Aquaporin-4 as the Main Element of the Glymphatic System for Clearance of Abnormal Proteins and Prevention of Neurodegeneration: A Review

IGOR SHIROLAPOV[1,2], ALEXANDER ZAKHAROV[1, 3], SAIKAT GOCHHAIT[1,4], VASILIY PYATIN[1, 2], MARIYA SERGEEVA[1,2], NATALIA ROMANCHUK[1,2], YULIYA KOMAROVA[1], VLADIMIR KALININ[3], OLGA PAVLOVA[2], ELENA KHIVINTSEVA[3]

[1]Research Institute of Neurosciences,
Samara State Medical University,
RUSSIA

[2]Department of Physiology,
Samara State Medical University,
RUSSIA

[3]Department of Neurology,
Samara State Medical University,
RUSSIA

[4]Symbiosis International (Deemed University),
INDIA

Abstract: - **Background**: In the last decade, the concept of the Glymphatic system as a complexly organized perivascular transport has been formed, it "connects" the cerebrospinal fluid with the lymphatic vessels of the meninges through the extracellular space of the brain. The exact molecular mechanisms of the functioning of the glymphatic pathway have not been fully characterized, but its key role in the cerebral clearance of metabolites and neurotoxic substances is noted. Neurodegenerative diseases affect millions of people around the world, and the most common pathologies from this heterogeneous group of diseases are Alzheimer's disease and Parkinson's disease. Their pathogenesis is based on abnormal protein aggregation, formation of neurofibrillary insoluble structures, and inefficient removal of neurotoxic metabolites. **Aim:** This article reviewed the evidence linking glymphatic system dysfunction and the development of human neurodegenerative diseases, and noted the key role of aquaporin-4 in the clearance of metabolites from the brain. **Setting and Design:** The actual sources of data were compiled and reviewed from PubMed, Scopus, and Web of Sciences from 2012 to 2023. **Result and Discussion:** Glial-dependent perivascular transport promotes the clearance of interstitial solutes, including beta-amyloid, synuclein, and tau protein, from the parenchymal extracellular space of the brain in normal and pathological conditions. An increase in the proportion of metabolites and pathological proteins in the dysfunction of the glymphatic pathway enhances the progression of cognitive impairment and neurodegenerative processes. In turn, the aging process, oxidative stress, and neuroinflammation in Alzheimer's disease and Parkinson's disease contribute to reactive astrogliosis and may impair glymphatic clearance. **Conclusion:** This review describes in detail the features of the glymphatic system and discusses that its dysfunction plays a fundamental significance in the pathological accumulation of metabolites during the progression of neurodegeneration and neuroinflammation. Understanding these processes will make it possible to take new steps in the prevention and treatment of neurodegenerative diseases.

Key-Words: - glymphatic system, neurodegenerative diseases, amyloid, tau protein, aquaporin-4, astrocytes.

Received: May 21, 2022. Revised: August 24, 2023. Accepted: September 19, 2023. Published: October 9, 2023.

1 Introduction

Imbalances in homeostatic functions that maintain fluid exchange and solutes included in the brain tissue, which can be observed both in normal conditions and in the development of neuropathology, have long-term consequences from impaired synaptic signaling to the onset of neurodegenerative diseases (ND), [1]. Recent studies of the glymphatic system form new insights into metabolite clearance and natural sleep function

during physiological aging and the pathogenesis of ND. The glial-dependent pathway functions predominantly during natural sleep and promotes the excretion of neurotoxic substances in the CNS, [2], [3], [4]. This highly organized cerebral transport system includes perivascular spaces and astrocyte cells, as well as aquaporin-4 (AQP4) water channels. Studies have shown that the glymphatic system is responsible for the clearance of proteins responsible for the development of ND, including Alzheimer's disease and Parkinson's disease, and in experiments on mice, a significant age-related decrease in glymphatic activity has been noted, [5], [6], [8], [9]. These observations may explain the increased vulnerability to neurodegenerative processes and cognitive decline in the elderly, as glymphatic pathway dysfunction initiates further accumulation of neurotoxic proteins and progression of ND, [10].

Failure of glymphatic transport has significant and long-term consequences for humans, [11]. The importance of the glymphatic system in cerebral hydrodynamics, the features of its functioning during brain aging, and possible disorders make it relevant to study it in depth and many ways in conjunction with the pathogenesis of neurodegeneration characterized by abnormal protein aggregation and insufficient removal of neurotoxic metabolites.

2 Literature Review

Neurodegeneration and aging

Selective and progressive death of neurons is a characteristic feature of neurodegeneration processes and leads to certain neuronal dysfunctions. Neurodegenerative diseases, the most known of which are Alzheimer's disease and Parkinson's disease, are responsible for a significant proportion of cognitive and motor impairments in the elderly. These pathologies affect more than 50 million people worldwide, with the vast majority of cases being sporadic, [12]. ND is based on the processes of abnormal aggregation of proteins such as Aβ-amyloid, α-synuclein, tau protein, TDP-43, and others, the formation of neurofibrillary insoluble structures and their deposition in the form of histopathological inclusions in the tissues of the nervous system, [13] . It is noted that the frequency of ND increases with age, which is considered the most important non-modifiable risk factor for their development. Determination of the level of Aβ42-peptide is used as a biomarker of Alzheimer's disease, with the progression of the disease, its amount changes due to accumulation in the tissue. Since extracellular amyloid-beta takes a certain amount of time to be removed before it can be incorporated into plaques, stable isotope tracers have found that its turnover rate slows down with age, [14], [15], [16].

