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Review Paper

Glymphatic System Reconstruction in the Management of Alzheimer's Disease

Ashkan Asgari Gashtrodkhani[1], Roxana Kaveh[2], Zoheir Reihanian[3], Shahrokh Yousefzadeh-Chabok[2, 3], Sasan Andalib[2,4, 5, 6*]

1. School of Medicine, Guilan University of Medical Sciences, Rasht, Iran.
2. Guilan Road Trauma Research Center, Trauma Institute, Guilan University of Medical Sciences, Rasht, Iran.
3. Department of Neurosurgery, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran.
4. Research Unit of Neurology, Department of Clinical Research, Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark.
5. Department of Neurology, Odense University Hospital, Odense, Denmark.
6. Neuroscience Research Center, Trauma Institute, Guilan University of Medical Sciences, Rasht, Iran.

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ABSTRACT

Alzheimer's disease (AD) is a major public health challenge. The exact cause of AD is unknown, but it is characterized by progressive impairment in cognitive and memory functions and pathological changes in the brain, such as aggregation of two main proteins, amyloid-beta (Aβ) and neurofibrillary tangles (NFTs) of tau. Nonetheless, the pathogenesis of AD appears to be complicated by vascular changes, neuroinflammation, synaptic loss, and impaired clearance of cellular waste products. Currently, the limited efficacy of available treatments underscores the need for alternative therapeutic strategies. The glymphatic system is a paravascular network in the central nervous system, responsible for the removal of cellular waste. The present review discusses the glymphatic system and its reconstructive surgery as a potential treatment approach for AD. Both experimental and human studies have demonstrated the role of the impaired glymphatic system in the pathogenesis of AD by increasing the accumulation of Aβ and tau proteins, thus holding potential as a new target for AD treatment. Moreover, glymphatic system dysfunction can lead to neurodegeneration, cognitive decline, and disease progression. Studies have also shown the potential role of microsurgical lymphatic reconstruction as a possible therapeutic target for AD treatment. Glymphatic system dysfunction may be a possible contributing factor to the pathogenesis and progression of AD. Moreover, glymphatic and meningeal reconstruction microsurgery may have the potential for the treatment of AD.

*** Corresponding Author:**
Sasan Andalib, PhD.
Address: *Research Unit of Neurology, Department of Clinical Research, Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark.*
E-mail: *sasan.andalib@health.sdu.dk*

Highlights

- Deposition of Aβ and NFTs may play a role in the pathogenesis of AD.
- The glymphatic clearance pathway removes cerebral waste products from the brain.
- The glymphatic system impairment is related to the brain waste accumulation and AD.
- Glymphatic system reconstruction may serve as a potential therapeutic approach in AD.

Plain Language Summary

Alzheimer's disease (AD) is the most common cause of dementia and leads to memory impairment, changes in behavior, and difficulties with thinking and daily activities. It is assumed that one of the characteristics of this disease is the buildup of toxic proteins such as amyloid-beta (Aβ) and tau in the brain. The brain has a clearance system, the glymphatic system, that removes waste products. When this system is impaired, neurotoxic proteins accumulate in the brain, hastening neurodegeneration and, in turn, AD.

It has recently been demonstrated that dysfunction of the brain's lymphatic drainage system may play an important role in AD. Preclinical studies have shown that when these waste-clearance systems are disrupted, the deposition of waste proteins increases in the brain, and memory deteriorates. Evidence from human studies also indicates that reduced glymphatic system activity is associated with greater accumulation of neurotoxic proteins and worsens cognitive decline.

A promising approach in AD treatment may be microsurgical reconstruction of the brain glymphatic system, which may help the brain clear waste materials more effectively. Limited available preclinical and human studies have shown that this approach might reduce toxic protein buildup, improve brain function, and even lead to better memory test scores. In spite of these findings, research in this area is still in its early stages. Most human studies in this regard involve only a few patients, and therefore, further investigation is required to test the safety and efficacy of glymphatic or lymphatic reconstruction. Yet, this approach offers a potential new direction for AD treatment by targeting the brain's natural cleaning systems.

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common form of dementia. AD is characterized by different clinical presentations, mainly affecting cognitive and memory functions. Progression of the disease gradually impairs short-term memory, speech, executive functions, and social communication, further limiting daily activities [1]. In addition to cortical atrophy and diffuse white matter degeneration [2], enlargement of the brain ventricles occurs related to disease progression [3].

Brain changes, including deposits of amyloid-beta (Aβ) and neurofibrillary tangles (NFTs) of hyperphosphorylated tau protein, are proposed to have a key role in the pathogenesis of AD; however, the exact cause is not well identified. The accumulation of Aβ and NFTs in the brain further contributes to neuroinflammation. This association involves a complex interplay, wherein the interactions depend on different stages of AD [4]. Cerebrovascular changes [5] and synaptic loss [6] are other pathological factors related to the complex pathology of AD.

