Journal of MTU 2025;4(1):16-22
Doi: 10.58651/jomtu.1675339

MALATYA TURGUT OZAL UNIVERSITY

Journal of Medical Topics & Updates

Review Article / Derleme Makalesi

Clinical reflections of the glymphatic system and neurodegenerative diseases

Glimfatik sistemin ve nörodejeneratif hastalıkların klinik yansımaları

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ARTICLE INFO

Article History:
Received: 14.04.2025
Accepted: 25.04.2025
Publication: 30.04.2025

Citation:
Doğan Z, Çetin S. Clinical reflections of the glymphatic system and neurodegenerative diseases. Journal of MTU. 2025;4(1):16-22.
https://doi.org/10.58651/jomtu.1675339

ABSTRACT

Objective: The brain is one of the main elements of the central nervous system and is protected within the bone structure formed by the skull bones. The nervous system and endocrine system play a fundamental role in maintaining brain homeostasis. The brain; How are the wastes that occur as a result of these biochemical events eliminated when it has such basic and important tasks? Until 2012, it was thought that there was no lymphatic system in the brain. Our aim with this literature review is to make it easier to find answers to these questions.
Materials and Methods: For this review research, the existing literature was systematically reviewed in terms of the glymphatic system.
Results: The glymphatic system is the brain's waste clearance mechanism. Many anatomical structures are involved in the glymphatic system. Astrocytes and aquaporin-4 channels were the most notable of these.
Conclusion: The glymphatic system is a waste clearing mechanism in the brain that has many important function mechanisms. Although it has been the subject of current research with human and animal experiments in recent years, it is still an area that preserves its mystery. Although it has been the subject of current research with human and animal experiments in recent years, it is still an area that remains mysterious. Disruption of this system is closely associated with neurodegenerative diseases. We believe that this system, which plays a vital role in brain health, should be the subject of more scientific research to clarify its functioning mechanism.
Keywords: Brain, lymphatic system, neurodegenerative diseases, neuroanatomy

MAKALE BİLGİLERİ

Makale Geçmişi:
Geliş Tarihi: 14.04.2025
Kabul Tarihi: 25.04.2025
Yayım Tarihi: 30.04.2025

Atıf Bilgisi:
Doğan Z, Çetin S. Glimfatik sistemin ve nörodejeneratif hastalıkların klinik yansımaları. Journal of MTU. 2025;4(1):16-22.
https://doi.org/10.58651/jomtu.1675339

ÖZET

Amaç: Beyin, merkezi sinir sisteminin ana unsurlarından biri olup kafatası kemiklerinin oluşturduğu kemik yapısı içerisinde korunmaktadır. Ayrıca özel bir zar sistemi ve seçici geçirgen bir kan bariyeri de bulunmaktadır. Peki her madde beyne rastgele giremiyorsa atık maddeler beyinden nasıl uzaklaştırılıyor? 2012 yılına kadar beyinde lenf sistemi olmadığı düşünülüyordu. İnsan vücudu bir makine gibi düzenli bir sistemle çalışır ve buna vücudun homeostazisi denir. Sinir sistemi ve endokrin sistemi bu dengeyi sağlamada temel bir rol oynar. Sinir sisteminin ana unsurlarından biri olan beyin; bu kadar temel ve önemli görevleri varken, bu biyokimyasal olaylar sonucu oluşan atıklar nasıl uzaklaştırılıyor? Bu literatür incelemesiyle amacımız bu sorulara daha kolay cevap bulmanızı sağlamaktır.
Materyal ve Metot: Bu derleme araştırması için mevcut literatür glimfatik sistem açısından sistematik olarak tarandı.
Bulgular: Glimfatik sistem beynin atık temizleme mekanizmasıdır. Glimfatik sistemde birçok anatomik yapı yer alır. Astrositler ve aquaporin-4 kanalları bunların en dikkat çekenleriydi.
Sonuç: Glimfatik sistem beyinde atık temizleme mekanizması olup birçok önemli fonksiyon mekanizmasına sahiptir. Her ne kadar son yıllarda insan ve hayvan deneyleri ile güncel araştırmalara konu olsa da hala gizemini koruyan bir alandır. Bu sistemin bozulması nörodejeneratif hastalıklarla yakın ilişkilidir. Beyin sağlığı açısından hayati rol oynayan bu sistemin, işleyiş mekanizmasını netleştirmek için daha fazla bilimsel araştırmaya konu olması gerektiği düşüncesindeyiz.
Anahtar Kelimeler: Beyin, lenfatik sistem, nörodejeneratif hastalıklar, nöroanatomi