The past study has analyzed more than a thousand people aged 30-95 years and found an increase in the risk of Alzheimer's disease with age, especially in people over 70 years of age, [17]. Also, in cognitively healthy individuals, ligand retention progressively increases with age in PET examination with amyloids. The authors suggest that the presence of at least one marker of cerebral amyloidosis in the study of cerebrospinal fluid or PET scans of cognitively normal individuals may be sufficient to establish a diagnosis of an ND even in the absence of any clinical manifestations, [18], [19] . At the same time, determining the onset of the disease is especially important for its prevention, since it is impossible to establish what proportion of healthy people with positive biomarkers will progress to the clinical state of Alzheimer's disease. A meta-analysis of the age-associated prevalence of a positive beta-amyloid biomarker in three thousand people with normal cognitive abilities revealed that between the ages of 50 and 90 years, amyloid pathology increased from 10% to 44%. Simultaneously, a 20-30-year time interval was noted between the first determination of a positive amyloid biomarker and the onset of clinical manifestations of dementia, [20] Even though great progress has been made in understanding the pathogenesis of neurodegeneration to date, initially most of the research was focused on the study of biomarkers and not on the analysis of principal pathophysiological mechanisms, [21], [22], [23].

Glymphatic Pathway

With the accumulation of neurotoxic proteins in the extracellular space, the immune effectors of the CNS are activated, removing them and simultaneously secreting pro-inflammatory cytokines, [24], [25]. Amyloid-like proteins in misfolded conformations and as neurotoxic oligomers induce a reactive microglial response that contributes to the subsequent degeneration of synapses and neurons. Such proteins are highly productive: for example, for β-amyloid, the frequency is up to one molecule per second for each neuron. Neurotoxic effects and microglial response require highly efficient clearance mechanisms to prevent their accumulation and progression of neuroinflammation and neurodegeneration, [26]. The cleaning can occur through degradation by enzymes or cellular uptake by neurons and glia. There is strong evidence for clearance of Aβ and tau protein into the cerebrospinal fluid, and the blood-brain barrier is not the only CNS pathway for these proteins, [27]. Animal studies have identified

alternative clearance pathways in which solutes and specific tracers that are not normally able to cross the blood-brain barrier in large numbers are cleared along the blood vessels into the meningeal lymphatics, [28]. The so-called "glymphatic pathway" is a glial-mediated highly organized fluid transport system and can be considered the central clearance system in the brain in both animals and humans. The concept of the glymphatic system is proposed based on scientific studies in which the authors demonstrated predominantly convective pathways for the movement of cerebrospinal fluid and solutes using MRI neuroimaging. Dynamic contrast-enhanced MRI has made it possible to deeply study cerebral hydrodynamics in experimental animals and has contributed to real-time neuroimaging of perivascular inflow and fluid exchange, [29], [30], [31], [32], [33]. After intracisternal injection of a fluorescently labeled tracer, the scientists observed a subarachnoid influx of CSF into the periarterial spaces and further into the brain parenchyma, where it mixed with the interstitial fluid, followed by perivenous outflow. It was shown that the rate of elimination of substances was significantly higher than in the study of diffusion processes, and the pulsation of cerebral arteries is a key factor in perivascular exchange. The cervical lymph nodes, which have a higher level of amyloid compared to other regional lymph nodes, are considered the primary gateway for the entry of amyloid excreted from the brain parenchyma into the systemic lymphatic circulation, [34], [35]. Thus, the consideration of certain mechanisms of cerebral transport of substances contributed to the discovery that a significant part of the liquor enters the brain tissue by the perivascular route, and in the same way it is removed.

The pathological relationship between the development of neurodegenerative processes and dysfunction of the glymphatic pathway is confirmed in animal experiments, [36]. In mouse models of neurodegeneration, a significant decrease in interstitial solute clearance has been found concomitant with an increase in β-amyloid levels. These results have been observed in AQP4-knockout rodents, suggesting that this cerebral fluid transport is controlled by a specialized bidirectional astrocyte water channel. In particular, dynamic contrast-enhanced MRI showed a 55% reduction in parenchymal clearance of Aβ protein, [28], [37], [38]. These results support the hypothesis that a significant fraction of soluble amyloid is excreted by the perivascular route, as opposed to local removal across the blood-brain barrier.

