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Review

AGING BRAIN, DEMENTIA AND IMPAIRED GLYMPHATIC PATHWAY: CAUSAL RELATIONSHIPS

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SUMMARY

Cellular and molecular processes that are of key importance in the development of neuroinflammation and increased cytokine response, activation of microglia and astrogliosis, contributing to the accumulation of metabolites and aberrant proteins in the brain tissue due to their overproduction and insufficient clearance, concomitant disturbance of architecture and sleep patterns are interconnected and induce brain aging with the formation its complex neurobiological mechanism. The study of these processes brings us closer to understanding the main determinants of healthy and unhealthy aging, primary prevention and preclinical diagnosis of age-related diseases, as well as to solving problems of longevity and increasing quality of life. The imbalance of homeostatic functions that support the exchange of fluids and solutes in the brain tissue is observed both in physiological aging and in the development of pathology of the nervous system with long-term consequences - from impaired synaptic signaling to the development of neurodegenerative diseases. Dementia is one of the major health problems worldwide and is very complex in terms of pathophysiology. Therefore, one of the priorities of fundamental neurobiology is to elucidate the main morbid mechanisms of Alzheimer's disease as the most common form of dementia. The hypotheses of β-amyloid and tau protein largely explain the main pathological features of Alzheimer's disease, however, there remains a need for further research on biomarkers with high validity and predictive applicability in people without cognitive impairment and clinical symptoms and in the early stages of the disease. There is a need to intensify the search for effective solutions to slow or stop the progression of the disease, especially therapeutic approaches that modify the disease at the preclinical stage, when it is most beneficial to change its course. At the same time, the discovery of aquaporin-dependent clearance pathways in the brain made it possible to identify new mechanisms underlying the etiology and progression of neurodegeneration and neuroinflammation. Glial-mediated clearance plays a fundamental role in the process of physiological aging, the development of age-related changes in the brain, and neurodegenerative processes. We analyzed 273 articles posted in PubMed database selected by keywords "glymphatic system, Alzheimer's disease, dementia, amyloid Aβ, aquaporin, aging, brain clearance". A total of 102 full-text articles were included in this review. This article presents up-to-date evidence on the causes and consequences in the study of the relationship between dysfunction of the glymphatic pathway and the accumulation of pathological proteins with insufficient excretion of toxic metabolites from the brain parenchyma, which is considered a key factor in the development of Alzheimer's dementia.

Key words: *glymphatic - dementia - neurodegeneration - Alzheimer's disease - amyloid Aβ - aquaporin - aging - brain clearance*

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INTRODUCTION

Dementia is the leading cause of disability and one of the most economically burdensome diseases. With a prevalence of 5-7% in people over 60 years of age and an increasing life expectancy of the population, more than 70 million people are expected to have dementia by 2030 (Revi et al. 2020, Guo et al. 2020). At the same time, Alzheimer's disease (AlzD) is the most common type of dementia with an estimated lifetime prevalence of 3-4%, characterized by abnormal expression and processing of specific proteins - amyloid Aβ and tau protein, which, when accumulated, aggregate and form toxic amyloid plaques and neurofibrillary tangles (Bondi et al. 2017, Tarutani et al. 2022). One of the modern tasks of fundamental science and applied medicine in expanding knowledge about Alzheimer's dementia is to elucidate the key pathogenetic mechanisms of the development of this proteinopathy and to find solutions to slow down and stop its progression. Although current pharmacological approaches can delay cognitive decline, there are still no global disease-modifying therapeutic strategies (Atri 2019, Tahami Monfared et al. 2022).

