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REVIEW ARTICLE

GLYMPHATIC SYSTEM DISORDERS IN ALZHEIMER'S DISEASE

ZABURZENIA UKŁADU GLIMFATYCZNEGO W CHOROBIE ALZHEIMERA

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ABSTRACT

Introduction

Dysfunction of the glymphatic system (GS) impairs the removal of metabolites from the central nervous system, promoting neurotoxic change and the progression of Alzheimer's disease (AD). AD is characterised by the abnormal accumulation of neurotoxic amyloid-β (Aβ) and tau proteins within the brain.

Aim

In this review, we aim to summarize current knowledge on GS dysregulation and its association with AD development and progression.

Materials and methods

A literature search was carried out using five scientific databases to identify English-language studies on GS alterations in AD in humans published within the last five years. After screening and eligibility assessment, 44 articles were included.

Results

According to our research AD appears to be associated with GS impairment. The most frequently reported indicators of GS dysfunction were the analysis along the perivascular space (ALPS) index, choroid plexus (CP) enlargement, and enlarged perivascular spaces (EPVS). A low ALPS-index is used as an indicator of GS dysfunction. Patients with AD show significantly reduced ALPS-index and an increased number of EPVS than controls. CP plays a crucial role in Aβ clearance, and CP enlargement is considered a manifestation of its dysfunction, as observed in patients with AD. GS dysfunction may also be indicated by genetic factors and physiological modulations.

Conclusions

The review demonstrated that dysfunction of the GS disrupts the drainage of cerebrospinal and interstitial fluid, leading to impaired removal of metabolites, accumulation of Aβ, and progressive neurodegeneration in AD.

Keywords: glymphatic system, neurodegeneration, Alzheimer's disease

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STRESZCZENIE

Wstęp

Dysfunkcja układu glimfatycznego (GS) upośledza usuwanie metabolitów z ośrodkowego układu nerwowego, sprzyjając zmianom neurotoksycznym i progresji choroby Alzheimera (AD). AD charakteryzuje się nieprawidłowym gromadzeniem neurotoksycznych białek amyloidu β (Aβ) oraz tau w mózgu.

Cel

Celem przeglądu było podsumowanie aktualnej wiedzy na temat deregulacji GS oraz jego związku z rozwojem i progresją AD.

Materiały i metody

Przeprowadzono przegląd literatury z wykorzystaniem pięciu baz naukowych w celu identyfikacji anglojęzycznych badań dotyczących zmian w GS w przebiegu AD u ludzi, opublikowanych w ciągu ostatnich pięciu lat. Po etapie selekcji i kwalifikacji włączono 44 artykuły.

Wyniki

Z przeprowadzonych badań wynika, że AD jest związana z upośledzeniem funkcji GS. Najczęściej opisywanymi wskaźnikami dysfunkcji GS były wskaźnik ALPS (analysis along the perivascular space), powiększenie splotu naczyniówkowego (CP) oraz poszerzone przestrzenie okołonaczyniowe (EPVS). Niska wartość wskaźnika ALPS uznawana jest za marker dysfunkcji GS. U pacjentów z AD stwierdza się istotnie obniżony wskaźnik ALPS oraz większą liczbę EPVS w porównaniu z grupą kontrolną. CP odgrywa kluczową rolę w usuwaniu Aβ, a jego powiększenie, obserwowane u chorych na AD, uznawane jest za przejaw dysfunkcji. Na zaburzenia GS mogą również wpływać czynniki genetyczne i modulacje fizjologiczne.

Wnioski

Przegląd wykazał, że dysfunkcja GS prowadzi do zaburzeń drenażu płynu mózgowo-rdzeniowego i śródmiąższowego, upośledzonego usuwania metabolitów, akumulacji Aβ oraz postępującej neurodegeneracji w AD.

Słowa kluczowe: układ glimfatyczny, neurodegeneracja, choroba Alzheimera

Introduction

Alzheimer's disease (AD) is a prevalent form of progressive and degenerative dementia that affects the central nervous system (CNS), leading to a decline in daily living skills, cognitive deterioration, and the manifestation of aberrant behaviours. AD is characterised by the abnormal accumulation of neurotoxic proteins, including amyloid-β (Aβ) and hyperphosphorylated tau neurofibrillary tangles within the brain. These accumulations disrupt neuronal function and contribute to neurodegeneration [1]. The accumulation of neurotoxins within the CNS occurs long in advance of the onset of cognitive decline. The diagnosis of mild cognitive impairment (MCI), which usually precedes the diagnosis of AD, can be facilitated by neuropsychological tests, diffusion tensor imaging (DTI) to demonstrate structural connectivity in the brain, and functional magnetic resonance imaging (fMRI) to assess functional connectivity in the brain. Moreover, recent studies have demonstrated the potential of the analysis along the perivascular space (ALPS) index as a diagnostic tool for cognitive decline, exhibiting a negative correlation with Aβ and tau accumulation [2–4].