The clearance of Aβ and NFTs appears to play an important role in the pathogenesis of AD. It is further considered that the discrepancy between the production and clearance of the cellular waste products, including Aβ and NFTs, may contribute to AD progression. While the amyloid hypothesis of AD discusses this imbalance between the production and clearance of Aβ [7], evidence for Aβ overproduction in AD patients has also been proposed [8, 9]. However, It is demonstrated that impaired Aβ clearance is a contributor to its aggregation in AD pathogenesis [10].

The paravascular glia-lymphatic (glymphatic) system is the brain's mechanism involved in the clearance of waste products, which are ultimately drained into the cervical lymphatics. Glymphatic system dysfunction impairs the clearance of waste products from the brain, and therefore, it is associated with the development of AD [11]. Glymphatic reconstructive microsurgery has been proposed as a potential therapeutic option for AD [12]. The present review discusses the glymphatic system and its reconstructive surgery as a potential treatment approach for AD.

2. Discussion

Cerebral and glymphatic waste clearance system

The brain produces large amounts of waste products, including misfolded proteins, metabolic byproducts, cellular debris, and other molecules, which should be removed to maintain homeostasis and prevent further complications. Interstitial fluid (ISF) helps with clearing the brain parenchyma of these waste products generated by neurons and glial cells [13]. The ISF then exchanges them with the cerebrospinal fluid (CSF), which fills the brain ventricles and subarachnoid space [14]. CSF is primarily produced by the choroid plexus in the brain ventricles and flows into the subarachnoid space, enclosing the brain and the spinal cord [15]. CSF in the subarachnoid space is absorbed by the meningeal (dural) lymphatic vessels and further drains to the deep cervical lymph nodes (dcLNs) to be reabsorbed into the bloodstream [16]. The integrity of these draining pathways and their proper physiological function are important for the clearance of cerebral waste products from the brain and also prevent the development of certain neurodegenerative disorders, such as AD [17].

There have been developments in the understanding of the cerebral waste-clearance pathways and mechanisms. Discoveries proposed a hypothesis about cerebral drainage, beginning with the glymphatic system, which clears the waste products from the brain's parenchyma, and is further accompanied by the meningeal lymphatic system, draining the CSF and waste products away from the brain to the dcLNs.

Structure of the glymphatic system

A study by Iliff et al. used in vivo two-photon imaging of fluorescent tracers in mice to observe the paravascular CSF cycle through the brain parenchyma and clearance of ISF [18]. The results showed that the CSF from the subarachnoid space flows into the periarterial space (Virchow-Robin space), infiltrating the brain parenchyma and mixing with the ISF. CSF-ISF mixture carrying the waste products exits the brain parenchyma along the perivenous space. They also suggested that both the CSF influx from the periarterial space toward the brain parenchyma and CSF-ISF efflux along the perivenous space are mediated by polarized aquaporin 4 (AQP4), water channels expressed by astrocyte endfeet [18]. The flow rate of CSF influx through this process is primarily driven by arterial pulsation during the cardiac cycle and is tightly dependent on the arterial diameter [19]. The systolic cardiac cycle increases the artery diameter; conversely, the diastolic cardiac cycle decreases the artery diameter. The difference in the arterial diameter during the cardiac cycle pushes the CSF toward the Virchow-Robin space and further into the brain parenchyma [19]. This process, which clears the brain parenchyma from waste products, is termed the glymphatic system. As the brain lacks a typical lymphatic system, the glymphatic system functions similarly and is mediated by glial cells.

Meningeal lymphatic system

The central nervous system is surrounded by three distinct meningeal layers. From deep to superficial, these three layers are known as the pia mater, arachnoid mater, and dura mater. The spaces between these layers are filled with fluids, which play a crucial role in maintaining homeostasis and protecting the brain and spinal cord. The CSF fills the space between the pia mater and the arachnoid mater, named the subarachnoid space. Moreover, there is a space between the dura mater and the arachnoid mater, known as the subdural space, which is filled with serous fluid. Furthermore, the meningeal lymphatic vessels (mLVs) are located on the dorsal and basal surfaces of the brain within the dura mater and have an important role in the clearance of CSF and waste products [16, 20].

The mLVs absorb the waste-laden CSF from the subarachnoid space and drain into the dcLN via the foramina at the base of the skull [16].