INTRODUCTION

DISCOVERY AND IMPORTANCE OF THE GLYMPHATIC SYSTEM

The waste disposal mechanism of the central nervous system has been the subject of research for many years has not been clarified for many years in the history of medicine. The existence of this system was first demonstrated in animal experiments in 2012, and its existence in humans was proven in 2017. In the same year, with the discovery of the meningeal lymphatic network, this mechanism was accepted in the scientific community (1). Now the glymphatic system has taken its place in the literature as a new and rapidly developing research area in the field of neuroscience (2). Our study was designed to present current scientific developments regarding the clinical applications of the glymphatic system and to guide future studies in this field.

GLYMPHATIC SYSTEM: AN ALTERNATIVE MECHANISM THAT CLEARS WASTE FROM THE BRAIN

The presence of the blood-brain barrier, the disruption of classical waste clearance pathways in peripheral tissues, and the absence of lymphatic capillaries suggest that an alternative waste clearance system is required for the brain. The glymphatic system, which clears metabolic waste from the brain, meets this need as a specialized fluid drainage network.

In this system, cerebrospinal fluid (CSF) entering from the periarterial spaces mixes with the interstitial fluid (ISF) and is transported out of the perivenous spaces to remove waste products. After this process, it is excreted through various pathways in the subarachnoid space of the brain.

The main elements of the glymphatic system are CSF, periarterial space and perivenous spaces, astrocytes, ISF, meningeal lymph vessels (MLV) (2,3).

Cerebrospinal fluid

CSF undertakes tasks such as providing structural support throughout the neuraxis, transporting nutrients, and removing metabolic waste. It is organized in a regular and compact structure consisting of 99% water and various ions and macromolecules. It has a total volume of approximately 150 ml in an adult individual, of which 25 ml is in the ventricular system and 125 ml in the subarachnoid space (surrounding the brain and spinal cord). CSF production is primarily carried out by the choroid plexuses in the ventricular system and the ependymal cells lining the subarachnoid space. In healthy individuals, daily CSF production ranges between 400–600 ml, indicating that the fluid is completely renewed 4 to 5 times per day. Choroid plexus epithelial cells play a crucial role in this production process through their microvilli structures, capillary network, and endothelial barrier. CSF is produced in the lateral ventricles and flows through the third and fourth ventricles via the cerebral aqueduct before reaching the central canal. During its circulation, a portion of the CSF passes into the superior sagittal sinus via the arachnoid granulations and joins the venous circulation. Another portion passes through the perisinusoidal spaces via dural lymphatic vessels, reaches the extravascular epithelial spaces, and is subsequently drained by the lymphatic capillaries located there. CSF and ISF exchange occurs in the periarterial spaces. Rhythmic expansion of the arterial walls with pulse waves increases fluid movement in the perivascular spaces (periarterial spaces), which determines the direction of flow between CSF and ISF. CSF removes metabolic waste accumulated in the extracellular space. Waste-laden fluid is removed from the brain by perivenous spaces connected to the periarterial spaces (2, 4).

Interstitial fluid

ISF has an important role in maintaining brain homeostasis. This fluid fills the spaces between blood vessels, neurons, and glial cell membranes. While it ensures the transportation of nutrients to the cells, it is also responsible for the removal of metabolic waste (5). The flow of ISF is shaped by arterial pulse waves and especially AQP4 water channels found in astrocytes (6). This circulation is very important for the brain parenchyma to remain healthy. The literature presents that ISF joins the CSF not only through main pathways but also through alternative flow pathways that progress towards the cortex. An obstacle that disrupts this flow may cause consequences such as protein accumulation and deterioration in brain functions (7).