Currently, the concept of the glymphatic system has been formed, which hydrodynamically connects the cerebrospinal fluid with the lymphatic vessels of the meninges through the interstitium of the brain (Iliff et al. 2012, Nedergaard 2013). The molecular mechanisms of the functioning of the glymphatic pathway continue to be studied, however, the main patterns of solute transport and metabolite clearance are largely determined (Hladky et al. 2022). The glymphatic system has been shown to clear amyloidogenic proteins mediating the development of Alzheimer's dementia, with a significant age-related decrease in glymphatic activity noted in mouse models (Peng et al. 2016). Disruption of glial-mediated transport can initiate a cascade of events affecting the clearance of waste products and metabolites in the brain, which subsequently leads to neurodegeneration and dementia (Nedergaard et al. 2020, Bah et al. 2023). In general, the significance of the glymphatic system in cerebral hydrodynamics (Figure 1), the features

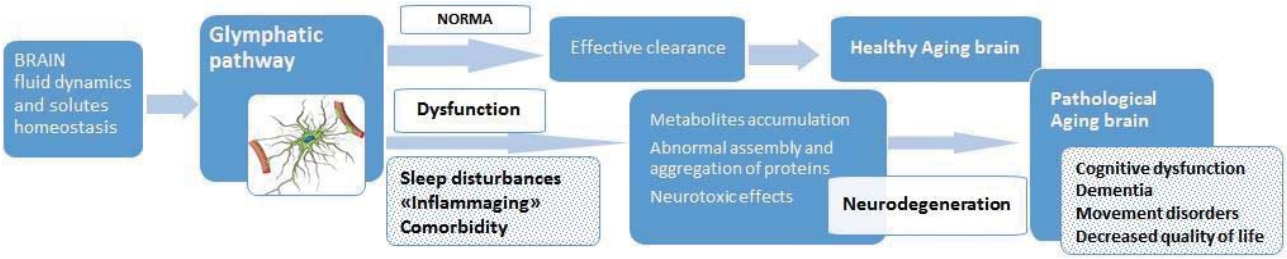

Figure 1. Glymphatic transport of water and solutes in normal and pathological conditions. Pathway to healthy or pathological aging of the brain

of its functioning in concomitant cerebral pathology, and possible dysfunction during aging determine its key role in the pathogenesis of neurodegenerative proteinopathies characterized by abnormal protein aggregation and insufficient removal of neurotoxic metabolites, in particular, in the development cognitive impairment and dementia (Rasmussen et al. 2018, Wu 2021).

ALZHEIMER'S DISEASE AS THE MOST COMMON TYPE OF DEMENTIA

Dementia as a polyetiological neuropsychiatric syndrome is characterized by impaired memory and other cognitive dysfunctions. The number of people with dementia worldwide is currently 55 million, up from 20 million in 1990 and estimated to reach over 70 million by 2030 (Gauthier et al. 2021, Erkkinen et al. 2018). Population aging is seen as the main reason for the increase in the prevalence of dementia. Since there is a pronounced upward trend in life expectancy, and the phenomenon of aging is global, affecting the population of both developed and developing countries, more than 130 million people with dementia can be predicted by 2050 (Aramadaka et al. 2023). Alzheimer's disease, as a neurodegenerative disease, is the most common type of dementia, followed by vascular dementia, Lewy bodies disease, and frontotemporal dementia. Overall, Alzheimer's dementia accounts for up to 70% of all cases (Revi et al. 2020, Fang et al. 2023).

A heterogeneous group of neurodegenerative diseases is characterized by the deposition in the brain of aggregated proteins such as Aβ-amyloid, tau, α-synuclein, TDP-43 (Goedert 2015, Sengupta et al. 2022). In the sporadic form of AlzD, amyloid accumulation begins more than 20 years before the onset of the disease without any symptoms due to impaired excretion of metabolites and neurotoxic brain debris, and not only due to overproduction of amyloidogenic peptides (Livingston et al. 2020). AlzD is characterized by continuous progression from the preclinical stage to the stage of mild cognitive impairment and subsequently to dementia with disability in everyday life. Amyloid-beta plaques and tau protein phosphorylation in intraneuronal neurofibrillary tangles are the main and classic features of AlzD pathology (Patterson et al. 2015). Amyloidogenic protein aggregates are neurotoxic and cause neuroinflammation and neurodegeneration, but in general AlzD has a heterogeneous etiology and multifactorial pathogenesis (Mawuenyega et al. 2010, Jack et al. 2015, Gordleeva et al. 2020, Zakharov et al. 2021, Frolov et al. 2023). To ensure effective therapy and prevention of dementia, it is necessary to intervene as early as possible in the pathogenesis of the neurodegenerative process. Disease-modifying therapies in the preclinical stages of dementia may be most effective, but early and highly specific tools are required to assess and monitor the onset and progression of the disease, even before significant cognitive decline occurs (Diack et al. 2016, Abubakar et al. 2022).