Aquaporin-4 and its key significance

The terminal feet of astrocytes are attached to the wall of cerebral vessels; as a result, an exchange of substances can occur between endotheliocytes and the brain parenchyma. Glymphatic transport facilitates the clearance of interstitial solutes, including beta-amyloid and tau, from the parenchymal extracellular space of the brain, [39], [40]. Astrocytes release various bioactive substances, neurotrophic factors, cytokines, and express transport proteins and receptors, one of which is the AQP4 water channel. A close correlation between this protein and glymphatic function was found in studies in AQP4 knockout mice in which deletion of the water channel caused impaired glymphatic clearance and intraneuronal accumulation of amyloid proteins, [41], [42], [43].

Currently, the physiological mechanism of AQP4-associated regulation of perivascular-parenchymal transport continues to be studied. Expression of aquaporin-4 on the plasma membrane of astrocytes regulates cerebral water homeostasis, and its pharmacological inhibition contributes to the formation of edema, [43], [44]. This highly selective water channel is maximally expressed at the terminal perivascular sites of astrocytes, where it covers a large percentage of the surface due to association with DAC. The size of astrocyte terminals varies along the vascular network, correlating with the diameter of the vessels. In fluid dynamics modeling, this change provides a nearly constant flow through the glial spaces, [45]. Solutes can pass from the periarterial spaces into the brain parenchyma directly through the AQP4 and astrocyte bodies or the gaps between the astrocytic end feet. This process is modulated, and the deletion of this water channel, and the defection of its localization or polarization reduces glymphatic flow, [46] . It is assumed that various biomolecules can act as mediators and activators of glymphatic transport, facilitating AQP4-dependent hydrodynamics. In particular, studies using DCE-MRI are investigating the significance of the TGN-073, which has been shown to increase diffusional water transport in the rat brain, [47] .

Impaired perivascular polarization of aquaporin-4 correlates with a progressive decline in the efficiency of glymphatic clearance in the aging brain, [48]. In the mouse model of Alzheimer's disease with extensive Aβ-amyloid deposits, glymphatic transport of radioiodine-labeled protein in older animals was reduced by 40% more than in younger animals. Glymphatic clearance is reduced to significant amyloid deposits in younger APP/PS1 mice expressing amyloid precursor protein and mutant presenilin-1, compared to age-matched controls, [49]. Soluble amyloid oligomers, as their

more toxic form, are found predominantly not in the cerebral parenchyma, but perivascularly near AQP4-positive astrocytes. Moreover, compared with young mice, the levels of soluble and insoluble Aβ40 and Aβ42 were increased almost 2-fold, and the number of soluble oligomers was increased 6-fold in older mice .

A comparative analysis of the AQP4 cerebrospinal fluid level in patients with clinically confirmed ND revealed an almost 2-fold increase compared to healthy people, [4]. A positive correlation of the level of tau protein was noted with signaling proteins and molecules involved in the processes of expression and fixation of aquaporin-4 at the perivascular ends of astrocytes, which additionally links the role of this water channel with the pathogenesis of proteinopathic diseases. In mouse models, deletion of aquaporin-4 significantly increased levels of tau in the cerebrospinal fluid of transgenic mice expressing mutant tau and promoted increased deposition of its phosphorylated form, exacerbating subsequent neuronal degeneration, [50], [51] . Genetic studies of single nucleotide polymorphisms showed a functional relationship between the genetic variability of the AQP4 channel and its efficiency, impact on accumulation and clearance of amyloid, cognitive decline, progression of the ND and its outcome, [52], [53], [54].

Since oligomers and neurofibrillary lesions stimulate the release of pro-inflammatory cytokines with the participation of microglia, inflammation is an important link in the pathogenesis of the neurodegenerative process. In experiments on knockout mice, the microglial response increases phagocytosis of Aβ-amyloid in the cerebral cortex. At the same time, the selective elimination of microglia in the frontal cortex of mice leads to the deposition of Aβ protein. Simultaneously, suppression of the expression of Apolipoprotein E reduces intraneuronal amyloid levels in a mouse model of neurodegeneration and the deletion of aquaporin-4 in such mice, [55].

Pharmacological enhancement or long-term stimulation of slow-wave sleep in animal models of Parkinson's disease and Alzheimer's disease promotes glymphatic transport, perivascular expression of AQP4, and reduces the accumulation of α-synuclein and β-amyloid. A potential relationship between the activity of the glymphatic system and the quality of sleep, dysfunction of clock genes, and dysregulation of circadian rhythms in ND was noted, [56], [57], [58]. The correlation between proteinopathies and disorders in the sleep-wake cycle confirms the fundamental role of normal natural sleep in the elimination of neurotoxic substances. It has been established that glymphatic activity is significantly increased during natural sleep: perivascular CSF inflow and interstitial solute outflow occur faster during sleep compared to the waking brain, [59]. At the same time, age-related disturbances in the regulation of the sleep-wake cycle, and 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 amyloidogenic proteins and the progression of neurodegenerative processes in humans and animal experiments, [60], [61], [62], discovered perivascular aggregation of α-synuclein and abnormal polarization of AQP4 in a mouse model of Parkinson's disease. In combination with glymphatic dysfunction, neurodegeneration, and α-synuclein aggregation were further enhanced by cervical lymph node ligation, [62]. Thus, glymphatic turnover is a physiologically regulated process in which perivascular CSF inflow and clearance occur faster during sleep and are altered by circadian dynamics, [63], [64] .

