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Glymphatic Impairment in Neurodegeneration: A Narrative Review of Pathogenesis and Biomarker Trajectories

Aakanksha Aakanksha[1], Mariam Vashakidze[1] , Mariam Dvaladze[1], Lizi Lomtatidze[1], Sipranjali Subudhi[2], Guga Khutsishvili[1]

[1]Tbilisi State Medical University, Tbilisi, Georgia; [2]David Tvildiani Medical University

**corresponding author:* Aakanksha Aakanksha, Faculty of Medicine, Tbilisi State Medical University, 33 Vazha Pshvela avenue, Tbilisi, Georgia, Mobile: +995592139065, Email: *aakankshasaharan1@gmail.com*

**ORCID:* Aakanksha Aakanksha: 0009-0005-8568-8928; Mariam Vashakidze: 0009-0003-2997-4482; Mariam Dvaladze: 0009-0008-5028-4394; Lizi Lomtatidze: 0009-0005-8927-997X; Sipranjali Subudhi: 0009-0009-9311-1407; Guga Khutsishvili: 0009-0005-6885-5448.

Abstract

The glymphatic system has emerged as an important pathway for maintaining central nervous system (CNS) homeostasis by facilitating the clearance of interstitial solutes, including neurotoxic proteins such as amyloid-β, tau, and α-synuclein. It functions through perivascular channels supported by astrocytic aquaporin-4 (AQP4) water channels. This system enables cerebrospinal fluid (CSF) influx and interstitial fluid (ISF) efflux across the brain parenchyma. Increasing evidence indicates that dysfunction of the glymphatic system plays a critical role in the early pathogenesis and progression of several neurodegenerative diseases. This narrative review synthesizes recent human-based studies published between 2020 and 2025, focusing on glymphatic dysfunction in Alzheimer's disease, Parkinson's disease, Huntington's disease, multiple sclerosis, and behavioral variant frontotemporal dementia. Findings suggest that impaired clearance of neurotoxic proteins due to AQP4 depolarization, loss of perivascular localization, and disruption of CSF-ISF (Cerebrospinal Fluid- Interstitial Fluid) dynamics contributes to protein aggregation, neuroinflammation, and cognitive decline. The review also highlights how changes in sleep architecture, cardiovascular health, and environmental exposures may influence glymphatic activity. Furthermore, it explores the growing significance of imaging techniques such as diffusion tensor imaging along perivascular spaces (DTI-ALPS) and the measurement of CSF biomarkers like AQP4 and neurofilament light, which may serve as early indicators of glymphatic dysfunction and disease progression. Particular attention is given to the interplay between choroid plexus enlargement, inflammation, and glymphatic disruption in multiple

sclerosis, as well as compensatory glymphatic responses observed in early neurodegeneration. These insights suggest that assessing glymphatic function could enhance diagnostic accuracy, allow for earlier intervention, and inform the development of targeted therapies. While the field is still evolving, and limitations exist in current imaging and biomarker specificity, the glymphatic system holds promise not only as a window into the underlying mechanisms of neurodegeneration but also as a potential therapeutic target. This review aims to bridge the gap between emerging mechanistic understanding and clinical translation, providing a framework for future research into glymphatic-based diagnostics and interventions.

Keywords: Glymphatic System, Neurodegenerative Disorders, Disruption, Potential Biomarker, Cerebrospinal Fluid (CSF) Clearance.

Introduction

Traditionally, the brain was considered the only organ in the human body without any lymphatic system. However, recent scientific research has unveiled a vital and intricate network within the CNS parenchyma. This system, now termed the glia-lymphatic or glymphatic system, fundamentally redefines our understanding of brain waste removal. The glymphatic system consists of tiny extravascular channels located between the blood vessels of the brain and the surrounding perivascular astrocytes, through which the brain's interstitial fluid is connected to the body's lymphatic system.

The glymphatic system is a "drainage system" responsible for removing metabolic waste products from the brain, such as extracellular electrolytes and peptides like amyloid-beta and alpha-synuclein, which are known to accumulate in neurodegenerative diseases (1). This system relies on the dynamic movement of cerebrospinal fluid (CSF) and interstitial fluid (ISF). CSF enters the brain tissue through periarterial channels around the arteries and mixes with the ISF through aquaporin-4 (AQP4) water channels on astrocytes to collect metabolic waste. The waste-laden fluid then exits the brain through perivenous spaces and enters the lymphatic system.