The glymphatic system (GS), comprising perivascular spaces (PVS) surrounding the blood vessels of the brain and astrocyte processes, plays a pivotal role in the elimination of metabolic waste and toxins from the CNS via cerebrospinal fluid (CSF). The aquaporin-4

(AQP4) channel located in the terminal part of astrocytes is believed to be critical for GS function. In AD, alterations in the blood-brain barrier and PVS disrupt GS function, thereby decreasing protein clearance. Neuroinflammation could be a contributing factor to GS dysfunction, resulting in inadequate removal of waste metabolites. Above mentioned processes may contribute to the early symptoms of cognitive decline, sleep disturbances, and elevated concentrations of core biomarkers in the CSF, leading after prolonged exposure to neurodegenerative diseases, such as AD. The assessment of GS function in the context of neurodegenerative diseases has the potential to facilitate early detection, continuous monitoring of progression, and effective treatment of AD [5–7]. Some forms of treatment targeting Aβ, such as lecanemab, seem to stabilize the GS function [8].

Aim

The present narrative review summarises the current state of knowledge regarding the dysregulation of the GS and its association with the development and progression of AD.

Materials and methods

A literature search was carried out in PubMed, Scopus, EBSCOhost, Web of Science and Embase to identify English-language studies on GS alterations in AD in humans published within the last five years. Search terms included "glymphatic system", "glymphatic system disorders", "Alzheimer", and "Alzheimer's disease" combined with AND; open-access filters were applied when possible. After screening and eligibility assessment, 37 original and 7 review articles were included. The eligibility assessment involved evaluating whether the studies met predefined methodological and thematic criteria.

Results

We identified the most frequently discussed topics, trends in publications, and the most often used methodologies. The most frequently discussed issues are presented in

Table 1. Key issues concerning knowledge about glymphatic system dysregulation and its relationship to the development and progression of Alzheimer's disease in reviewed articles

Classification criteria	Issue
Methodologies	Structural neuroimaging
	Functional neuroimaging
	Positron emission tomography
	Biomarkers
	Genetic factors
	Computational and machine-learning models
Topics	Pathophysiology of the glymphatic system in neurodegenerative diseases
	Neuroimaging of glymphatic system function
	Sleep and circadian rhythm
	Haemodynamic and vascular indicators
	Role of choroid plexus
	Role of aquaporin-4
	Genetic factors
	Early manifestations of glymphatic system dysfunction
Trends	Research based on early stages of cognitive decline
	Highlighting the importance of sleep and circadian rhythms in glymphatic system function

Table 1, followed by a discussion of specific issues in the text.

Discussion

Methodologies: structural neuroimaging, functional neuroimaging, positron emission tomography (PET), biomarkers, genetic factors and computational and machine-learning models.

DTI-ALPS: Recent advances in non-invasive neuroimaging have enabled *in vivo* assessment of the GS using DTI-ALPS. Higher values of the ALPS-index reflect more efficient flow. A reduced ALPS-index consistently characterises MCI and AD, correlating with executive dysfunction and gray-matter atrophy in memory-related regions such as the entorhinal cortex [2,4]. Notably, ALPS-index deterioration predicts regional AD-signature volume loss, higher white-matter hyperintensity (WMH) burden, and elevated plasma/CSF AD biomarkers, indicating that glymphatic dysfunction may lead to measurable cognitive decline [4].

EPVS: PVS are typically not visible on MRI. Their enlargement (EPVS) is a marker of impaired interstitial clearance. EPVS are prominent in the basal ganglia (BG), centrum semiovale (CS), and midbrain, increasing with age, inflammation, and cerebral small vessel disease (CSVD). EPVS in the CS correlates strongly with cerebral amyloid angiopathy (CAA) and Aβ deposition assessed by PET [9]. Integrating DTI-ALPS and EPVS, both structural (EPVS volume/count) and functional (ALPS-index) markers are altered in amnestic MCI [3], with EPVS burden negatively correlating with the ALPS-index and positively with cognitive impairment. EPVS, especially in CS, are also associated with CSF tau and tau-PET signals, indicating impaired tau clearance [10].