3 Conclusion

Disturbance of cerebral hydrodynamics and glymphatic clearance is involved in the pathogenesis of a number of brain diseases, in particular neurodegenerative and demyelinating diseases, and sleep disorders. Changes in the glymphatic system and aquaporin-4 expression as its main determinant are reported in hydrocephalus, stroke, traumatic brain injury, cerebral amyloid angiopathy, multiple sclerosis, diabetes mellitus, and other pathologies, [65], [66], [67]. A decrease in glymphatic activity and an increase in amyloid levels can be considered as an early biomarker of the onset of neurodegeneration, and the development of methods and therapeutic approaches to restore the normal clearance of metabolites from the brain can provide an advantage in the prevention of normal aging and the treatment of ND at the preclinical stage, [68] .

In recent years, the discovery and multifaceted study of the glymphatic pathway has demonstrated its importance in maintaining cerebral homeostasis. Scientists have identified long-term consequences of an imbalance in this system of perivascular clearance, as well as significance in the progression of neurological disorders (Figure 1). Since certain neuropathology and age-related disorders occur only in humans, we believe that it is necessary to continue to look for new and offer alternative methods, including in vitro, theoretical network, and mathematical models that provide the maximum level of control and personalization,

taking into account the patient features, [69], [70], [71]. In general, metabolite clearance dysregulation associated with the assembly and accumulation of pathological proteins can be fully extrapolated to any experimental models of neurodegeneration, since it is equally associated with impaired glymphatic turnover, [72], [73].

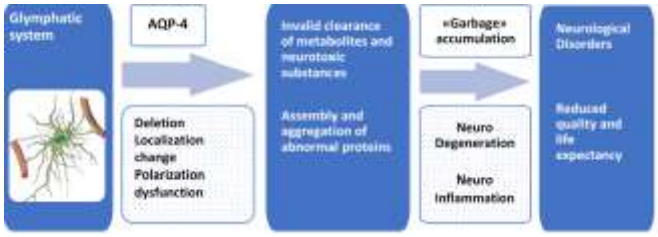

Fig. 1: Schematic demonstration of the importance of the glymphatic system in the pathogenesis of neurological disorders

References:

[1] Plog, B.A., Nedergaard, M., 2018. The Glymphatic System in Central Nervous System Health and Disease: Past, Present, and Future. Annu Rev Pathol, Vol. 13, pp. 379-394.

[2] Nedergaard, M., & Goldman, S. A., 2020. Glymphatic failure as a final common pathway to dementia. Science (New York, N.Y.), Vol. 370 No 6512, pp. 50–56.

[3] Bohr, T., Hjorth, P. G., Holst, S. C., Hrabětová, S., Kiviniemi, V., Lilius, T., 2022. The glymphatic system: Current understanding and modeling. iScience, Vol. 25 No 9, p. 104987.

[4] Xie, L., Kang, H., Xu, Q., Chen, M. J., Liao, Y., Thiyagarajan, M., O'Donnell, J., Christensen, D. J., Nicholson, C., Iliff, J. J., Takano, T., Deane, R., & Nedergaard, M., 2013. Sleep drives metabolite clearance from the adult brain. Science (New York, N.Y.), Vol. 342 No 6156, pp. 373–377.

[5] Yamada K., 2023. Multifaceted Roles of Aquaporins in the Pathogenesis of Alzheimer's Disease. International journal of molecular sciences, Vol. 24, No 7, p. 6528.

[6] Kitchen, P., Salman, M. M., Halsey, A. M., Clarke-Bland, C., MacDonald, J. A., Ishida, H., 2020. Targeting Aquaporin-4 Subcellular Localization to Treat Central Nervous System Edema. Cell, Vol. 181, No 4, pp. 784–799.e19.6429, pp. 880–884.

[7] Iliff, J. J., Lee, H., Yu, M., Feng, T., Logan, J., Nedergaard, M., & Benveniste, H., 2013. Brain-wide pathway for waste clearance captured by contrast-enhanced MRI. The Journal of clinical investigation, Vol. 123 No 3, pp. 1299–1309.

[8] Salman, M. M., Kitchen, P., Iliff, J. J., & Bill, R. M., 2021. Aquaporin 4 and glymphatic flow have central roles in brain fluid homeostasis. Nature reviews. Neuroscience, Vol. 22 No 10, pp. 650–651.

[9] Rasmussen, M. K., Mestre, H., & Nedergaard, M., 2018. The glymphatic pathway in neurological disorders. The Lancet. Neurology, Vol. 17 No 11, pp. 1016–1024.

[10] Bah, T. M., Goodman, J., & Iliff, J. J., 2019. Sleep as a Therapeutic Target in the Aging Brain. Neurotherapeutics: The Journal of the American Society for Experimental NeuroTherapeutics, Vol. 16 No 3, pp. 554–568

[11] Hablitz, L. M., & Nedergaard, M., 2021. The Glymphatic System: A Novel Component of Fundamental Neurobiology. The Journal of Neuroscience: the official journal of the Society for Neuroscience, Vol. 41 No 37, pp. 7698–7711.