Its function is regulated by complex driving forces: arterial pulsation is the main mechanism, creating the flow of CSF in the periarterial spaces and promoting its advancement through pressure gradients. Respiration, via changes in intrathoracic pressure and mechanical stimulation of veins, also contributes to CSF-ISF exchange. Body position, particularly the supine position, enhances CSF inflow. Cerebral autoregulation, the brain's ability to maintain blood flow despite fluctuations in pressure or CO_2, plays a fundamental role in modulating glymphatic flow. The system reaches peak efficiency during deep sleep (slow-wave activity, SWA), when interstitial space expands, facilitating increased waste clearance (1).

Damage to the glymphatic system, manifested as decreased fluid flow efficiency, may occur due to mechanisms such as dysfunction or depolarized localization of AQP4 channels, reduced arterial pulsation, sleep deprivation, occlusion or abnormal enlargement of perivascular spaces (PVS),

decreased CSF production, chronic meningeal lymphatic vessel damage, and traumatic brain injury (TBI). These impairments lead to the accumulation of neurotoxic substances such as amyloid-beta (Aβ) and tau protein, contributing to neurodegeneration and progressive cognitive decline. Additionally, glymphatic dysfunction can exacerbate cerebral edema, worsen hydrocephalus, and intensify neuroinflammation by reducing cytokine clearance, while also impairing the removal of brain injury biomarkers such as GFAP, S100B, and NSE (2).

The aforementioned mechanisms of reduced fluid flow efficiency are observed in various neurological disorders: in hemorrhagic stroke, blood components block perivascular spaces and reduce glymphatic perfusion; in Alzheimer's disease, mislocalization of AQP4 leads to Aβ and tau accumulation; in Parkinson's disease, impaired glymphatic drainage contributes to α-synuclein buildup; in cerebral edema, excessive fluid accumulates; and in hydrocephalus, CSF circulation and absorption are disrupted (2).

Research indicates that glymphatic function may serve as a promising biomarker for brain diseases such as subjective cognitive decline (SCD) and Alzheimer's disease (AD). One approach is the ALPS index (Analysis along the Perivascular Space) derived from diffusion tensor imaging (DTI-MRI). A low ALPS index directly reflects impaired glymphatic clearance, correlating with poor elimination of Aβ and increased risk of cognitive deterioration in early disease stages (3). Zhang et al. (2025) demonstrated that assessing glymphatic system function may predict and monitor post-stroke cognitive impairment (PSCI) (4). Fan et al. (2024) also applied the ALPS index in Parkinson's disease (PD), finding a correlation between impaired clearance and accelerated disease progression (5). Another study showed the glymphatic system could be used to diagnose or monitor idiopathic normal pressure hydrocephalus (iNPH), and to evaluate treatment response via restored glymphatic flow (6). In mild-to-moderate chronic TBI, the ALPS index may identify glymphatic dysfunction as a prognostic marker for cognitive decline or recovery (7).

Methodology

Study Design:

This is a narrative review based on recent human studies investigating the role of glymphatic dysfunction in the early pathogenesis and biomarker development of neurodegenerative diseases. The review explores the emerging role of the glymphatic system in these conditions, including mechanical insights, diagnostic approaches, and potential biomarkers.

Data Sources and Search Strategy:

The literature search was conducted primarily through databases such as **PubMed** and **Google Scholar**. The review focused on articles published between **2020 and 2025**, emphasizing recent publications with strong, evidence-based findings.

Search terms included **MeSH terms** and **keywords** such as:

- Glymphatic system
- Neurodegenerative diseases
- MRI and glymphatic imaging
- Biomarkers related to neurodegenerative diseases
- Parkinson's disease, Alzheimer's disease, and multiple sclerosis
- Beta-amyloid plaques
- CSF clearance

Boolean operators AND, OR, and NOT were used to refine the search.

- **AND** was used to narrow results, combining terms related to both the glymphatic system and neurodegenerative diseases.
- **OR** was used to broaden the search, including multiple diseases (e.g., *Parkinson's disease OR Alzheimer's disease OR multiple sclerosis*).
- **NOT** helped exclude irrelevant articles.