Perivascular spaces

They are fluid-filled spaces located around the vessels and are surrounded by astrocyte end-feet. They have functions such as regulating CSF circulation, facilitating waste clearance, and maintaining immune homeostasis. Periarterial spaces establish connections with perivenous spaces. CSF and ISF exchange occurs in the periarterial spaces. CSF removes metabolic waste accumulated in the extracellular space. The waste-laden fluid is removed from the brain by the perivenous spaces connected to the periarterial spaces (2, 4).

Astrocytes

They help maintain homeostatic balance by providing mechanical support, maintaining the integrity of the blood-brain barrier, regulating ion homeostasis, and regulating synaptic activity. They are glial cells found in the CNS. Their end feet contain aquaporin-4 (AQP4) channels. These channels allow CSF to pass from the perivascular spaces to the interstitial space to remove metabolic waste products. Astrocytes, glial cells that regulate glymphatic flow, are positioned around blood vessels (2, 8).

Meningeal lymphatic vessels

It is located in the outer layer of the meninges and is distributed along the dural venous sinuses. Its primary functions include the clearance of metabolites, cellular waste, and misfolded proteins, as well as the transport of CSF, immune cells, and antigens. These vessels serve as a critical connection between the brain and the immune system (9). The mixture of CSF and ISF is transported to the deep cervical lymph nodes through the foramina located at the base of the skull. Additionally, some lymphatic fluid may travel along the olfactory nerves and reach the superficial cervical lymph nodes via the cribriform plate. The brain lymphatic system maintains homeostasis within the neuronal interstitial space and contributes to the regulation of the immune response by facilitating the transport of immune cells (10).

SLEEP AND THE GLYMPHATIC SYSTEM

The relationship between the glymphatic system and sleep is important. While the brain's capacity to clear waste increases during sleep, this activity decreases during wakefulness. This has been supported by studies on mice; traceable agents such as Gadobutrol have been shown to distribute more limitedly during wakefulness but provide more effective clearance during sleep (11). Melatonin hormone and dark environment have been found to benefit glymphatic flow by increasing AQP4 production (12). Additionally, chronic sleep fragmentation disrupts the positioning of AQP4 water channels, inhibits flow in perivascular spaces, and causes Aβ plaque accumulation (13, 14). A relationship between decreased glymphatic flow and cognitive dysfunction has also been reported in patients with Obstructive Sleep Apnea (15). Considering all this information, quality sleep is an important element affecting the glymphatic system. Sleep-wake regulators such as melatonin have been observed to contribute positively to this process.

MATERIALS AND METHODS

For this review research, examined in detail was systematically in terms of the glymphatic system. All scientific data, especially after 2020, was scanned in Turkish and English. bMed, Google Scholar, ScienceDirect and Web of Science's data were used during the searches. Data from researches on human and animal experimental models are included in this review. Keywords were used: Brain, Lymphatic System, Glymphatic System, Neurodegenerative Transmission, Sleeping.

RESULTS

In our literature study, we observed that the cerebrospinal fluid enters the artery and cleans the wastes through the brain dura sinuses and venous drainage. Many anatomical structures are involved in the cleaning of metabolic waste in the brain (Table 1 (16-18), Figure 1). Between these anatomical structures that are responsible for the clearance of metabolic waste in the brain, the most striking ones were astrocytes and aquaporin 4 channels. Considering the data our have obtained, it is clear that this system, which cleans brain waste, is active during sleep. It is possible to say that in cases such as inadequate quality of the glymphatic system, waste cannot be cleared and neurodegeneration increases. Disorders, especially in the Non-REM sleep process, cause this system to become inadequate and waste to be removed from the brain. The increase in CSF during the non-REM period can be shown as evidence of this. We highlighted the importance of this waste removal system for the brain, one of the most active organs in the body, by emphasizing its relationship with neurodegenerative diseases.

