THE GLYMPHATIC SYSTEM AND ITS POTENTIAL IMPLICATIONS FOR NEURODEGENERATIVE DISORDERS: A NARRATIVE REVIEW

Mariam Gigiadze[1],
Keti Kebadze[1],
Mariam Beriashvili[1],
Elene Vardosanidze[3],
Liza Mariamidze[1],
Giorgi Mariamidze[1]
[1]Tbilisi State Medical University, Faculty of Medicine, Tbilisi Georgia;
[2]Caucasus International University, Faculty of Medicine, Tbilisi Georgia;
[3]Tbilisi State Medical University, Faculty of Public Health, Tbilisi Georgia;

Supervisors:
Giorgi Lomidze[1],
Erekle Gigiadze[2],
Mariam Surguladze[3]
[1] MD. PhD. European University; Curatio Clinic; Tbilisi Georgia;
[2] MD. PhD. K. Eristavi National Center of Experimental and Clinical Surgery; Tbilisi Georgia;
[3] MD. Raymann Clinic; Tbilisi Georgia.

Abstract

The Glymphatic system, proposed by Jeffrey Iliff and Maiken Nedergaard in 2012, refers to a macroscopic waste clearance system in the brain that resembles the peripheral lymphatic system. Numerous studies indicate that the Glymphatic system significantly influences the distribution of various substances in the brain, including its primary waste clearance function and the transport of nutrients like glucose, treatment substances and glial calcium signaling. Three components that make up the Glymphatic system: a trans-parenchymal component that depends on astroglial water transport, a paravenous ISF clearance pathway, and a para-arterial CSF influx pathway. The Glymphatic system has many unexplored aspects, particularly regarding its driving forces and its connection to sleep and neurodegenerative disorders. The interaction between the Glymphatic system and inflammation appears to be cyclical and potentially synergistic. The researches indicate that inflammation aggravates Glymphatic system dysfunction. The impaired Glymphatic system exacerbates the neurodegenerative disorders progression and neurodegenerative disorders progression promotes inflammation. Both inflammation and Glymphatic system dysfunction are the common pathological features

in AD, PD, and other neurodegenerative disorders. The present researches about Glymphatic function could lead to new treatments that will likely be most effective when used early in disease onset. Way to assess Glymphatic flow with magnetic resonance imaging is currently under development as clinical diagnostic tool.

Keywords: Glymphatic system; Neurodegenerative disorders; Inflammation; MRI imaging;

Introduction

The Glymphatic system, proposed by Jeffrey Iliff and Maiken Nedergaard in 2012, refers to a macroscopic waste clearance system in the brain that resembles the peripheral lymphatic system (Hablitz LM et al.2021). Numerous studies indicate that the Glymphatic system significantly influences the distribution of various substances in the brain, including its primary waste clearance function and the transport of nutrients like glucose, treatment substances (e.g., recombinant adeno-associated viral vectors), and glial calcium signaling (Hablitz LM et al.2021). Three components that make up the Glymphatic system: a trans-parenchymal component that depends on astroglial water transport, a paravenous interstitial fluid (ISF-Brain interstitial fluid) clearance pathway, and a para-arterial CSF influx pathway (Suescun et al. 2019). The perivascular space (PVS) between these astrocytic processes and the vascular wall is filled with CSF, serving as the main operational site for the Glymphatic system. The water channel aquaporin-4 (AQP4) is found on about 50% of the surface area of astrocyte processes adjacent to blood vessels. CSF entering the stroma through AQP4 pushes ISF to the perivenous space, allowing solutes to flow out of the brain into the cervical lymphatic system. Thus, astrocytes, supported by the PVS and the AQP4-dependent transport system, form the core of the Glymphatic system (Suescun et al.2019). AQP4, sleep, and arterial pulsation are the primary factors that influence the Glymphatic system. Due to its critical physiological role, the Glymphatic system is implicated in the onset and progression of various diseases, including neurodegenerative disorders like Alzheimer's and Parkinson's disease, as well as mood disorders. It is generally believed that intracranial arterial pulsation is a key driving force behind the Glymphatic system's function. Experiments have shown that the efficiency of cerebrospinal fluid (CSF) flow into the brain correlates positively with arterial pulsation. For instance, a 10-beat reduction in heart rate leads to a 20% increase in β-amyloid (Aβ) levels in the brain, while a 30-beat increase results in a 30% decrease in Aβ levels. [5]