Additionally, **reference lists** of included articles were screened for relevance according to the inclusion and exclusion criteria.

Inclusion Criteria:

- Peer-reviewed articles
- Human-based studies focusing on neurodegenerative diseases linked to glymphatic dysfunction
- Articles addressing biomarkers or imaging techniques
- Publications in English
- Studies published between 2020 and 2025

Exclusion Criteria:

- Animal studies
- Studies unrelated to either the glymphatic system or neurodegenerative diseases
- Articles in languages other than English
- Studies lacking robust mechanisms or sufficient data

Study Selection:

All articles were screened for relevance to the research topic. Only studies meeting the inclusion criteria and providing scientifically supported results were selected for final review.

Data Extraction:

A structured approach was used to extract information from the selected studies. For each article, the following data points were collected: title, year of publication, study design, the relationship between the glymphatic system and specific neurodegenerative diseases, and associated biomarkers. This process enabled effective organization and analysis of the findings.

Data Synthesis:

A **thematic analysis** was performed to categorize and synthesize results under four main domains:

1. Structural and functional overview of the glymphatic system
2. Evidence indicating glymphatic dysfunction in neurodegenerative diseases
3. Biomarkers of glymphatic activity
4. Diagnostic and imaging techniques used to study glymphatic processes and associated diseases

Discussion

The glymphatic system functions as a drainage pathway within the CNS, similar to the peripheral lymphatic system. It operates via a brain-wide perivascular route, facilitating cerebrospinal fluid (CSF) influx into the brain parenchyma and interstitial fluid (ISF) efflux along with soluble neurotoxins such as amyloid-β (Aβ) and α-synuclein. Aquaporin-4 (AQP4), a water channel predominantly expressed on astrocytic endfeet, is a crucial component of this clearance system, regulating the exchange between CSF and ISF. Recent research has underscored the glymphatic system's vital role in clearing metabolic waste and maintaining CNS homeostasis. These insights have prompted investigations into its dysfunction as a contributing mechanism in proteinopathies such as Alzheimer's and Parkinson's disease (8).

Aβ, primarily found in the ISF, is predominantly cleared via the glymphatic system rather than through the blood-brain barrier. Impaired AQP4 function significantly hampers Aβ clearance, potentially contributing to its accumulation and the pathogenesis of neurodegenerative disorders like Alzheimer's disease. In AD, Aβ aggregates form senile plaques, and hyperphosphorylated tau protein detaches from microtubules to form insoluble neurofibrillary tangles. Concurrently, AQP4 channels become depolarized, further impeding clearance efficiency.

Evidence suggests that AQP4 levels in the CSF are significantly elevated in patients with neurodegenerative diseases compared to healthy individuals and correlate with tau protein markers. This supports the hypothesis that AQP4 may serve as a biomarker not only for dementia but also for

glymphatic system functionality. Quantifying AQP4 in body fluids could provide novel insights into disease pathogenesis and open avenues for diagnostic and therapeutic advancements (9).

Postmortem human studies have demonstrated increased AQP4 expression and mislocalization in elderly individuals, particularly those with Alzheimer's disease. Mislocalization from the astrocytic endfeet appears to exacerbate Aβ accumulation. Interestingly, cognitively intact individuals aged over 85 exhibit well-polarized AQP4, suggesting that preserved perivascular localization of AQP4 may serve as an indicator of healthy aging. These findings imply that AQP4 mislocalization, rather than its absolute expression level, plays a more critical role in glymphatic dysfunction and subsequent disease progression (10).

Emerging studies also link glymphatic dysfunction with other neurodegenerative disorders beyond AD and Parkinson's. In Huntington's disease (HD), caused by the mutant Huntingtin protein (mHTT) from expanded CAG repeats in the HTT gene, mHTT is released into the CSF both passively from cell death and actively via the endosomal-lysosomal pathway. In the early stages of neurodegeneration, the glymphatic system may act as a compensatory mechanism. However, when impaired, the accumulation of toxic proteins and cellular debris exacerbates disease progression. Elevated CSF mHTT levels may thus reflect glymphatic dysfunction, offering potential as a diagnostic marker and therapeutic guide in HD (11).