Biomarkers of AlzD and cognitive impairment based on the study of peripheral blood and CSF continue to be intensively developed, the classical ones are quantitative indicators of Aβ and tau protein. Also, in accordance with the results of large cohort studies, the content of pathological proteins in plasma correlates with Aβ load, assessed using amyloid PET (Jack et al. 2013. Hernaiz et al. 2022). The combination of these blood-based biomarkers can predict the onset of AlzD, however, they are not definitive diagnostic points for assessing response to therapy, as a reduction in amyloid deposition on PET is not always associated with an improvement in cognitive function (Abubakar et al. 2022, Carrera-Gonzalez et al. 2022). In general, it is quite difficult to assess mild changes in cognitive decline in the preclinical stages (Jansen et al. 2015). For therapeutic intervention at an earlier stage of the disease, classical neuropsychological approaches are ineffective when it is necessary to detect very minor changes. The assessment of "surrogate markers" seems to be extremely useful in the study of severe life-threatening diseases, since it makes it possible to determine the risk of their development at an early stage and to implement the necessary preventive measures. Therefore, the development of highly informative surrogate biomarkers for the early detection of cognitive impairment is vital to reduce the risk of dementia. Thus, neuroimaging of the efficiency of metabolite removal and waste excretion pathways from the brain parenchyma is a potential target in the development of surrogate biomarkers and may be useful for assessing the progression of AlzD (Klostranec et al. 2021).

ACCUMULATION AND CLEARANCE OF ABNORMAL PROTEINS

Modern scientific data indicate that impaired cerebral clearance mechanisms play a special role in the development and progression of the pathology of abnormal protein aggregation, the formation of their fibrillar insoluble structures and deposition in the form of histopathological inclusions during the development of neurodegenerative processes (Ivanisevic et al. 2016, Keil et al. 2022). In particular, the use of stable isotopes, mass spectrometry, and dynamic neuroimaging shows that sporadic forms of late-onset AlzD have a reduced Aβ clearance rate in the CSF as a key mechanism in the pathogenesis of neurodegeneration; at the same time, the hereditary familial form of early-onset AlzD is initially associated with an increased rate of Aβ production (Suzuki et al. 2015, Carare et al. 2020). Because Aβ and tau clearance can be mediated by a combination of various intracellular or extracellular mechanisms, including enzymatic degradation and transport across the blood-brain barrier, the autophagic-lysosomal pathway, the ubiquitin-proteasome system, and the recently described glial-mediated transport pathway, dysfunction of these mechanisms may initiate and contribute to a worsening of AlzD prognosis (Harrison et al. 2020).

The problem that combines the pathological accumulation of neurotoxic protein and the search for ways to correct this disorder may be due to a lack of understanding of the dynamics of solute clearance in the brain. Cerebral interstitial fluid and cerebrospinal fluid (CSF) are two types of extracellular fluid with specific hydrodynamics in the CNS. Interstitial fluid surrounds and fills the gaps between the cells of the brain parenchyma and makes up to 15-20% of the brain fluid (Plog et al. 2018). CSF surrounds the brain and spinal cord, filling the cerebral ventricles and subarachnoid space, accounting for about 10% of intracranial fluid volume. These extracellular fluids not only provide a protective cushioning effect on the brain, but also play a critical homeostatic role in promoting nutrient and metabolic transport, electrolyte balance, and signaling (Mehta et al. 2022). Water homeostasis in these compartments is regulated by specialized water channels, the most specific of which are type 4 aquaporin (AQP-4). The absence of AQP-4 leads to a decrease in the volume-dependent clearance of interstitial solutes, pathological proteins and neurotoxic metabolites by up to 70% (Peng W. et al. 2016, Vargas-Sanchez et al. 2021).