[12] Diack, A. B., Alibhai, J. D., Barron, R., Bradford, B., Piccardo, P., & Manson, J. C., 2016. Insights into Mechanisms of Chronic Neurodegeneration. International Journal of Molecular Sciences, Vol. 17 No 1, p. 82.

[13] Goedert M., 2015. Alzheimer's and Parkinson's diseases: The prion concept in relation to assembled Aβ, tau, and α-synuclein. Science (New York, N.Y.), Vol. 349 No 6248, p. 1255555.

[14] Carrera-González, M. D. P., Cantón-Habas, V., & Rich-Ruiz, M., 2022. Aging, depression and dementia: The inflammatory process. Advances in clinical and experimental medicine: official organ Wroclaw Medical University, Vol. 31 No 5, pp. 469-473.

[15] Fang, Y. C., Hsieh, Y. C., Hu, C. J., & Tu, Y. K., 2023. Endothelial Dysfunction in Neurodegenerative Diseases. International journal of molecular sciences, Vol. 24 No 3, p. 2909.

[16] Patterson, B. W., Elbert, D. L., Mawuenyega, K. G., Kasten, T., Ovod, V., Ma, S., ., 2015. Age and amyloid effects on human central nervous system amyloid-beta kinetics. Annals of Neurology, Vol. 78 No 3, pp. 439–453.

[17] Jack, C. R., Jr, Wiste, H. J., Weigand, S. D., Knopman, D. S., Vemuri, P., Mielke, M. M., ., 2015. Age, Sex, and APOE ε4 Effects on Memory, Brain Structure, and β-Amyloid Across the Adult Life Span. JAMA neurology, Vol. 72 No 5, pp. 511–519.

[18] Jack, C. R., Jr, Wiste, H. J., Weigand, S. D., Knopman, D. S., Lowe, V., Vemuri, P., ., 2013. Amyloid-first and neurodegeneration-first profiles characterize incident amyloid PET positivity. Neurology, Vol. 81 No 20, pp. 1732–1740.

[19] Tarutani, A., Adachi, T., Akatsu, H., Hashizume, Y., Hasegawa, K., Saito, Y., ., 2022. Ultrastructural and biochemical classification of pathogenic tau, α-synuclein and TDP-43. Acta neuropathologica, Vol. 143 No 6, pp. 613–640.

[20] Jansen, W. J., Ossenkoppele, R., Knol, D. L., Tijms, B. M., Scheltens, P., Verhey, F. R., ., 2015. Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. JAMA, Vol 313 No 19, pp. 1924–1938.

[21] Vargas-Sanchez, K., Losada-Barragán, M., Mogilevskaya, M., Novoa-Herrán, S., Medina, Y., Buendía-Atencio, C., 2021. Screening for Interacting Proteins with Peptide Biomarker of Blood-Brain Barrier Alteration under Inflammatory Conditions. International journal of molecular sciences, Vol. 22 No 9, p. 4725.

[22] Hernaiz, A., Toivonen, J. M., Bolea, R., & Martín-Burriel, I., 2022. Epigenetic Changes in Prion and Prion-like Neurodegenerative Diseases: Recent Advances, Potential as Biomarkers, and Future Perspectives. International journal of molecular sciences, Vol. 23 No 20, p. 12609.

[23] Chen, H. L., Chen, P. C., Lu, C. H., Tsai, N. W., Yu, C. C., Chou, K. H., Lai, Y. R., Taoka, T., & Lin, W. C., 2021. Associations among Cognitive Functions, Plasma DNA, and Diffusion Tensor Image along the Perivascular Space (DTI-ALPS) in Patients with Parkinson's Disease. Oxidative medicine and cellular longevity, Vol. 2021, p. 4034509.

[24] Carare, R. O., Aldea, R., Agarwal, N., Bacskai, B. J., Bechman, I. ., 2020. Clearance of interstitial fluid (ISF) and CSF (CLIC) group-part of Vascular Professional Interest Area (PIA): Cerebrovascular disease and the failure of elimination of Amyloid-β from the brain and retina with age and Alzheimer's disease-Opportunities for Therapy. Alzheimer's & dementia (Amsterdam, Netherlands), Vol. 12 No 1, p. e12053.

[25] Ivanisevic, J., Stauch, K. L., Petrascheck, M., Benton, H. P., Epstein, A. A., Fang, M., ., 2016. Metabolic drift in the aging brain. Aging, Vol. 8 No 5, pp. 1000–1020.

[26] Kamagata, K., Andica, C., Takabayashi, K., Saito, Y., Taoka, T., Nozaki, H., ., 2022. Association of MRI Indices of Glymphatic System With Amyloid Deposition and Cognition in Mild Cognitive Impairment and Alzheimer Disease. Neurology, Vol. 99 No 24, pp. e2648–e2660.

[27] Nedergaard M., 2013. Neuroscience. Garbage truck of the brain. Science (New York, N.Y.), Vol. 340 No 6140, pp. 1529–1530.