Similarly, studies in multiple sclerosis (MS) reveal glymphatic impairment as a secondary pathogenic mechanism alongside chronic inflammation. Impaired clearance contributes to gray matter atrophy, structural damage, and enlarged lesions, particularly near lateral ventricles and deep gray matter nuclei. Demyelination and astrocytic dysfunction further compromise AQP4-mediated clearance, intensifying neurotoxic buildup (12).

Arterial pulsations are the primary drivers of glymphatic flow. Cardiovascular deficiencies that reduce pulsatility, as well as environmental exposures such as airborne ultrafine particulate matter (PM), negatively affect this system. PM exposure triggers neuroinflammation, impairs cardiovascular and respiratory function, and disrupts sleep, collectively leading to Aβ plaque formation and glymphatic dysfunction. These findings underscore the importance of environmental and lifestyle factors in preserving glymphatic integrity and potentially delaying neurodegeneration (13).

Notably, a recent study on behavioral variant frontotemporal dementia (bvFTD) highlighted the significance of perivascular space (PVS) abnormalities as an imaging biomarker of glymphatic impairment. Serial MRI scans over 12 months showed that although PVS volume did not change markedly, PVS burden correlated with elevated CSF biomarkers like total tau and neurofilament light, even in non-progressive cases. These findings suggest that PVS alterations may reflect impaired glymphatic clearance and could serve as a non-invasive biomarker for neurodegenerative diseases such as bvFTD (14).

Taken together, these studies emphasize the critical role of AQP4 in glymphatic function, proposing it as a potential therapeutic target. However, drug delivery across the blood-brain barrier remains a major

challenge in early AD. Preclinical studies have identified agents such as 5-Caffeoylquinic Acid that can restore AQP4 localization and enhance clearance of neurotoxins, thereby improving cognitive outcomes (15).

Beyond its clearance role, AQP4 is also a modulator of neuroinflammation, a key process in early neurodegeneration. Astrocytes, the primary expressers of AQP4, mediate both impaired waste clearance and the amplification of CNS inflammatory responses (16).

Advanced imaging techniques, such as diffusion tensor imaging along perivascular spaces (DTI-ALPS), when combined with CSF AQP4 quantification, have revealed early alterations in glymphatic activity and corresponding brain atrophy. In patients with neurodegenerative dementia, increased AQP4 expression was linked to elevated white matter free water content. Nonetheless, further research is needed, as MRI results can be confounded by underlying brain damage (17).

A recent study employing contrast-enhanced serial MRI and DTI-ALPS in patients with mild cognitive impairment demonstrated that faster clearance correlated with shorter sleep latency, altered Aβ1–42/Aβ1–40 ratios, and elevated tau levels. This suggests a compensatory upregulation of local glymphatic activity in early neurodegeneration. However, while this might aid short-term clearance, it fails to prevent cognitive decline and may even promote tau propagation within the CNS, worsening disease severity.

The following key findings illustrate its role in the context of individual neurodegenerative disorders.

Alzheimer's Disease

Alzheimer's disease (AD) is the most common neurodegenerative disorder, characterized by extracellular Aβ plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein. Tau is primarily degraded intracellularly via the proteasome or lysosomal pathways, but can also be released extracellularly. The glymphatic system contributes to its clearance.

Substantial evidence supports that Aβ and tau accumulation drive AD progression and cognitive decline. Changes in glymphatic efficiency may occur even in preclinical stages before Aβ deposition is detectable by PET imaging. At later stages, the ALPS index (a proxy for glymphatic function) shows a secondary decrease after an initial plateau. Although the association between glymphatic dysfunction and AD biomarker accumulation is well documented, a clear causal relationship has yet to be established.

If decreased ALPS index precedes clinical AD onset, it may hold promise as a predictive biomarker for early intervention, though further research is required to validate its prognostic utility (18).

A similarly ambiguous link exists between AQP4 and Aβ accumulation. AQP4 depolarization is associated with increased Aβ burden, yet it is unclear whether Aβ accumulation causes AQP4 dysfunction or vice versa. AQP4 is anchored to astrocytic endfeet via the dystrophin-associated complex (DAC), which includes dystroglycan (DAG1) and alpha-syntrophin (SNTA1). Elevated levels

of these proteins have been associated with increased tau in the temporal cortex. Another gene, MCL1, encoding a membrane transporter involved with DAC, is also correlated with higher tau levels. This suggests that astrocytic endfoot components, rather than AQP4 alone, may drive AQP4 mislocalization and subsequent dysfunction (19).