Until recently, neuronal extracellular protein aggregates were thought to be removed by known physiological pathways such as cellular uptake, enzymatic degradation, and transport across the blood-brain barrier (Tarasoff-Conway et al. 2015). However, the recently formed concept of the glymphatic system, which determines the volumetric flow of fluid and solutes through the brain parenchyma, mediated by astrocyte function and the expression of specific aquaporin-4 water channels, opens up new horizons for understanding the clearance of metabolites and neurotoxic products (Iliff et al. 2012, Jessen et al. 2015, Nedergaard et al. 2020, Hablitz et al. 2021, Bohr et al. 2022). The use of dynamic contrast-enhanced MRI has revealed age-associated impairment of the glymphatic pathway during brain aging (Iliff et al. 2013, Ringstad et al. 2018, Kamagata et al. 2022). According to the classical amyloid hypothesis, a key event in the pathogenesis of Alzheimer's neurodegeneration is an imbalance in the production and removal of amyloid. In the aging brain, structural and functional changes in the glymphatic system cause dysfunction in the perivascular clearance of abnormal proteins and CSF and may result in subsequent cognitive decline (Reeves et al. 2019). In AlzD patients, this is also confirmed by PET scan using indicators specific to Aβ dynamics (Schubert et al. 2019). Such neuroimaging of the clearance of specific proteins and metabolites in the brain shows its effectiveness in assessing disease progression in the pathobiology of dementia (Eide et al. 2018, Klostranec et al. 2021). Over time, the pathophysiological process of the course of AlzD is characterized by the formation of a vicious circle, including the production of aberrant proteins, glymphatic dysfunction, and the subsequent accumulation of Aβ and tau biomass, which leads to impaired function and damage to neurons.

AQUAPORIN-DEPENDENT BRAIN GLYMPHATIC PATHWAY

Aquaporins are a family of transmembrane proteins that function as channels selectively permeable to water. The structure of water channels is highly conserved across phyla and species, reflecting the critical role of these proteins in maintaining water balance in cells and tissues (Yamada et al. 2023). AQP type 4 is the most abundant water channel in the brain, characterized by predominantly perivascular expression on the plasma membrane of astrocytes (Peng S 2023).

The functions of AQP-4 under physiological conditions remained uncertain until its role in extracellular fluid flow, cerebral fluid dynamics, and as a key molecule in the brain's glymphatic system was discovered (Mestre et al. 2018, Ding et al. 2023). The glymphatic pathway is mediated by the activity of astroglia and has functional similarities and a final exit to the peripheral lymphatic system, which is reflected by the authors in its title (Iliff et al. 2012, Nedergaard 2013, Kress et al. 2014, Jessen et al. 2015). The concept of the glial-dependent perivasal transport in the brain continues to evolve. The current model includes a network of extravascular channels that circulate CSF and interstitial fluid through the brain parenchyma. The influx of cerebrospinal fluid from the ventricular system into the subarachnoid spaces and subsequently into the

periarterial canals organizes a volumetric flow due to arterial pulsation, changes in inspiratory and expiratory pressure, and CSF production. Periarterial glymphatic transport is then mediated by astroglial AQP-4 and directed to the brain interstitium, where CSF is mixed with brain extracellular fluid containing abnormal proteins, neurotoxic products, and other metabolites. Eventually, fluid with solutes drains through the perivenous space or crosses the dura mater and is cleared into the cervical lymphatics (Louveau et al. 2017, Lundgaard et al. 2017, Salman et al. 2021, Nauen et al. 2022).

The glymphatic cerebral transport pathway was first discovered and characterized in animal experiments, subsequent studies using dynamic contrast-enhanced MRI showed that it is also present in humans, and arterial pulsation is one of the driving forces of this convective flow (Eide et al. 2018, Albargothy et al. 2018, Ringstad et al. 2018). The specialized AQP-4 water channel is critical for the normal functioning of the glymphatic system, and its key role has been confirmed in AQP-4 gene knockout mice, as well as in pharmacological blockade with inhibitors of the astroglial water channel. Compared to the diffusion transport of molecules, the expression of aquaporins on plasma membranes increases water permeability and hydrodynamics in general up to 10 times (Zhang J et al. 2022, Alghanimy et al. 2023).