Parenchymal CSF (pCSF): Multi-echo T2 relaxometry enables pCSF mapping, offering specificity for glymphatic fluid over traditional diffusion free-water (FW) metrics. pCSF moderately correlates with DTI-FW and PVS burden but shows the strongest association with Aβ deposition, highlighting its potential as a direct glymphatic marker. The pCSF mapping directly targets a specific component of glymphatic fluid, making it more sensitive to changes in the GS [11]. DTI-derived FW in white matter (FW-WM) reflects early interstitial fluid (ISF) accumulation, correlating with EPVS and appearing independent of white matter (WM) or grey matter (GM) atrophy [10].

Choroid plexus (CP): CP enlargement in AD correlates with cognitive impairment, WM injury, and lower ALPS-index, indicating reduced glymphatic efficiency [12,13]. CP FW fraction associates with cortical tau burden, synaptic loss, and WMH progression, rising faster in Aβ-positive individuals, suggesting a dynamic marker of CSF-glymphatic dysregulation [14].

Global blood-oxygen-level-dependent CSF (gBOLD-CSF) coupling: Resting-state fMRI-derived gBOLD-CSF coupling quantifies glymphatic pulsatility. Reduced coupling predicts faster clinical decline, higher amyloid deposition, and greater cognitive impairment [15,16].

PET and fluid biomarkers: Lower ALPS-index and higher FW-WM correlate with reduced fluorodeoxyglucose PET metabolism, higher Aβ burden, and poorer cognitive performance [17]. Reduced ALPS-index predicts increased tau PET in temporal/frontal cortices, decreased CP Aβ, and worsening executive function [2]. Elevated CSF AQP4, plasma biomarkers phosphorylated tau 181/217, and altered Aβ ratios further reflect impaired glymphatic clearance, modulated by sleep physiology [10,18–20].

Genetic factors: Several key genetic factors affect GS in AD. The *apolipoprotein E* ε4 allele (APOE-ε4), a major cholesterol carrier, accelerates parenchymal and perivascular Aβ accumulation, while the rs744373 polymorphism in the *bridging integrator 1* (*BIN1*) gene, which is involved in the retrieval of synaptic vesicles, influences tau clearance

and PVS enlargement, suggesting impaired vascular-glymphatic homeostasis. In addition, *AQP4* single nucleotide polymorphisms (SNPs) show synergistic effects on FW accumulation, predicting faster cognitive decline [21,22].

Unique mechanistic insights: Olfactory dysfunction (OD) occurs in preclinical AD, correlating with higher Aβ PET, reduced hippocampal/cortical integrity, and elevated plasma tau and neurofilament-light, potentially reflecting early glymphatic impairment via olfactory CSF drainage pathways [23]. Ultrafast magnetic resonance encephalography demonstrates altered cardiovascular brain impulse propagation in AD, including reversed waves in mesiotemporal and periventricular regions overlapping with early Aβ deposition, indicating perivascular narrowing and impaired CSF clearance [24].

Computational and machine-learning models: Coupled transport-damage models using immersed finite-element isogeometric analysis simulate CSF-driven glymphatic transport and amyloid diffusion; however, cortical/hippocampal plaque deposition remains underestimated, highlighting the need for improved modelling of CSF velocity and vascular pulsatility [17]. Explainable artificial intelligence analyses of *AQP4* SNPs reveal sex-dependent synergistic effects on brain amyloid burden, validated across the Alzheimer's Disease Neuroimaging Initiative database and independent A4 cohorts, supporting astroglial water-channel contributions to early amyloid aggregation [25].

Pathophysiology of the GS in neurodegenerative diseases

Recent research has identified the GS as a key mechanism for clearing metabolic waste from the brain, which plays a role not only in the development of AD, but also in MCI, amyotrophic lateral sclerosis, and Parkinson's disease [26–28]. Studies involving populations with MCI and subjective cognitive decline (SCD) link glymphatic inefficiency to lower Mini-Mental State Examination (MMSE) scores. Proper functioning of astrocytes expressing AQP4 on their endfeet is essential for maintaining cognitive function [29,30].

Neuroimaging of GS function

DTI-ALPS measures passive water diffusion within PVS, but it cannot determine the directionality of flow, limiting its value as a definitive indirect marker of GS function. Alterations in PVS detected by DTI-ALPS may reflect either GS dysfunction or vascular damage [31]. ALPS-index is limited by its reliance on regions of interest, as DTI-ALPS can evaluate only one region at a time.