Methodology

The Glymphatic system has many unexplored aspects, particularly regarding its driving forces and its connection to sleep and neurodegenerative disorders. Further investigation into its

relationship with various diseases is essential. This review focuses on recent researches into the Glymphatic system's role in common central nervous system disorders. The article discusses possible structural and functional abnormalities within the Glymphatic system that may arise before or during disease progression, as well as the underlying mechanisms involved. Additionally, the review highlights the relationship between neurodegenerative disorders and the Glymphatic system under pathological conditions and summarize the imaging techniques currently available for studying this system. [3]

Discussion

All biological processes, including locomotion, digestion, and cognition, necessitate energy, which in turn produces metabolic waste. The accumulation of these metabolic by-products can be detrimental if not adequately eliminated. The Glymphatic system is responsible for the clearance of metabolic waste throughout the body. In the brain, which is particularly energy-intensive, the blood-brain barrier poses a significant limitation on the influx of plasma ultrafiltrate that facilitates waste clearance in peripheral tissues. Unlike the peripheral lymphatic system, the Glymphatic system is uniquely structured to optimize fluid transport.

Astrocytes play a pivotal role in modulating both perivascular and interstitial fluid dynamics. Their endfeet undergo size alterations in response to changes in arterial diameter, and protein complexes, such as the dystrophin-associated complex, anchor aquaporin-4 (AQP4) water channels at the membrane. The localization of AQP4 at astrocytic endfeet is crucial for establishing Glymphatic flow, beginning in the circle of Willis during early development and continuing into postnatal maturation. Disruption of AQP4 polarization in adult astrocytes leads to diminished Glymphatic flow. [8] [12] (Fig.1)