Defects in AQP-4 promote the development of neurofibrillary tangles pathology and neurodegeneration in the posttraumatic brain (Wang Y et al. 2022). Decreased glymphatic clearance with concomitant impairment of AQP-4 perivascular expression, pathological changes in cerebral hydrodynamics in patients with AlzD confirm that brain aging and neurodegeneration processes are associated with glymphatic dysfunction (Peng W et al. 2016, Buccellato et al. 2022). Neuroimaging using methods PET and MRI demonstrate reduced CSF water influx in AlzD patients compared to controls and in APP transgenic mice (Tang et al. 2022, Aramadaka et al. 2023). Genetic analysis revealed that single nucleotide polymorphisms in the noncoding AQP-4 regions are associated with cognitive decline in follow-up of patients after diagnosis of AlzD. AQP-4-deficient mice exhibit increased amyloid deposition, cognitive dysfunction, and epileptiform neuronal activity in a mouse model of Aβ pathology (Xu Z et al. 2015, Burfeind et al. 2017, Silva et al. 2021) Deletion of AQP-4 in tau transgenic mice not only increases the levels of a specific protein in the CSF, but also significantly exacerbates tau pathology and neuronal loss, pointing to glymphatic clearance dysfunction as one of the causes of tau-related neurodegeneration (Abe et al. 2020).

While AQP-4 deficiency increases the pathology of both Aβ and tau, accumulation of these aberrant proteins may in turn affect AQP-4 expression or localization. Loss of perivascular AQP-4 expression correlates with decreased glymphatic clearance, which is suppressed in α-syntrophin knockout mice (Ishida et al. 2022, Wang M et al. 2021). Expression of AQP-4 shows a pronounced perivascular polarization in wild-type mice, however, such expression is impaired in known mouse models of AlzD, where there is a significant increase in the parenchymal localization of the water channel. In particular, the experiments revealed a decrease in glymphatic clearance with a concomitant functional decrease in the exchange of interstitial and CSF flows in APP transgenic mice, as well as dysfunction of AQP-4 polarization in rTg4510-tau mice, modeling important aspects of tau pathology (Xu et al. 2015, Harrison et al. 2020, Marin-Moreno et al. 2023). Similar to the results in experimental animals, post-mortem histological analysis of human brain tissues also demonstrated a violation of the perivascular localization of AQP-4 and an association with pathology of Aβ-amyloid and phosphorylated tau. Despite the fact that the number of AQP-4 molecules, according to immunohistochemical analysis, even increased with age, the polarity of the specialized water channel was preserved only in older people without cognitive impairment; moreover, the loss of AQP-4 perivascular expression correlated with clinically confirmed cases of dementia and disease stage. (Zeppenfeld et al. 2017, Simon et al. 2022). In general, such observations confirm the presence of a vicious circle between glymphatic clearance and the formation of AlzD pathology.

Reactive gliosis as a sign of degeneration of the glymphatic system and its initial pathophysiological changes can directly induce AQP-4 overexpression in astrocytes, as demonstrated by increased levels in the CSF. An alternative theory considers neurodegeneration to be the cause of the loss of protein selectivity at the astrocyte plasma membrane, which slows down glymphatic flow, thus requiring overexpression of specialized water channels as a positive feedback mechanism (Wang M et al. 2021, Salman et al. 2021, Arighi 2022). In general, whether neurodegeneration causes glymphatic dysfunction or vice versa remains a matter of debate to date. However, clinical studies and studies of fundamental molecular relationships confirm that both mechanisms act synergistically with a direct link, highlighting the special role of astroglial-mediated metabolite transport in the pathogenesis of storage diseases in general and the development of AlzD in particular (Zhou et al. 2020, Gouveia-Freitas et al 2021, Mogensen et al. 2021).