Ahn et al. conducted a study to evaluate the differences and importance of the basal and dorsal mLVs in the drainage of CSF in mice, and morphological differences between them were observed [21]. In contrast to dorsal mLVs, the basal mLVs had a larger diameter and also contained lymphatic valves and capillaries located adjacent to the subarachnoid space. Moreover, basal mLVs were morphologically more similar to peripheral lymphatics. The results also showed that the basal part of mLVs is the main pathway for the drainage of CSF

waste products from the glymphatic system into the dcLN. The mLVs serve as a crucial component of the clearance mechanism of cerebral waste products.

The glymphatic and meningeal system as a therapeutic target for AD

Mice-model studies

Patel et al. conducted a study to assess the effect of the cerebral dural lymphatic system on the clearance of tau protein by using imaging studies and plasma measurements of tau protein levels in the parenchyma of wild-type and transgenic (Tg) mice, lacking a functional cerebral lymphatic system [22]. The authors concluded that the dural lymphatic system is involved in the clearance of tau protein, and in the lack of a functional lymphatic system, greater amounts of tau were retained in the brain parenchyma of Tg-mice compared to wild-type.

A study in an AD mouse model investigated the role of microglia in the prevention of Aβ formation in association with the glymphatic system [23]. In this study, microglial cells were selectively eliminated in the Tg-AD mice, and AQP4 gene deletion was also performed. The results revealed that microglia have a protective effect against Aβ plaque formation through the glymphatic system during the early stages of AD. Additionally, AQP4 gene deletion was related to glymphatic clearance pathway dysfunction.

More recently, Feng S et al. conducted a study to evaluate the beneficial effects of high-intensity interval training (HIIT) on the AD mouse model [24]. They used various measurement modalities to observe the regulatory function of the astrocyte phenotype-associated AQP4 polarization in enhancing the clearance of abnormal Aβ and tau proteins from the brain through the glymphatic system. The results showed that the polarized distribution of AQP4 was more highly related to the A2 phenotype than the A1 phenotype, contributing to neuroprotective effects in AD. The authors also found that HIIT regulates astrocyte phenotype-associated AQP4 polarization, which favors the clearance of cerebral waste products through the glymphatic system, ultimately improving AD.

In another study, non-invasive, near-infrared light was used to modulate mLVs in both aged and AD mice [25]. The findings demonstrated that Aβ accumulation, neuroinflammation, and neuronal loss were reduced in the treated mice. It was also concluded that mLVs potentiation by light enhances the lymphatic clearance function, consequently improving cognitive function in both aged and AD mice.

In a more recent study, Wu et al. investigated the association between long-term cervical lymphadenectomy (cLE) and tauopathy in mice [26]. According to the results, cLE exacerbates sleep and psychiatric disorders by activating the extracellular signal-regulated kinase signaling pathway, thereby enhancing tau accumulation in young mice. The authors concluded that long-term cLE is linked to impaired clearance of cerebral waste products, consequently accelerating cognitive decline and AD progression.

Human studies

Huang et al. performed a study to observe the potential role of glymphatic system impairment in predicting the progression of AD in participants with AD dementia, mild cognitive impairment (MCI), along with normal controls, using diffusion tensor image analysis along the perivascular space (DTI-ALPS) [27]. They demonstrated that a lower ALPS index was correlated with higher Aβ-related changes, neurodegeneration, and cognitive decline. The authors suggested that glymphatic system dysfunction is possibly linked to the clinical progression of AD. Furthermore, the ALPS index could serve as a marker for predicting Aβ accumulation, brain atrophy, and cognitive decline in AD. Similarly, in another study, the DTI-ALPS index was used as a marker to evaluate the effects of the glymphatic system dysfunction in association with AD in participants with AD and cognitively normal controls [28]. The study showed that a lower ALPS index was associated with decreased glymphatic flow, proposing it as a potential predictor of brain atrophy and cognitive decline in the progression of AD.

A recent retrospective study assessed the relationship between glymphatic system dysfunction and Aβ-related AD by measuring the DTI-ALPS index in 140 patients with different stages of AD, including early-onset, late-onset, MCI, and subjective cognitive decline [29]. The findings revealed that glymphatic system impairment is linked to AD progression.

Chao et al. performed a retrospective study to evaluate the dementia incidence rate in patients with head and neck cancer undergoing lymph node dissection [30]. The authors found that the dementia risk was higher in patients who underwent bilateral lymph node dissection, compared to those with unilateral lymph

node dissection, and therefore indicated that the cervical lymphatic dysfunction is possibly associated with the dementia presentation.

The abovementioned findings suggest that the brain lymphatic dysfunction serves as a possible contributor to the complex pathogenesis of AD. Thus, the therapeutic surgical procedures of lymphatic reconstruction could have a potential role in AD treatment.