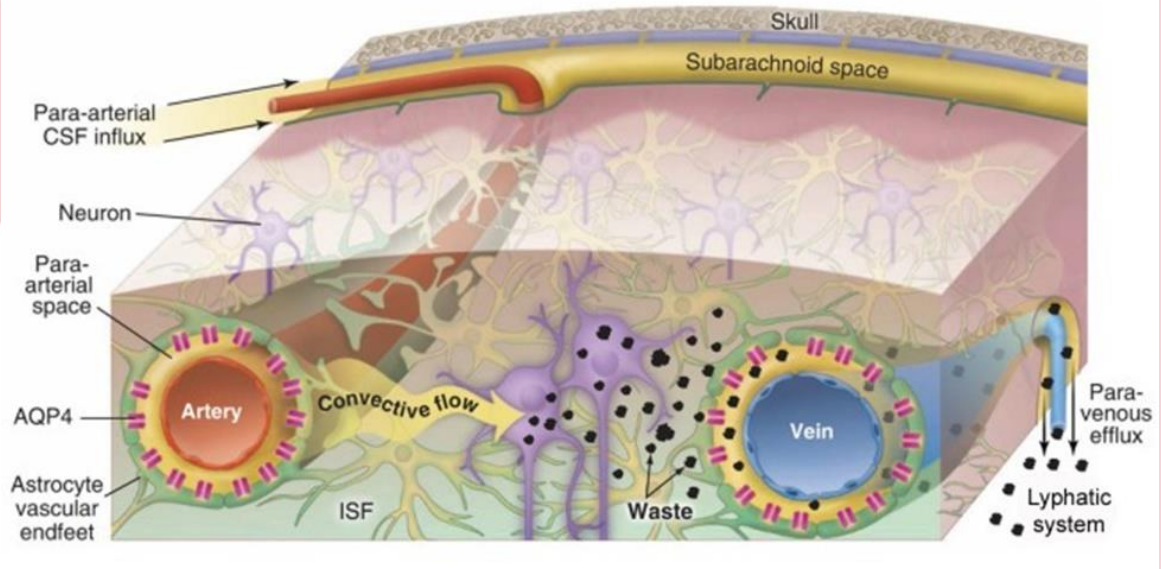

Fig.1

Glymphatic system inflow, CSF-ISF exchange, and efflux: CSF enters the brain via para-arterial routes and then exchanges with ISF. Interstitial metabolic waste and mixed CSF and ISF are transported to the lymphatic system via paravenous channels. In both veins and arteries, AQP4 water channels are crucial for lowering the resistance to CSF flow between the interstitium and paravascular regions. Reproduced from Cerebrospinal fluid (CSF); interstitial fluid (ISF); astrocytic aquaporin-4 (AQP4).
Jiang Q. MRI and glymphatic system. Stroke Vasc Neurol. 2019 Apr 5;4(2):75-77. doi: 10.1136/svn-2018-000197. PMID: 31338214; PMCID: PMC6613867.

Glymphatic system and sleep:

While the Glymphatic system is most active during sleep, various factors, such as blood pressure and cerebral blood flow, are low during this time, presenting a contradiction. However, a study on non-human primates found that solute clearance in the brain is significantly impaired with CSF leakage, suggesting a connection between CSF circulation and the Glymphatic system. This indicates that the relationship between arterial pulsation and the Glymphatic system is not fully understood yet.

The brain exhibits distinct electrical activity patterns during sleep, encompassing both rapid eye movement (REM) and non-REM (NREM) sleep. Notably, the activation of Glymphatic fluid transport during sleep may elucidate its neurobiological purpose. Enhanced Glymphatic function correlates with NREM sleep, while chaotic brain activity in REM sleep and wakefulness appears to inhibit this system, potentially to maintain synaptic integrity.

Some studies indicate that the Glymphatic system is inhibited during wakefulness but is enhanced during sleep. Sleep may influence the Glymphatic system by altering the volume of the brain stroma. Research has shown that the interstitial volume fraction in the brains of asleep and anesthetized mice is greater than in awake mice, which decreases the resistance to cerebrospinal fluid (CSF) flow into the brain stroma, facilitating Glymphatic function. Additionally, norepinephrine, a key neurotransmitter associated with wakefulness, plays a role in this process. A sudden surge in norepinephrine levels during awakening can increase cell volume in the brain parenchyma, potentially hindering CSF inflow by reducing interstitial volume. While there is ongoing debate about whether the choroid plexus is the primary source of CSF production, several studies have demonstrated that norepinephrine directly affects choroid plexus epithelial cells, inhibiting CSF production. This mechanism may contribute to the observed inhibition of the Glymphatic system during sleep. [2] [3]

Glymphatic system and its relations with disorders:

The Glymphatic system has been implicated in a range of neurological disorders, including stroke, traumatic brain injury, and neurodegenerative diseases such as Alzheimer's disease. The phenomenon of "Glymphedema," or fluid accumulation within the Glymphatic system following stroke, exemplifies its relevance to brain health. Historical hypotheses regarding the mixing of CSF and ISF in the perivascular space date back to the 19th century, but recent advances in in vivo microscopy and our understanding of astrocytic function have propelled the Glymphatic system into the forefront of contemporary neuroscience. Studying this system is crucial, given its significant implications for neurological health and disease. [9]

Alzheimer's disease (AD) - The development of senile plaques by amyloid β protein (Aβ), neurofibrillary tangles brought on by aberrant tau protein accumulation, and AQP4 depolarization are all connected to the pathophysiology of AD. The accumulation of toxic Aβ is linked to Glymphatic system transport dysfunction, which is measured by the solute's input from CSF into the brain and its removal from the brain using radio-labeled tracers. Notably, Aβ40 entering and accumulating in the perivascular spaces is linked to AQP4 depolarization and impaired Glymphatic system transport. Thus, serious amyloid-β deposits preceded Glymphatic system dysfunction.