[28] Jessen, N. A., Munk, A. S., Lundgaard, I., & Nedergaard, M., 2015. The Glymphatic System: A Beginner's Guide. Neurochemical research, Vol 40 No 12, pp. 2583–2599.

[29] Iliff, J. J., Wang, M., Liao, Y., Plogg, B. A., Peng, W., Gundersen, G. A., ., 2012. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β. Science translational medicine, Vol. 4 No 147, p. 147ra111.

[30] Kress, B. T., Iliff, J. J., Xia, M., Wang, M., Wei, H. S., Zeppenfeld, D., ., 2014. Impairment of paravascular clearance pathways in the aging brain. Annals of neurology, Vol. 76 No 6, pp. 845–861.

[31] Ringstad, G., Valnes, L. M., Dale, A. M., Pripp, A. H., Vatnehol, S. S., Emblem, K. E., Mardal, K. A., & Eide, P. K., 2018. Brain-wide glymphatic enhancement and clearance in humans assessed with MRI. JCI insight, Vol. 3 No 13, p. e121537.

[32] Eide, P. K., Vatnehol, S. A. S., Emblem, K. E., & Ringstad, G., 2018. Magnetic resonance imaging provides evidence of glymphatic drainage from human brain to cervical lymph nodes. Scientific reports, 8(1), 719433. Albargothy N., Johnston D., MacGregor-Sharp M., . Convective influx/glymphatic system: tracers injected into the CSF enter and leave the brain along separate periarterial basement membrane pathways. Acta Neuropathologica, Vol. 136 No 1, pp. 139-152.

[33] Albargothy, N. J., Johnston, D. A., MacGregor-Sharp, M., Weller, R. O., Verma, A., Hawkes, C. A., & Carare, R. O., 2018. Convective influx/glymphatic system: tracers injected into the CSF enter and leave the brain along separate periarterial basement membrane pathways. Acta neuropathologica, Мщдю 136 No 1, pp. 139–152.

[34] Nauen, D. W., & Troncoso, J. C., 2022. Amyloid-beta is present in human lymph nodes and greatly enriched in those of the cervical region. Alzheimer's & dementia: the journal of the Alzheimer's Association, Vol. 18 No 2, pp. 205–210.

[35] Kamagata, K., Andica, C., Takabayashi, K., Saito, Y., Taoka, T., Nozaki, H., ., 2022. Association of MRI Indices of Glymphatic System With Amyloid Deposition and Cognition in Mild Cognitive Impairment and Alzheimer Disease. Neurology, Vol. 99 No 24, pp. e2648–e2660.

[36] Xiao, M., Hou, J., Xu, M., Li, S., & Yang, B., 2023. Aquaporins in Nervous System. Advances in experimental medicine and biology, Vol. 1398, pp. 99–124.

[37] Xu, Z., Xiao, N., Chen, Y., Huang, H., Marshall, C., Gao, J., ., 2015. Deletion of aquaporin-4 in APP/PS1 mice exacerbates brain Aβ accumulation and memory deficits. Molecular neurodegeneration, Vol. 10, pp. 1–16.

[38] Zhang, R., Liu, Y., Chen, Y., Li, Q., Marshall, C., Wu, T., Hu, G., & Xiao, M., 2020. Aquaporin 4 deletion exacerbates brain impairments in a mouse model of chronic sleep disruption. CNS neuroscience & therapeutics, Vol. 26 No 2, pp. 228–239.

[39] Keil, S. A., Braun, M., O'Boyle, R., Sevao, M., Pedersen, T., Agarwal, S., Jansson, D., & Iliff, J. J., 2022. Dynamic infrared imaging of cerebrospinal fluid tracer influx into the brain. Neurophotonics, Vol. 9 No 3, p. 031915.

[40] Tithof, J., Boster, K. A. S., Bork, P. A. R., Nedergaard, M., Thomas, J. H., & Kelley, D. H., 2022. A network model of glymphatic flow under different experimentally-motivated parametric scenarios. iScience, Vol. 25 No 5, p. 104258.

[41] Marín-Moreno, A., Canoyra, S., Fernández-Borges, N., Espinosa, J. C., & Torres, J. M., 2023. Transgenic Mouse Models for the Study of Neurodegenerative Diseases. Frontiers in bioscience (Landmark edition), Vol 28 No 1, p. 21.

[42] Zhou, Y., Cai, J., Zhang, W., Gong, X., Yan, S., Zhang, K., Luo, Z., Sun, J., Jiang, Q., & Lou, M., 2020. Impairment of the Glymphatic Pathway and Putative Meningeal Lymphatic Vessels in the Aging Human. Annals of neurology, Vol. 87 No 3, pp. 357–369.

[43] Ishida, K., Yamada, K., Nishiyama, R., Hashimoto, T., Nishida, I., Abe, Y., Yasui, M., & Iwatsubo, T., 2022. Glymphatic system clears extracellular tau and protects from tau aggregation and neurodegeneration. The Journal of experimental medicine, Vol. 219 No 3, p. e20211275.