EPVS, frequently observed in older adults and individuals with cognitive impairment, likely results from impaired clearance and waste accumulation, contributing to CSVD. CAA, a subtype of CSVD often coexisting with AD, is caused by Aβ deposition in arteriole walls and impaired waste drainage along PVS. GS dysfunction is proposed as a potential causative factor in CAA pathology [32].

Emerging evidence links water diffusion metrics and PVS volume to AD and cognitive decline. Research demonstrated a negative correlation between FW-WM and CSF Aβ 42, functional activities questionnaire scores, and MMSE scores in AD patients. Additionally, higher PVS volume in all regions and in WM was observed in patients with MCI compared to healthy controls. Enlarged water volume in PVS was primarily detected in the CS and, in some cases, in the BG. The ALPS-index in AD patients was significantly lower than in controls; however, no significant decrease in ALPS-index was found in MCI participants [27].

Sleep and circadian rhythm

Circadian rhythms are key factors influencing GS function. Studies have demonstrated that glymphatic performance peaks during slow-wave sleep. Sleep deprivation,

common among AD patients, is increasingly recognised as an exacerbating factor for AD symptoms. Impaired glymphatic function, as measured by the ALPS-index, correlates with poorer Pittsburgh Sleep Quality Index scores, supporting the association between sleep disorders and reduced glymphatic circulation [19]. However, there is a lack of studies investigating the effects of specific sleep interventions on GS function, as well as the longitudinal impact of sleep disorders on AD progression.

Haemodynamic and vascular indicators

Vascular health and haemodynamic factors critically shape GS efficacy. GS function is also affected by vascular parameters, particularly arterial pulsatility, which significantly influences CSF flow dynamics. An increased arterial pulsatility index, often resulting from greater arterial stiffness, reduces the efficiency of ISF clearance. Reduced fluid influx facilitates the accumulation of Aβ and tau proteins in brain tissue, thereby accelerating the progression of AD [24,33].

Role of the CP

Changes in CP volume and structure may influence glymphatic drainage in AD. The CP is a critical brain structure responsible for CSF production and plays a significant role in immune response by mediating immune cell migration [28]. Studies integrating CP and CSF volume measurements along with DTI-ALPS, demonstrate a positive correlation between CP volume and cognitive impairment, as well as a negative correlation with the ALPS-index. These results suggest that structural changes in the CP may impair glymphatic drainage [34,35]. CSF volume is an independent biomarker of GS function that demonstrates stability even after correction for brain atrophy. It is hypothesised to influence glymphatic drainage through AQP4-related mechanisms. However, the specific pathways connecting these processes remain unidentified [12].

Role of AQP4

The role of AQP4 is to facilitate the flow of fluid from PVS into the parenchyma, which removes neurotoxic substances such as Aβ and phosphorylated tau. Overexpression, caused by neuroinflammation, and mislocalization of said channels in AD patients are potential mediators of GS dysfunction [36]. Studies have shown a correlation between elevated levels of CSF AQP4 and raised CSF biomarkers and hallmarks of AD, as well as poorer cognitive performance measured by MMSE scores [10]. The efficiency of the GS depends on the polarisation of the AQP4 water channel in astrocytes [37]. When AQP4 is overexpressed, glymphatic clearance does not improve because of the loss of normal AQP4 polarisation, resulting in reduced ISF transport efficiency [26].

Unfortunately, our review identified no longitudinal studies examining the relationship between AD progression and AQP4 concentrations. Another limitation is the very few studies considering AQP4 allelic variants, as well as the lack of control for potential confounding factors such as sleep disturbances and cardiovascular risk.

Considering all the above information, it can be concluded that glymphatic clearance-targeted pharmacological interventions could be effective. Based on cell studies, the modulators of AQP4 might be a potentially novel and viable strategy [38].

Genetic factors

Studies indicate a significant role for genetic factors in the functioning of GS and the development of AD.

The *BIN1* gene has been identified as a risk locus for AD by altering tau clearance, contributing to the progression of tau pathology associated with AD [21]. The *BIN1* rs744373 polymorphism has been described as a modulator of tau clearance. It comprises two alleles: A (major allele) and G (minor allele). The G allele is associated with AD and is considered a risk allele [21]. Significant associa-

tions were found between *BIN1* rs744373 in the CS region and EPVS. The study suggests that carriers of the G allele have an increased risk of PVS enlargement compared to carriers of the A allele. *APOE* plays a key role in Aβ metabolism, and the presence of the APOE-ε4 allele promotes its accumulation already in the asymptomatic stages of AD. This data only applies to carriers of APOE-ε4, which triggers Aβ accumulation. No associations were found in other *APOE* genotypes, suggesting that only individuals with a higher genetic predisposition to AD are associated with EPVS in CS [21,39].