Parkinson's disease - The researches show that the Glymphatic inflow of CSF tracer in the mice's brain was decreased when meningeal lymphatic drainage was blocked by ligating the deep cervical lymph nodes of A53T mice (PD model). This led to more severe α-syn accumulation, neuroglia activation, inflammation, loss of dopaminergic neurons, and dyskinesia. Protein monomers increased but oligomers did not, indicating that AQP4 deletion prevented the brain from clearing α-syn. These show that the clearance of α-syn soluble monomers is partially attributed to AQP4 and meningeal lymphatic drainage, pointing to a possible avenue for PD symptom relief.

Stroke - Glymphatic system abnormalities and associated pathological damage are caused by subarachnoid hemorrhage. Notably, a novel approach to hemorrhagic stroke treatment may involve the targeted enhancement of cerebral Glymphatic clearance. Similar pathological alterations to subarachnoid hemorrhagic stroke can be seen in the ischemic stroke model, including perivascular space expansion and a shift in the distribution of AQP4 polarity from a normal perivascular pattern to a dispersed parenchymal pattern. Thus, preserving and promoting the lymphatic system's regular operation will help reduce stroke damage and enhance stroke-related cognitive impairment.

Brain edema- Early cytotoxic and later vasogenic phases are the two classic classifications for brain edema. Energy deprivation brought on by hypoxia in cytotoxic edema reduces ISF efflux

and encourages CSF influx in the Glymphatic system. Furthermore, there is a significant correlation between the degree of cerebral edema and the expression of the AQP4 protein.

Amyotrophic Lateral Sclerosis (ALS) - Insoluble proteins like tau protein and TDP-43 are found in the brain of almost 97% of ALS patients. Additionally, ALS is caused by upper motor neuron degeneration, which is indicated by an increase in tau protein in CSF. Thus, promoting the clearance of tau protein by Glymphatic system could be a useful treatment for ALS.

Traumatic Brain Injury (TBI) - Aβ and tau protein buildup from TBI is a risk factor for neurodegenerative illnesses (such as PD, AD, etc.). Similarly, damage to the brain parenchyma of mice results in the loss of AQP4's polarity distribution on the astrocyte endfeet. Consequently, the Glymphatic system's function declines by roughly 60% and persists for a minimum of one month. These suggest that tau protein aggregation and neurodegenerative assaults in the brain following trauma may be mostly caused by prolonged damage to the Glymphatic system following TBI. Thus, more research on the Glymphatic system may help identify strategies for reducing TBI and halting its progression into degenerative illnesses.

Diabetes-related cognitive impairment - Fluorescence imaging examination indicated that the Type-2 diabetic rats' MRI analysis revealed a three-fold slower clearance rate of the contrast agent Gd-DTPA in CSF from the interstitial space in the hippocampus compared to the non-DM animals (diabetes rat model). These findings suggest that type-2 diabetes can damage the function of the Glymphatic system by obstructing the passage of CSF and ISF. The perivascular space's increase could be the cause of the impairment. The perivascular area will continue to enlarge as a result of an inflammatory response brought on by the metabolic wastes that have collected there. This mechanism is yet unknown and needs profound research. [6] [9]

Glymphatic system imaging using MRI

MRI methods can be sensitized to motion by observing signal loss due to a loss of phase coherence in a voxel. With small length and strength gradient, measuring a phase difference, proportional to blood velocity, when encoding along a vessel, calculating the volume flow rate becomes possible (coherent motion in one direction, macroscopic). Recent approaches also use phase contrast MRI to measure CBF. When using DWI with at least 6 different diffusion gradient orientations over a sphere, one can assess the diffusion tensor of water averaged over a voxel, which is diffusion tensor imaging (DTI), and giving diffusion constants along the brain fibers and the fiber orientation. Key advantages are that it is completely non-invasive and has wide availabilities, including the corresponding data analysis software on clinical MR systems. It should also be noted that since water molecules can be present in various spaces in

the brain (CSF spaces, ISF, blood, intercellular space) the signal origins in diffusion-based Glymphatic studies are often nonspecific.