Parkinson's Disease

Recent studies in Parkinson's disease (PD) have examined how glymphatic dysfunction correlates with regional cortical atrophy and cognitive impairment. Since cognitive decline is a prominent non-motor symptom of PD, understanding this link is critical.

A positive correlation was found between DTI-ALPS indices (glymphatic function) and MMSE scores (cognitive performance) in PD patients. As individuals with other neurological or psychiatric conditions were excluded, PD was the sole contributing factor in this association.

Additionally, DTI-ALPS indices were positively associated with volumes of specific cortical regions, including the temporal pole, posterior orbital gyrus, and anterior cingulate gyrus. These findings illustrate the interplay between glymphatic dysfunction, α-synuclein aggregation, cortical atrophy, and cognitive decline in PD (20).

A key pathological feature of PD is the formation of Lewy bodies composed of aggregated α-synuclein, which inversely correlates with AQP4 expression. Since AQP4 mediates glymphatic clearance through perivascular routes, reduced AQP4 impairs clearance and exacerbates protein aggregation (8).

Sleep quality is another crucial factor. PD primarily affects individuals over 50, and with aging, the proportion of slow-wave NREM Stage 3 sleep, essential for glymphatic clearance, declines. After age 60, Stage 3 NREM may be absent entirely, sleep is fragmented, and total duration is reduced (21). Since glymphatic flow is strongest during slow-wave sleep, these changes impair waste clearance and facilitate PD pathogenesis (22)

Multiple Sclerosis

Multiple sclerosis (MS) is a neuroinflammatory demyelinating disease in which glymphatic dysfunction also plays a role. A major pathological feature in MS is choroid plexus (CP) enlargement. As the CP regulates CSF production, volumetric changes may impair glymphatic flow.

In relapsing-remitting MS (RRMS) patients with cognitive impairment, increased CP volume and reduced DTI-ALPS index were observed, mirroring findings in PD. Notably, cognitively intact RRMS patients had DTI-ALPS values similar to healthy controls, suggesting that glymphatic impairment becomes more prominent with advancing disease and cognitive decline (23).

Additional studies have identified BBB disruption and enlarged Virchow-Robin spaces in MS patients unrelated to age or brain atrophy, indicating inflammation-driven glymphatic impairment. Elevated

IL-6 in the basal ganglia also correlates with enlarged perivascular spaces, reinforcing the link between inflammation and impaired waste clearance (24).

Unlike PD or AD, inflammation is central in MS pathogenesis. Glymphatic dysfunction, CP enlargement, and inflammation are interconnected. CP abnormalities are specific to MS and contribute to altered CSF dynamics, leading to white matter lesions and tissue loss. The CP also acts as an immunomodulator and forms part of the blood-CSF barrier. In MS, increased CP vascular permeability and adhesion molecule expression drive chronic inflammation and worsen glymphatic flow.

Demyelination, another hallmark of MS, is closely tied to CP enlargement, glymphatic dysfunction, and progressive brain volume loss.

However, DTI-ALPS, though widely used, may not be a definitive measure of glymphatic flow. The index lacks specificity, and its reliability as a standalone proxy for glymphatic activity remains under question (25).

Conclusion

This review underscores the critical role of the glymphatic system in clearing metabolic waste products from the central nervous system, including extracellular electrolytes and neurotoxic peptides such as amyloid-β and α-synuclein (1). Disruption of this clearance pathway contributes to the pathogenesis of several neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, Huntington's disease, multiple sclerosis, and behavioral variant frontotemporal dementia.

Research has demonstrated that glymphatic dysfunction is closely associated with specific biomarkers. In particular, the **DTI-ALPS index** and **AQP4 expression** provide valuable insights into the functionality of the glymphatic system. Monitoring these markers is especially important for the **early detection** of neurodegenerative diseases, guiding **therapeutic strategies**, and **evaluating treatment efficacy** over time (6).

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