP4) water channels on astrocytes.⁵
2. Interstitial fluid exchange: Waste products are cleared through para-venous pathways⁹
3. Sleep-dependent activity: Glymphatic activity is most active during sleep, underscoring the importance of restorative sleep in neuroprotection.

2.1.1. Meningeal lymphatic vessels

Located in the dura mater, these vessels connect the brain's glymphatic system to peripheral lymph nodes. Meningeal lymphatic vessels facilitate:

Immune surveillance: Allowing immune cells to monitor the CNS environment.¹⁰

Waste clearance: Transporting macromolecules and immune cells to cervical lymph nodes.¹¹

Figure 3 illustrates the anatomy and function of the brain's lymphatic vessels, specifically focusing on the lymphatic system's involvement in cerebrospinal fluid (CSF) drainage. It includes a comparison of the intact and impaired vascular systems.^{8,12}

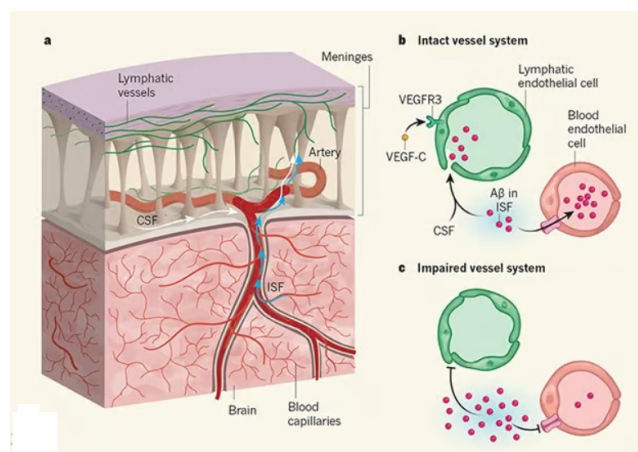


Figure 3: Lymphatic vessels cross the Neorolaptic system (Image Source: <https://www.genspark.ai/spark/what-is-the-lymphatic-system-what-is-its-function-and-how-does-it-handle-waste-and-transport-it-to-the-blood/ac91ff06-d04d-49da-bce9-ab2159ec7334>)

1. Panel a depicts the structure of the lymphatic vessels surrounding the brain, with emphasis on their connection to the blood-brain barrier and cerebrospinal fluid dynamics.
2. Panel b illustrates a healthy lymphatic system where VEGF-C (vascular endothelial growth factor C) promotes the function of lymphatic endothelial cells, facilitating CSF drainage and maintaining brain homeostasis.
3. Panel c shows the impaired system, where dysfunction in the lymphatic vasculature leads to reduced clearance of waste and increased buildup of harmful molecules in the brain, a mechanism that could contribute to neurodegenerative diseases like Alzheimer's.

This figure can be included as Figure 3 in your review article to support discussions on the role of the brain's lymphatic system in neurodegeneration, particularly in the context of diseases like Alzheimer's and the challenges in managing such conditions. It may also relate to therapies targeting the restoration of these vessels for improved drug delivery or waste removal from the brain.¹³

3. Role in Brain Clearance Mechanisms

3.1. Removal of metabolic waste

The brain generates substantial metabolic waste products such as reactive oxygen species (ROS), amyloid- β , tau proteins, and other byproducts of neural activity. These compounds, if not effectively cleared, can lead to oxidative stress and aggregation, contributing to neurodegeneration. The glymphatic system aparavascular clearance pathway-plays a pivotal role in flushing out these solutes through cerebrospinal fluid (CSF) exchange. Disruptions in glymphatic function are associated with the accumulation of

toxic metabolites, a key factor in various neurodegenerative diseases.¹⁴

3.2. Neuroimmune communication

Meningeal lymphatic vessels act as conduits between the central nervous system (CNS) and the peripheral immune system. They facilitate the transport of antigens and cytokines, allowing immune surveillance and communication. Dysregulation of this pathway can contribute to chronic inflammation and immune dysfunction within the CNS, as observed in diseases like multiple sclerosis.^{15,16}

3.2.1. Regulation of intracranial pressure (ICP)

The brain's lymphatic pathways help maintain intracranial pressure by draining excess CSF. This regulation is crucial for preventing conditions such as hydrocephalus, where increased ICP can cause severe neurological impairments.¹⁷ The balance between CSF production and lymphatic clearance is an area of active research, with implications for treating ICP-related disorders.¹⁸

This describes various diagnostic and monitoring techniques employed to assess intracranial and neurological parameters. These methods are categorized into invasive and non-invasive approaches, targeting different anatomical and functional aspects of the bra.¹⁹

The red-labeled techniques represent invasive monitoring systems, such as:

1. Intra-parenchymal optical probes: Used for direct measurement of cerebral tissue oxygenation and other metabolic parameters.
2. Intra-ventricular or lumbar catheters: Typically employed for cerebrospinal fluid (CSF) drainage or intracranial pressure (ICP) monitoring.
3. Subdural systems: Applied for subdural pressure monitoring or sampling in clinical and research settings.²⁰

The blue-labeled techniques depict non-invasive methods, including:

1. Electroencephalography (EEG): Measures electrical brain activity to monitor neurological function or detect abnormalities such as seizures.
2. Ocular ultrasound: Utilized to assess optic nerve sheath diameter as an indirect marker of raised intracranial pressure.
3. MRI and CT imaging: Gold standard imaging techniques for structural evaluation of the brain, aiding in the diagnosis of lesions, hemorrhage, or other abnormalities.
4. Transcranial Doppler Ultrasound (TCDU): A non-invasive method to evaluate cerebral blood flow dynamics.

5. Audiological techniques: Used to assess auditory brainstem responses, which may reflect intracranial pressure changes.¹³

3.3. Implications for neurodegenerative disorders

3.3.1. Alzheimer's disease (AD)

Amyloid- β clearance: The glymphatic system's impairment reduces amyloid- β clearance, leading to its accumulation—a hallmark of Alzheimer's disease. Amyloid- β aggregation contributes to plaque formation, disrupting neural communication and causing cognitive decline.^{14,21}

This provides a comprehensive visual representation of the progressive neurodegenerative changes associated with Alzheimer's disease (AD). It highlights the transition from a healthy brain to one affected by mild and severe stages of AD, demonstrating the hallmark pathological and structural alterations.

1. **Brain atrophy:** As the disease advances, significant shrinkage of brain tissue is evident, particularly in the cerebral cortex and hippocampus, regions critical for memory and cognition.¹²
2. **Neuron damage:** The image depicts damaged neurons characterized by the accumulation of amyloid plaques and neurofibrillary tangles, which are pathological hallmarks of AD. These abnormal protein aggregates disrupt neuronal function and connectivity.
3. **Astrocyte involvement:** Astrocytes, shown here, play a dual role in AD. While they are essential for maintaining homeostasis and supporting neuronal health, their dysregulation in AD contributes to inflammation and disease progression.³
4. **Comparison of normal and Alzheimer's disease neurons:** The magnified sections illustrate the structural differences between healthy neurons and neurons affected by AD. In diseased neurons, the presence of amyloid plaques, tau tangles, and disrupted synaptic connections are apparent.¹⁹

AQP4 polarization: Aquaporin-4 (AQP4), a water channel protein expressed on astrocytes, plays a vital role in facilitating glymphatic clearance. Disrupted AQP4 localization is linked to decreased glymphatic function and correlates with disease progression in AD patients.⁶

3.4. Parkinson's Disease (PD)

α -Synuclein Aggregation: In Parkinson's disease, reduced glymphatic clearance contributes to the accumulation of α -synuclein, a protein that forms toxic aggregates. These aggregates interfere with dopaminergic neurons, leading to motor dysfunction and neurodegeneration.

Parkinson's disease (PD) in Figure 4 a neurodegenerative disorder characterized by progressive motor and non-

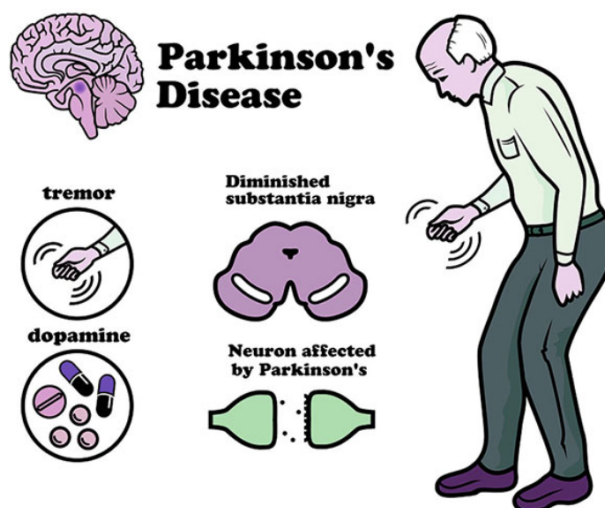


Figure 4: Parkinson's disease (Image Source: <https://medicaldialogues.in/neurology-neurosurgery/news/coffee-consumption-tied-to-lower-risk-of-developing-parkinsons-disease-study-70083>)

motor impairments. The visual representation highlights the diminished substantia nigra, reduced dopamine levels, and affected neuronal synapses, which are hallmark pathological features of PD.