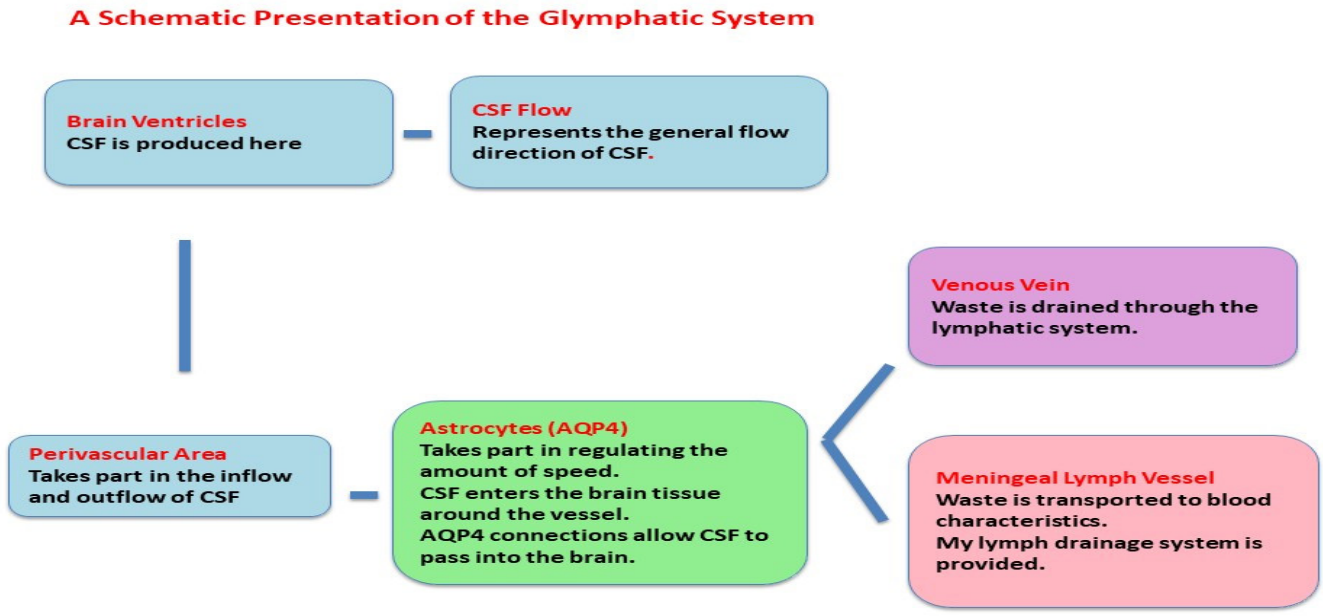

Figure 1. Schematic representation of the glyphatic system

Table 1. Major Anatomical Structures of the Glymphatic System	
Periarterial Space (Virchow–Robin Space)	* These are the spaces found around arteries and veins. * CSF enters these areas and reaches the brain parenchyma. * It serves as the initial entry point for the clearance of metabolic waste from the central nervous system.
Astrocytes and Aquaporin-4 (AQP4) Channels	* Astrocytes are star-shaped glial cells that serve as assistants to neurons. * They contribute to the formation of the blood-brain barrier. * Aquaporin-4; Astrocytic endfeet, enriched with aquaporin-4 (AQP4) channels, mediate bidirectional water transport across the blood–brain interface, thereby supporting glymphatic fluid dynamics. * It allows the passage of CSF into the brain tissue. * In the recent studies, they attract attention as the main carrier and guiding element of the glymphatic system.
Cerebrospinal fluid (CSF) circulatory system	* CSF is produced by ependymal cells in the cerebral ventricles (especially in the choroid plexus) and around the central canal. * Cerebrospinal fluid then traverses into the subarachnoid and perivascular compartments, where it contributes to the removal of interstitial waste products from the central nervous system.
Venous Veins	* After collecting waste products, CSF is withdrawn from the vicinity of the venous system (especially from around the large veins). * It is transferred to the systemic circulation.
Meningeal Vessels	* Located within the meninges (especially the dura mater). * It passes through the holes in the skull wall and connects the dura mater sinuses with the veins outside the skull. * It is the final route of excretion of waste from the glymphatic system. * It connects to the neck lymph nodes.
Subarachnoid Space	* It is the space between the brain and the skull where CSF circulates. * It is part of the waste transportation system. * It is the space between the arachnoid mater and the pia mater. It is found both around the brain and around the medulla spinalis. It is a continuation of each other.