The DTI analysis along the perivascular space (DTI−ALPS) approach has also been suggested to assess the Glymphatic system. This approach hypothesizes to measure the water contributions of motion in the perivascular space as a change in the diffusion constant with a decreased diffusivity of water indicating dysfunction of the Glymphatic system. A fundamental assumption in this method is that the perivascular space is perpendicular to white matter fibers close to the lateral ventricle body. DTI-APLS have also been used to investigate the relationship between the Glymphatic system and iron deposition in the normal brain. It was found that the regional iron deposition is significantly correlated with the APLS index, also APLS index decreased significantly with age, suggesting that the Glymphatic system gets impaired with normal aging. The DTI-ALPS method can be performed on standard DTI data or already collected DTI data. But, APLS is characterised that contributions of the perivascular space in white matter should be small to negligible based on knowledge from histology.

Dynamic gadolinium (Gd)-based MRI methods are usually used to evaluate cerebral blood flow, but they can also be implemented to evaluate the circulation of the Glymphatic system. T2 *-weighted dynamic susceptibility contrast (DSC) MRI-based on the theory of intravascular tracers is more commonly used clinically. In this case the focus lies on quantifying CBF, CBV, and mean transit time (MTT). Two important statements should be noted when using Gd-based methods to investigate the Glymphatic system: First, depending on the pulse sequence and imaging parameters applied, hyperintensities or high post-Gd signal changes not always are the sine of higher Gd concentration. Second, substantial partial volume effects from the blood compartment should be taken in consideratiion when interpreting the Gd-induced signal changes in the brain.

Dynamic glucose-enhanced (DGE) MRI is a newly developed contrast-enhanced imaging technique that uses natural sugar (d-glucose) or sugar analogues with dynamic Chemical Exchange Saturation Transfer (CEST) imaging to conduct information about glucose delivery, tissue transport, and metabolism. The D-glucose is affordable and easily available. However, DGE imaging produces a small effect size especially at clinical magnetic field strengths and long scan durations (>10 min) are required because large amount of D-glucose solution needed. There are many glucose transporters in brain capillary endothelial cells, as a result in D-glucose can travel in the BBB and the blood-CSF barrier (BCSFB). This is an unique characteristic which is used to check the integrity of BBB and the CSF exchange process with parenchyma. There are also other MRI methods such as Phase Contrast MRI, Spatial modulation of magnetization (SPAMM), Time-spatial labeling inversion pulse (Time-SLIP), arterial spin labeling (ASL). [4] [11]

Dysfunction of the Glymphatic system and inflammation

Dysfunction of the Glymphatic system can lead to a significant accumulation of protein and waste products, which can trigger inflammation. The interaction between the Glymphatic system and inflammation appears to be cyclical and potentially synergistic. The researches indicate that inflammation aggravates Glymphatic system dysfunction. The impaired Glymphatic system exacerbates the neurodegenerative disorders progression and neurodegenerative disorders progression promotes inflammation. Both inflammation and Glymphatic system dysfunction are the common pathological features in AD, PD, and other neurodegenerative disorders. Despite many milestone achievements in understanding the Glymphatic system and inflammation in neurodegenerative disorders, there is a limited number of studies specifically focusing on the effect of inflammation on the Glymphatic system. For instance, in the rat brain, chronic neuroinflammation significantly impaired waste clearance and resulted in significantly elevated levels of amyloid β within the hippocampus. The density of AQP-4 was also reduced in multiple brain regions. There is limited literature exploring and discussing the direct effect of inflammation on Glymphatic system function. In fact, according to previous studies, inflammation can affect almost all functional compartments of the Glymphatic system : the CSF flow in PVSs, astrocyte and AQP-4, the blood-brain barrier (BBB), and the meningeal lymphatic vessels (mLVs). [8] [10]

Glymphatic system and Blood–brain barrier (BBB)