Lymphatic reconstruction as a potential therapeutic method for AD

A recent study by Fang et al. evaluated the effects of a novel microsurgical method of cervical lymph node-to-vein anastomosis (LNVA) on the anastomotic patency of the brain lymphatic clearance pathway, both functionally and structurally, in a rat model [31]. The rats underwent bilateral cervical LNVA, end-to-side lymph node-to-venous anastomosis from the dcLNs to the external jugular vein. In addition, the anastomotic patency was confirmed intraoperatively by indocyanine green lymphangiography. The results revealed that this procedure could be a potential therapeutic intervention for the improvement of the brain clearance system and neurodegeneration.

Elsewhere, Li et al. studied the beneficial effects of a novel surgical procedure of shunting to unclog cerebral lymphatic systems in six patients with AD [32]. This procedure is analogous to lymphovenous anastomosis (LVA) and links the bilateral deep cervical lymphatic pathways to the low-pressure venous system. To date, the authors have presented the results from one patient, a 70-year-old woman with severe AD. The follow-up was done five weeks after the surgery, and the results showed improvement in cognitive function through the psychological and clinical assessments. Additionally, the tau-PET scan indicated a decrease in overall brain tau accumulation, while the 18-F-fluorodeoxyglucose PET scan exhibited a remarkable increase in the brain glucose metabolism.

Chen et al. investigated the efficacy and safety of deep cervical LVA in 26 patients with AD [33]. Preoperative and one-month follow-up neuropsychological observations performed by using the mini-mental state examination (MMSE), the Montreal cognitive assessment (MoCA), the neuropsychiatric inventory, and CSF biomarkers, including Aβ42, Aβ42/ Aβ40 ratio, p-tau, and t-tau, were collected and analyzed within 5-7 days after the surgery. The surgical procedure included deep cervical lymphatic-external jugular vein end-to-side anastomosis and deep cervical lymphatic-internal jugular vein endtoside anastomosis. Additionally, the post-anastomotic lymphatic patency was assessed by using indocyanine green fluorescence. The results at one-month follow-up showed that the procedure was safe, and no severe adverse events were reported. Quantitative analysis demonstrated a reduced level of CSF biomarkers following LVA surgery. However, the differences were not statistically significant. Also, cognitive assessments exhibited a statistically significant increase in MMSE scores, while the MoCA and neuropsychiatric inventory scores differences were not statistically significant. Overall, symptomatic improvements in patients were reported by 60% of caregivers. The authors suggested that deep cervical LVA may serve as a novel therapeutic strategy for the treatment of AD and the improvement of cognitive function.

In a case report study, the potential therapeutic role of lymphovenous bypass surgery in the cervical lymphatic pathway was assessed in a 58-year-old woman diagnosed with severe AD dementia [34]. Despite pharmacological treatments, her symptoms progressed to severe dementia, and the MMSE and the MoCA scores were both 0/30. The 18F-AV-45 PET/CT scan was used to detect the Aβ deposits in the brain both pre- and post-operatively. Lymphovenous bypass surgery was performed with a bilateral anastomosis of the lymphatic channel to the external jugular vein. Postoperatively, the MMSE and the MoCA scores, along with clinical symptoms, improved, and after 4 months of observation, the 18F-AV-45 PET/ CT scan showed a reduction in the Aβ plaques in the brain. Similarly, in another recent case-report study by Chen et al., the recovery outcome of deep jugular venous lymphatic anastomosis in a 74-year-old female with AD-type dementia refractory to medication and other treatments was evaluated [35]. During the deep jugular venous lymphatic anastomosis surgery, the proximal lymphatic vessels were anastomosed to the distal end of the jugular vein. No peri- or post-operative complications were reported. Her follow-up observations one and three months after the surgery showed improvements in her MMSE and AD Cooperative Study-instrumental Activities of Daily Living scores. The authors indicated that this surgical procedure can be a therapeutic option for AD treatment.

3. Conclusion

Brain lymphatic clearance system dysfunction can be a possible contributing factor to the pathogenesis and progression of AD. Moreover, glymphatic and meningeal reconstruction microsurgery is proposed as

a new potential therapeutic target for the treatment of AD, although this procedure is used rarely. While providing a comprehensive overview, this review paper has limitations. As a narrative review, it did not follow a systematic search, which may cause selection bias. Additionally, the included studies were not assessed using a quality assessment. Furthermore, the included clinical studies have a small sample size or are case reports. Therefore, there is a need for further investigations with a larger number of patients. Remarkable efforts are required to determine the most effective and optimal reconstruction method. Also, other relevant reconstruction methods may be investigated for their outcomes and side effects.

Ethical Considerations

Compliance with ethical guidelines

This article is a narrative review with no animal or human sample.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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