In the context of the lymphatic system's role in brain clearance mechanisms, this figure underscores the significance of impaired waste clearance in neurodegenerative conditions such as Parkinson's disease. The glymphatic system, a specialized network for the clearance of interstitial waste and neurotoxins from the brain, plays a crucial role in maintaining neuronal homeostasis. Dysfunction in this system can exacerbate the accumulation of α -synuclein aggregates, which are implicated in PD pathogenesis.⁵

Furthermore, reduced dopamine levels and neuronal degeneration may be influenced by impaired lymphatic drainage, which affects the removal of metabolic byproducts and inflammatory mediators from the brain microenvironment. The involvement of the glymphatic system in clearing such pathological proteins suggests a potential therapeutic target for slowing the progression of PD.

This figure serves as a visual connection between the pathological features of Parkinson's disease and the emerging understanding of brain clearance mechanisms, emphasizing the role of lymphatic dysfunction in neurodegenerative disorders.¹⁸

Neuroinflammation: Impaired lymphatic drainage exacerbates neuroinflammatory responses, further damaging neuronal pathways and accelerating disease progression.¹⁶ Multiple Sclerosis (MS).

Immune Cell Trafficking: Dysfunctional meningeal lymphatic vessels can alter immune cell trafficking,

contributing to the infiltration of immune cells into CNS lesions. This mechanism plays a critical role in the development and exacerbation of multiple sclerosis.²⁰

Chronic Inflammation: Persistent lymphatic dysfunction perpetuates inflammation within the CNS, exacerbating demyelination and neuronal damage in MS patients.²²

Brain inflammation, or neuroinflammation, refers to the immune response of the central nervous system (CNS) involving activation of glial cells (microglia and astrocytes) and the release of pro-inflammatory cytokines, chemokines, and reactive oxygen species. It plays a dual role in the CNS—protecting against infections and injuries but also potentially leading to neurodegeneration if unresolved.

3.4.1. Traumatic brain injury (TBI)

Post-TBI Glymphatic Impairment: Traumatic brain injury can disrupt glymphatic function, impeding the clearance of metabolic waste and accelerating neurodegeneration. This impairment is associated with increased risk for developing chronic traumatic encephalopathy and other neurodegenerative conditions.¹⁷

4. Discussion

Recent advances in imaging techniques, including two-photon microscopy and magnetic resonance imaging (MRI), have significantly enhanced our understanding of the brain's lymphatic pathways. These methods have revealed the dynamics of glymphatic and meningeal lymphatic systems, providing insights into their role in health and disease. Despite these advancements, many questions remain about the exact mechanisms underlying lymphatic dysfunction in various pathologies. Targeting these systems for therapeutic intervention could potentially revolutionize treatment strategies for neurodegenerative diseases.

4.1. Challenges

4.1.1. Imaging limitations

Visualizing lymphatic flow in humans poses significant technical challenges. Current imaging techniques often lack the resolution or specificity to fully capture lymphatic dynamics, particularly in deeper brain structures. Developing more advanced imaging modalities is crucial for better understanding these pathways.²³

4.1.2. Therapeutic targeting

Enhancing glymphatic activity or restoring AQP4 polarization requires precise intervention. Overactivation of these systems may lead to adverse effects, such as increased ICP or unwanted immune responses, highlighting the need for targeted therapies.²⁴

4.2. Future directions

4.2.1. Molecular Modulation

Developing drugs to enhance glymphatic clearance holds promise for treating neurodegenerative disorders. Potential targets include molecules involved in AQP4 polarization and pathways regulating CSF dynamics.²⁴

4.2.2. Biomarkers

Identifying biomarkers of lymphatic dysfunction could enable early detection of neurodegenerative diseases. Biomarkers specific to glymphatic activity could also help monitor therapeutic efficacy.

4.2.3. Lifestyle interventions

Lifestyle factors such as sleep and exercise have been shown to modulate glymphatic function. Optimizing sleep quality and incorporating regular physical activity may serve as non-invasive strategies to enhance waste clearance and mitigate neurodegeneration.

5. Conclusion

The discovery of brain lymphatic pathways has transformed our understanding of neurophysiology and the pathogenesis of neurodegenerative disorders. Dysfunction in glymphatic and meningeal lymphatic systems plays a critical role in disease progression. Therapeutic strategies aimed at restoring or enhancing these pathways offer promising avenues for mitigating the effects of neurodegeneration. Continued research is essential to translate these findings into clinical applications, potentially offering new hope for patients suffering from these debilitating conditions.

6. Source of Funding

None.

7. Conflict of Interest

None.

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Cite this article: Chouhan AS, Kumar S, Rathore M, Kumar H, Saxsena M. The role of the lymphatic system in brain clearance mechanisms implications for neurodegenerative disorders. *Indian J Clin Anat Physiol* 2024;11(4):205-210.