Table 1. Major Anatomical Structures of the Glymphatic System (16-18)

DISCUSSION

CLINICAL REFLECTIONS OF THE GLYMPHATIC SYSTEM AND NEURODEGENERATIVE DISEASES

The decreased function of the glymphatic system, which plays a key role in clearing metabolic waste from the brain, can lead to severe neuropathological consequences. Impairment of this clearance mechanism results in the accumulation of toxic metabolites within the brain, exerting detrimental effects on both neurons and glial cells. Increased oxidative stress, the initiation or exacerbation of neuroinflammatory processes, and subsequent neuronal loss and degeneration may occur. These pathological alterations primarily contribute to the deterioration of cognitive functions. Enhancing glymphatic system function may help preserve cognitive abilities by potentially slowing or even reversing the progression of neurodegenerative diseases (19).

Alzheimer's disease

Seven different proteins have been identified that are associated with glymphatic system function, immune regulation, and neurodegenerative processes. The health of the glymphatic system has been shown to correlate with various biological processes, including inflammation, immune response, angiotensin II signaling, fibroblast growth factor (FGF) signaling, and B cell activation. When the relationship between glymphatic clearance and the CSF proteomic profile was investigated, it was concluded that Alzheimer's disease risk might be influenced by immune-related proteins (20).

Regular physical exercise has been shown to alleviate cognitive impairments associated with Alzheimer's disease. This beneficial effect appears to be linked to mechanisms that promote Aβ clearance via the glymphatic pathway. Exercise has been reported to enhance aquaporin-4 (AQP4) expression in the hippocampus and to facilitate CSF–ISF exchange by regulating the polarity of astrocytic endfeet. Moreover, suppression of hippocampus-specific AQP4 expression was found to attenuate the cognitive benefits of exercise, highlighting the essential role of AQP4 in this process (21).

Although glymphatic system dysfunction is believed to occur in Alzheimer's disease, it remains unclear whether this impairment is a cause or a consequence of the disease. Therefore, reliable methods are needed to image and measure glymphatic function in the human brain (22).

Parkinson's disease

In recent studies, the relationship between Parkinson's disease and the glymphatic system has begun to be investigated more. The ALPS (Analysis Throughout Perivascular Space) index is based on the evaluation of perivascular spaces. This analysis monitors the progression of patients' motor function. By monitoring the ALPS index, glymphatic dysfunction and reduced

motor function can be detected early in Parkinson's patients. In Parkinson's disease, a disrupted glymphatic system leads to the progression of the disease due to insufficient clearance of ISF (23).

Degeneration of the locus coeruleus and disruption of glymphatic flow may impair cognitive functions. Functional impairment in the glymphatic system may indicate an important marker in the progression of Parkinson's disease (24).

In addition, the ALPS index is used as a biomarker representing clinical symptoms such as recurrent falls, wheelchair dependency, and dementia. These symptoms are directly proportional to the impairment of the glymphatic system in Parkinson's disease. Therapeutic strategies in glymphatic dysfunction also hold the potential to slow disease progression in Parkinson's disease (25).

Traumatic brain injury

Glymphatic flow within the brain is disrupted after traumatic brain injury. Particularly in the frontal regions of the brain, fluid flow slows down, while a faster movement is seen in the posterior regions. Additionally, a protein called AQP4 has been found to be reduced in the posterior regions of the brain, affecting glymphatic flow. Glymphatic drainage from the brain to the cervical lymph nodes is impaired, and blood accumulation occurs in these areas after traumatic brain injury. This disease can have serious effects on the glymphatic system. Improving this system may be a potential treatment avenue (26).

Multiple sclerosis

Multiple sclerosis is an inflammatory disease. It is thought that the inflammatory effect of the disease can cause sleep disorders. Problems such as sleep apnea and restless leg syndrome are also thought to worsen the course of this disease. The brain's waste system is actively working during sleep. Since deterioration in sleep quality directly affects the glymphatic system, this deterioration can also be effective in the disease process. Dysfunction in the glymphatic system is characterized by a decrease in the ALPS index. This may play a decisive role in the progression of Multiple Sclerosis. Glymphatic system dysfunction may be an important finding in MS progression, regardless of the severity and duration of the disease (27, 28).