[44] Hladky, S. B., & Barrand, M. A., 2022. The glymphatic hypothesis: the theory and the evidence. Fluids and barriers of the CNS, Vol. 19 No 1, p. 9.

[45] Soden, P. A., Henderson, A. R., & Lee, E., 2022. A Microfluidic Model of AQP4 Polarization Dynamics and Fluid Transport in the Healthy and Inflamed Human Brain: The First Step Towards Glymphatics-on-a-Chip. Advanced biology, Vol. 6 No 12, p. e2200027.

[46] Wu, C. H., Lirng, J. F., Ling, Y. H., Wang, Y. F., Wu, H. M., ., 2021. Noninvasive Characterization of Human Glymphatics and Meningeal Lymphatics in an in vivo Model of Blood-Brain Barrier Leakage. Annals of neurology, Vol. 89 No 1, pp. 111–124.

[47] Alghanimy, A., Martin, C., Gallagher, L., & Holmes, W. M., 2023. The effect of a novel AQP4 facilitator, TGN-073, on glymphatic transport captured by diffusion MRI and DCE-MRI. PloS one, Vol. 18 No 3, p. e0282955.

[48] Zeppenfeld, D. M., Simon, M., Haswell, J. D., D'Abreo, D., Murchison, C., Quinn, J. F., 2017. Association of Perivascular Localization of Aquaporin-4 With Cognition and Alzheimer Disease in Aging Brains. JAMA neurology, Vol. 74 No 1, pp. 91–99.

[49] Peng, W., Achariyar, T. M., Li, B., Liao, Y., Mestre, H., Hitomi, E., Regan, S., Kasper, T., Peng, S., Ding, F., Benveniste, H., Nedergaard, M., & Deane, R., 2016. Suppression of glymphatic fluid transport in a mouse model of Alzheimer's disease. Neurobiology of disease, Vol. 93, pp. 215–225.

[50] Simon, M., Wang, M. X., Ismail, O., Braun, M., Schindler, A. G., Reemmer, J., ., 2022. Loss of perivascular aquaporin-4 localization impairs glymphatic exchange and promotes amyloid β plaque formation in mice. Alzheimer's research & therapy, 14(1), 59.53. Harrison I., Ismail O., Machhada A., . Impaired glymphatic function and clearance of tau in an Alzheimer's disease model. Brain, 2020, Vol 143 No 8, pp. 2576-2593.

[51] Harrison, I. F., Ismail, O., Machhada, A., Colgan, N., Ohene, Y., Nahavandi, P., 2020. Impaired glymphatic function and clearance of tau in an Alzheimer's disease model. Brain : A Journal of Neurology, Vol 143 No 8, pp. 2576–2593.

[52] Burfeind, K. G., Murchison, C. F., Westaway, S. K., Simon, M. J., Erten-Lyons, D., Kaye, J. A., Quinn, J. F., & Iliff, J. J., 2017. The effects of noncoding aquaporin-4 single-nucleotide polymorphisms on cognition and functional progression of Alzheimer's disease.

Alzheimer's & dementia (New York, N. Y.), Vol. 3 No 3, pp. 348–359.

[53] Chandra, A., Farrell, C., Wilson, H., Dervenoulas, G., De Natale, E. R., Politis, M., & Alzheimer's Disease Neuroimaging Initiative., 2021. Aquaporin-4 polymorphisms predict amyloid burden and clinical outcome in the Alzheimer's disease spectrum. Neurobiology of aging, Vol. 97, pp. 1–9.

[54] Rainey-Smith, S. R., Mazzucchelli, G. N., Villemagne, V. L., Brown, B. M., Porter, T., Weinborn, M., ., 2018. Genetic variation in Aquaporin-4 moderates the relationship between sleep and brain Aβ-amyloid burden. Translational psychiatry, Vol 8 No 1, p. 47.

[55] Feng, W., Zhang, Y., Wang, Z., Xu, H., Wu, T., Marshall, C., Gao, J., & Xiao, M., 2020. Microglia prevent beta-amyloid plaque formation in the early stage of an Alzheimer's disease mouse model with suppression of glymphatic clearance. Alzheimer's research & therapy, Vol. 12 No 1, p. 125.

[56] Vasciaveo, V., Iadarola, A., Casile, A., Dante, D., Morello, G., Minotta, L., ., M., 2023. Sleep fragmentation affects glymphatic system through the different expression of AQP4 in wild type and 5xFAD mouse models. Acta neuropathologica communications, Vol. 11 No 1, p. 16.

[57] Fultz, N. E., Bonmassar, G., Setsompop, K., Stickgold, R. A., Rosen, B. R., Polimeni, J. R., & Lewis, L. D., 2019. Coupled electrophysiological, hemodynamic, and cerebrospinal fluid oscillations in human sleep. Science (New York, N.Y.), Vol 366 No 6465, pp. 628–631.

[58] Morawska, M. M., Moreira, C. G., Ginde, V. R., Valko, P. O., Weiss, T., Büchele, F., 2021. Slow-wave sleep affects synucleinopathy and regulates proteostatic processes in mouse models of Parkinson's disease. Science translational medicine, Vol. 13 No 623, p. eabe7099.