Studies have also shown that the BBB is anatomically and functionally interconnected with the Glymphatic system. The BBB transport and Glymphatic clearance have the same purpose in clear interstitial solutes such as Aβ from the brain and, in that sense, likely serve complementary roles and seemingly are partially overlapping mechanisms. BBB transport of Aβ is further facilitated by convective flow by the Glymphatic system moving Aβ toward the transporters. A study in mice has demonstrated that decreasing the number of endothelial transporters leads to a 55% decrease in Aβ clearance. BBB disruption can lead to Glymphatic dysfunction and aggravate brain diseases. It has become apparent that inflammation is a key element in the progression of BBB damage, resulting in brain injury. Accumulating evidence has indicated that the BBB has been shown to break down in inflammatory conditions and neuroinflammation-mediated brain diseases. [1] [7]

Conclusions

The Glymphatic system plays important role in the clearance of metabolic waste throughout the body. Due to its critical physiological role, the Glymphatic system is implicated in the onset and progression of various diseases. The new researches and discoveries may result in

novel therapies, which are probably going to work best when applied early in the course of the illness. As clinical diagnostic tools, methods for evaluating Glymphatic flow using magnetic resonance imaging or positron emission tomography are presently being developed.

References

1.Bradley G. Klein- "Cerebrospinal Fluid and the Blood-Brain Barrier" in Cunningham's Textbook of Veterinary Physiology (Sixth Edition), 2020

2.B.R. Peters,S.J. Sha , K. Yaffe – "Sleep and Cognitive Impairment" doi.org/10.1016/B978-0-12-804074-4.00004-2 , (2017)

3.Dianjun Zhang, Xinyu Li, Baoman Li – "Glymphatic System Dysfunction in Central Nervous System Diseases and Mood Disorders" PMID: 35547631 PMCID: PMC9082304 DOI: 10.3389/fnagi.2022.873697

4.Eide, P. K., Vatnehol, S. A. S., Emblem, K. E., and Ringstad, G. (2018). "Magnetic resonance imaging provides evidence of glymphatic drainage from human brain to cervical lymph nodes". Sci. Rep. 8:7194. doi: 10.1038/s41598-018-25666-4

5.Hablitz LM, Nedergaard M. "The Glymphatic System: A Novel Component of Fundamental Neurobiology". J Neurosci. 2021 Sep 15;41(37):7698-7711. doi: 10.1523/JNEUROSCI.0619-21.2021. PMID: 34526407; PMCID: PMC8603752.

6.Jérôme Badaut , Jean-François Ghersi-Egea- "The Choroid Plexus and Cerebrospinal Fluid System: Roles in Neurodegenerative Diseases" January 2016 DOI:10.1016/B978-0-12-801740-1.00008-1

7.J.J. Iliff , A.S. Thrane ,M. Nedergaard – "The Glymphatic System and Brain Interstitial Fluid Homeostasis" doi.org/10.1016/B978-0-12-803058-5.00003-5

8.Lauren M. Hablitz , Maiken Nedergaard – „The glymphatic system" PMID: 34526407 PMCID: PMC8603752 DOI: 10.1523/JNEUROSCI.0619-21.2021

9.M.K. Rasmussen, H. Mestre, M. Nedergaard-„The glymphatic pathway in neurological disorders" Lancet Neurol., 17 (2018), pp. 1016-1024

10.M. Nedergaard, S.A. Goldman –"Glymphatic failure as a final common pathway to dementia Science", 370 (2020), pp. 50-56

11.Prasuhn J, Xu J, Hua J, van Zijl P, Knutsson L. Exploring neurodegenerative disorders using advanced magnetic resonance imaging of the glymphatic system. Front Psychiatry. 2024 Apr 8;15:1368489. doi: 10.3389/fpsyt.2024.1368489. PMID: 38651012; PMCID: PMC11033437.

12.Zhao Ding, Xiaodi Fan, Yehao Zhang, Mingjiang Yao, Guangrui Wang, Yilei Dong, Jianxun Liu.Wenting Song-" The glymphatic system: a new perspective on brain diseases" .