Additional information about the relationship between the pathobiology of the development of the neurodegenerative process and glymphatic insufficiency was obtained by studying changes in the sleep-wake cycle and the pathology of natural sleep (Xie et al. 2013, Zhang R et al. 2020). Night sleep during aging is characterized by a number of features, including a decrease in the proportion of deep slow wave sleep with a signi-

ficant predominance of superficial stages. In addition, AlzD patients often experience impaired architecture and reduced sleep quality, including episodes of insomnia and daytime sleepiness, which correlate with cognitive decline (Fultz et al. 2019). According to current data, the glymphatic system is more active during natural sleep than during wakefulness, which may be due to changes in the extracellular space that modulate fluid resistance (Achariyar et al. 2016, Hablitz et al. 2020). A consequence of this physiological suppression of glymphatic clearance may explain why the levels of extracellular Aβ and tau in the interstitial fluid of the brain are higher during wakefulness (Holth et al. 2019). Pharmacological enhancement of slow-wave sleep or its long-term stimulation in mouse models of neurodegenerative diseases improves glymphatic function, perivascular expression of AQP-4, and reduces the accumulation of tau protein, α-synuclein, and β-amyloid (Ju et al. 2017, Vasciaveo et al. 2023). At the same time, age-related disturbances in the regulation of the sleep-wake cycle, changes in the architecture and depth of sleep not only correlate with a decrease in cognitive functions in the elderly, but also contribute to impaired glymphatic clearance of metabolites, the accumulation of amyloid proteins, and the progression of neurodegenerative processes (Reddy et al. 2020). Therefore, modulation and normalization of the sleep-wake cycle by pharmacological and non-pharmacological methods offers therapeutic potential for the regulation of glymphatic function and the prevention of dementia (Bah et al. 2019, Morawska et al. 2021).

Despite active scientific interest in the role of AQP-4 in the transport of neurotoxic metabolites and dysfunction of this pathway in the pathogenesis of neurodegenerative disorders, from a therapeutic point of view, the question remains how to effectively influence glymphatic clearance in order to slow down and prevent the progression of such diseases (Verghese et al. 2022, Soden et al. 2022). The astroglial water channel may be a promising therapeutic target in AlzD. In particular, the possibility of direct facilitation of the function of this transmembrane protein is being considered, another strategy is the regulation of the delivery and expression of AQP-4 to the plasma membrane (Lohela et al. 2022, Alghanimy et al. 2023). The study of AQP-4 polymorphisms has expanded knowledge of the genetic predisposition to neurodegenerative diseases and highlighted the association of AQP-4 polymorphisms with cognitive characteristics in the pathophysiology of Alzheimer's dementia (Burfeind et al. 2017, Rainey-Smith et al. 2018, Chandra et al. 2021). However, studies on the manipulation of the glymphatic system, such as with AQP-4 inhibitors or neuroprotective agents, are very limited (Tithof et al. 2022, Li et al. 2023). New approaches regarding the development of suitable in vitro models and theoretical network models for screening and studying the pharmacological regulation of AQP-4 function could significantly expand translational research in this area (Feng et al. 2020, Huang et al. 2021, Hajal et al. 2022, Spitz et al. 2023).

CONCLUSION

Transport and drainage of fluid and solutes in the brain is a complex integrated system, while the glymphatic pathway and its aquaporin-dependent clearance mechanism have deep causal relationships in the pathogenesis of cognitive impairment, the development and progression of dementia. A rational therapeutic intervention to modify the glymphatic system is unknown and is being actively studied. It is hypothesized that behavioral or pharmacological approaches that positively influence the architecture and quality of nocturnal sleep may improve glymphatic clearance, especially in the early stages of Alzheimer's disease. Thus, an increase in the function and efficiency of the glymphatic system can help prevent or slow down the accumulation of pathological proteins in the brain, which can rightly be considered a promising target in the areas of prevention and therapy of neurodegenerative diseases and the pursuit of active and successful longevity. Finally, it seems particularly important to identify informative neuroimaging markers for detecting changes in the glymphatic system, and to consider non-invasive methods as accessible and valid tools for detecting glymphatic dysfunction at preclinical stages and in cognitively healthy people.

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Contribution of individual authors:

Igor Shirolapov & Alexander Zakharov analyzed the data with advice from Daria Smirnova & Mariya Sergeeva.

Igor Shirolapov wrote the first draft of the manuscript, which has been revised by Alexander Zakharov, Daria Smirnova & Elena Khivintseva and upon input from the other co-authors.

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