[59] Holth, J. K., Fritschi, S. K., Wang, C., Pedersen, N. P., Cirrito, J. R., Mahan, T. E., ., 2019. The sleep-wake cycle regulates brain interstitial fluid tau in mice and CSF tau in humans. Science (New York, N.Y.), Vol. 363 No 6429, pp. 880–884.

[60] Achariyar, T.M., Li, B., Peng, W., Verghese P.B., Shi Y., McConnell E., 2016. Glymphatic distribution of CSF-derived apoE into brain is isoform specific and suppressed during sleep deprivation. Mol Neurodegeneration, Vol. 11 No 1, p. 74.

[61] Ju, Y. S., Ooms, S. J., Sutphen, C., Macauley, S. L., Zangrilli, M. A., Jerome, G., 2017. Slow wave sleep disruption increases cerebrospinal fluid amyloid-β levels. Brain : a journal of neurology, Vol. 140 No 8, pp. 2104–2111.

[62] Zou, W., Pu, T., Feng, W., Lu, M., Zheng, Y., Du, R., Xiao, M., & Hu, G., 2019. Blocking meningeal lymphatic drainage aggravates Parkinson's disease-like pathology in mice overexpressing mutated α-synuclein. Translational neurodegeneration, Vol. 8, pp. 1-17.

[63] Hablitz, L. M., Plá, V., Giannetto, M., Vinitsky, H. S., Stæger, F. F., Metcalfe, T., Nguyen, R., Benrais, A., & Nedergaard, M., 2020. Circadian control of brain glymphatic and lymphatic fluid flow. Nature communications, Vol. 11 No 1, p. 4411.

[64] Sundaram, S., Hughes, R. L., Peterson, E., Müller-Oehring, E. M., Brontë-Stewart, H. M., Poston, K. L., Faerman, A., Bhowmick, C., & Schulte, T., 2019. Establishing a framework for neuropathological correlates and glymphatic system functioning in Parkinson's disease. Neuroscience and biobehavioral reviews, Vol. 103, pp. 305–315.

[65] Tang, J., Zhang, M., Liu, N., Xue, Y., Ren, X., Huang, Q., Shi, L., & Fu, J., 2022. The Association Between Glymphatic System Dysfunction and Cognitive Impairment in Cerebral Small Vessel Disease. Frontiers in aging neuroscience, Vol. 14, p. 916633.

[66] Mehta, N. H., Suss, R. A., Dyke, J. P., Theise, N. D., Chiang, G. C., Strauss, S., 2022. Quantifying cerebrospinal fluid dynamics: A review of human neuroimaging contributions to CSF physiology and neurodegenerative disease. Neurobiology of disease, Vol. 170, p. 105776.

[67] Mogensen, F. L., Delle, C., & Nedergaard, M., 2021. The Glymphatic System (En)during Inflammation. International journal of molecular sciences, Vol. 22 No 14, p. 7491.

[68] Gouveia-Freitas, K., & Bastos-Leite, A. J., 2021. Perivascular spaces and brain waste clearance systems: relevance for neurodegenerative and cerebrovascular pathology. Neuroradiology, Vol. 63 No 10, pp. 1581–1597.

[69] Pyatin, V.F., Kolsanov, A.V., Shirolapov, I.V., 2017. Recent medical techniques for peripheral nerve repair: Clinico-physiological advantages of artificial nerve guidance conduits. Advances in Gerontology, Vol 7 No 2, pp. 148-154.

[70] Hajal, C., Offeddu, G. S., Shin, Y., Zhang, S., Morozova, O., Hickman, D., Knutson, C. G., & Kamm, R. D., 2022. Engineered human blood-brain barrier microfluidic model for vascular permeability analyses. Nature Protocols, Vol. 17 No 1, pp. 95–128.

[71] Zakharov, A. V., Bulanov, V. A., Khivintseva, E. V., Kolsanov, A. V., Bushkova, Y. V., & Ivanova, G. E., 2020. Stroke Affected Lower Limbs Rehabilitation Combining Virtual Reality With Tactile Feedback. Frontiers in robotics and AI, Vol. 7, p. 81.

[72] Spitz, S., Ko, E., Ertl, P., & Kamm, R. D., 2023. How Organ-on-a-Chip Technology Can Assist in Studying the Role of the Glymphatic System in Neurodegenerative Diseases. International journal of molecular sciences, Vol. 24 No 3, p. 2171.

[73] Zhang, J., Zhao, H., Xue, Y., Liu, Y., Fan, G., Wang, H., Dong, Q., & Cao, W., 2022. Impaired Glymphatic Transport Kinetics Following Induced Acute Ischemic Brain Edema in a Mouse pMCAO Model. Frontiers in neurology, Vol. 13, p. 860255.

Contribution of Individual Authors to the Creation of a Scientific Article (Ghostwriting Policy)

All authors have equally contributed to the study.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Conflict of Interest

The authors have no conflict of interest to declare.