Another factor described in the studies is the *AQP4* isoforms and polymorphisms. AQP4 proteins are an important component of the CSF-ISF exchange. The *AQP4* gene is translated into two isoforms, *AQP4*-M1 and *AQP4*-M23, which differ in structural properties and channel permeability, thereby influencing water transport and regulation of glymphatic flow. In the cerebral cortex of AD patients, a decreased ratio of M1 to M23 isoforms was associated with a loss of perivascular AQP4 localization, which increases susceptibility to Aβ aggregation and neurodegeneration [25].

Another study results showed that carrying the rs72878794 polymorphism, the minor allele of *AQP4*, was associated with slower cognitive decline in the Aβ-positive group, just as carrying the rs9951307 minor allele was associated with slower cognitive decline in individuals diagnosed with AD. It can be hypothesized that carrying these genetic polymorphisms delays brain function decline in individuals with AD [22,25,26].

Early manifestations of GS dysfunction

GS disorders associated with AD may present with various early clinical manifestations, such as OD, retinal vascular indices, and reduced ALPS-index.

OD occurs in up to 90% of patients with AD and precedes the onset of cognitive symptoms by several years. This is supported by the detection of early Aβ and tau proteins aggregates, among others, in the olfactory bulb and olfactory epithelium in cases of confirmed AD, probable AD, and MCI [23].

Incorporating retinal vascular parameters (RVPs) into the hippocampal PVS (Hip-PVS) analysis significantly improved diagnostic accuracy, supporting RVPs as a promising, non-invasive biomarker for early AD detection. Given the shared embryonic origin and structural similarities of retinal and brain microvessels, RVPs reflect CNS microvascular status and its changes, including decreased vessel density, are associated with cognitive decline. Both Hip-PVS and RVPs effectively distinguished AD patients from healthy controls, with RVPs correlating with glymphatic dysfunction and cognitive impairment. Assessed glymphatic dysfunction was shown to mediate the association between reduced retinal vessel density and cognitive impairment [34].

The reduced ALPS-index in MCI, SCD and prodromal AD indicates that glymphatic dysfunction and AD-related pathological changes occur very early in the disease. This may make the ALPS-index a valuable parameter for identifying individuals with Aβ pathology prior to the onset of dementia [3,40–42].

However, early stages of AD are characterised by focal rather than generalised Aβ and tau deposition, which limits the sensitivity of the DTI-ALPS method to the earliest lesions [43]. Other studies conducted in groups with varying degrees of cognitive impairment have shown that a higher ALPS-index reduces the risk of developing MCI by 40% and delays its onset by 1.4 years in the cognitively normal group, whereas in MCI group it delays the progression of MCI to AD by 2 years. A lower ALPS-index, on the other hand, correlated with an increased risk of MCI [2].

Research based on early stages of cognitive decline

GS is being studied not only in AD patients but also in healthy populations or those with

risk factors, providing a better understanding of changes that precede the development of dementia. The results of these analyses underscore the importance of biomarkers that identify glymphatic dysfunction before the onset of clinical symptoms [2,18].

Highlighting the importance of sleep and circadian rhythms in glymphatic function

Studies have shown that shorter sleep duration and reduced sleep quality promote increased Aβ accumulation, highlighting the importance of sleep in regulating brain clearance mechanisms [44]. Aging, a major risk factor for neurodegenerative diseases, including AD, is associated with circadian rhythm disruptions and sleep deficits that further exacerbate GS dysfunction. The glymphatic clearance relies on AQP4-dependent astrocytic fluid transport and becomes more than twice as effective during sleep. Research indicates that sleep disorders, aging, and neuroinflammation impair GS function, contributing to the accumulation of neurotoxic proteins and increasing the risk of AD development [26].

CONCLUSIONS

The GS function depends on the activity of astrocytes and AQP4. It is especially active during sleep and highly dependent on circadian cycles. GS impairment is a promoter leading to changes that disrupt normal CNS function, resulting, for example, in Aβ accumulation and neurodegeneration. The disorders of the GS appear not only in AD, but also in the early stages of cognitive disorders. Glymphatic function can be assessed using DTI-ALPS, imaging of EPVS, or increased volume of CP.

A more detailed understanding of the functioning of GS, the early symptoms of its dysfunction, and methods of monitoring it may contribute to early diagnosis, the development of drugs that can aid in the removal of neurotoxic molecules, and enable treatment monitoring.

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