Sleep disorders and chronic fatigue syndrome

It has been found that deterioration in sleep quality may indirectly shape pain perception by disrupting the function of the glymphatic system. This suggests that the glymphatic system may play a common regulatory role in both sleep and chronic pain processes (29).

Stroke

Impairment of glymphatic system function has been shown to play a critical role in both the formation and resolution of brain edema following ischemic stroke. The recovery of glymphatic function appears to parallel the regression of edema, and interventions targeting the glymphatic pathway can significantly influence the severity of brain edema after stroke (30, 31).

Epilepsy

In patients with late- onset epilepsy, especially those with cognitive decline, glymphatic system activity is reduced. It has been observed that glymphatic clearance becomes more impaired as the duration of the disease and age advances (32). The glymphatic system may play a role in the pathophysiology of epilepsy. A decrease in the DTI-ALPS index indicates impairment in the glymphatic system (33).

Aging

Glymphatic system function decreases with aging, causing accumulation of toxic metabolites in the brain, neuronal damage, degeneration, and cognitive loss. This can be both a cause and a consequence of aging. Protection of the glymphatic system may benefit the prevention and treatment of age-related diseases (34).

Brain tumors

In the examination of brain tumor and glymphatic system, low ALPS index on the side where the tumor is located is remarkable. Since a low ALPS index is already associated with glymphatic impairment, brain tumors may have indirectly supported this decrease (35).

Depression and anxiety

Loss of function in the glymphatic system may support the development of major depression. With this loss, the combination of other symptoms, especially fatigue, becomes easier. And it may play a role in the pathogenesis of depression, albeit indirectly (36).

There is also evidence suggesting that glymphatic system dysfunction may be associated with chronic migraine and hydrocephalus (37,38).

The glymphatic system and the peripheral immune system are interconnected and have an impact on the development and progression of neurodegenerative diseases. Peripheral immune cells and cytokines migrate to the central nervous system, increasing the activation of glial cells, triggering neuroinflammation and accelerating neuronal loss. Functional loss of the glymphatic system during this process further worsens the course of diseases. It may be useful to consider these interactions between the glymphatic system and the immune system in treatment approaches (39).

The Role of Exercise on the Glymphatic System

The importance of certain lifestyle practices for the healthy

functioning of the glymphatic system has been proven. Exercise, quality sleep, balanced blood pressure and AQP4 level have been documented as elements that support the functionality of this system. It has been reported that these elements may have different effects on the system depending on the type, duration and frequency of exercise and that more research is needed on this subject (40). It has been observed that aerobic exercises, especially swimming, support AQP4 expression and polarization by increasing the exchange of ISF with CSF, thereby strengthening the glymphatic transport system. At the same time, this type of exercise also reduces the accumulation of Amyloid Beta plaques seen in Alzheimer's disease (41). All these data suggest that regular physical activity is vital for brain health.

CONCLUSION

The brain is an important organ of the nervous system that ensures that the entire body remains balanced and functions smoothly. During this active and important task mechanism, many biochemical metabolites are released and they need to be removed from the tissue.

The glymphatic system is a mechanism similar to the lymphatic system that is responsible for clearing the brain of waste. Just like a vacuum cleaner sweeps waste at home, this system vacuums up all the waste that is produced as a result of the active activities of the brain.

Although it has been the subject of current research with human and animal experiments in recent years, it is still an area that preserves its mystery. We believe that this system, which plays a vital role in brain health, should be the subject of more scientific research to clarify its functioning mechanism.

Ethics Committee Approval: Ethics committee approval is not required for this study.

Financial Resource/ Sponsor's Role: No financial support was received for this study.

Conflict of Interest: The authors declare that there are no personal or financial conflicts of interest related to this study.

Author Contributions: Idea/Concept: Zümrüt DOĞAN; Design: Seda ÇETİN; Supervision/Consulting: Zümrüt DOĞAN; Data Collection and/or Processing: Seda ÇETİN; Analysis and/or Interpretation: Zümrüt DOĞAN; Literature Review: Zümrüt DOĞAN, Seda ÇETİN; Writing of the Article: Seda ÇETİN; Critical Review: Zümrüt DOĞAN; Resources and Funding: No financial support was received for this study.

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