The Glymphatic System and Neuroinflammation in Alzheimer's Disease: An Integrative Synthesis

Tereza Raquel Xavier Viana[a], Regiane Priscila Ratti[a], Larissa Teodoro Rabi[a]

[a]Department of Biomedicine, Centro Universitário Nossa Senhora do Patrocínio, Ceunsp, Itu, Brasil, espacotr@hotmail.com

Abstract. Alzheimer's disease (AD) is a neurodegenerative condition characterized by the accumulation of beta-amyloid (Aβ) plaques and tau tangles in the brain, resulting in synaptic dysfunction and neuronal death. The glymphatic system, a recently discovered network that facilitates the removal of metabolic waste from the brain, has been suggested as a critical component in the pathogenesis of AD. This integrative review aimed to synthesize the current evidence on the relationship between the glymphatic system and neuroinflammation in AD. It is an integrative review of the literature in databases such as the National Library of Medicine located at the National Institutes of Health (PubMed), Scientific Electronic Library Online (SciELO) and Virtual Health Library (VHL), including studies published in the last 5 years (2019 - 2024), full texts, in English and Portuguese, peer-reviewed, aligned with the proposed theme. The exclusion criteria were articles outside the selected period or that did not address the objective of the study. The interaction between the glymphatic system and neuroinflammation is fundamental to understanding neurodegeneration in AD. Glymphatic dysfunction, associated with inflammation and the accumulation of pathological proteins, plays an essential role in the progression of the disease. The AQP4 protein is vital for inflammatory modulation and brain clearance. Factors such as the gut-brain axis and the microbiome are also important. Future advances should focus on cytokines, modulation of the glymphatic system and biomarkers for diagnosis and treatment, with the aim of improving patients' quality of life.

Keywords. Alzheimer, Beta-Amyloid, Neurodegeneration, Glymphatic System, Tau.

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that represents the most common cause of dementia in older adults[1]. It is characterized by severe cognitive decline, including memory loss, language difficulties, behavioural problems and, eventually, loss of the ability to perform daily activities[2]. The pathogenesis of AD involves multiple factors, including extracellular deposits of beta-amyloid (Aβ) plaques and intracellular neurofibrillary tangles of hyperphosphorylated tau protein, which culminate in synaptic dysfunction and neuronal death [3].

The glymphatic system plays a crucial role in cerebral homeostasis by facilitating the removal of metabolic waste from the central nervous system (CNS). This system operates through a network of perivascular channels that allow the circulation of cerebrospinal fluid (CSF) and interstitial fluid (ILF), promoting the elimination of potentially neurotoxic substances such as Aβ and tau [3]. The efficient function of this system is vital for maintaining brain health.

The function of the glymphatic system is particularly active during sleep, a critical period for the removal of metabolic waste. Studies indicate that glymphatic activity increases significantly during deep sleep, suggesting a link between healthy sleep patterns and the effectiveness of brain cleansing. This “washing” mechanism is essential for preventing the accumulation of toxic proteins that can contribute to neurodegeneration [4]. Understanding the relationship between the efficient function of the glymphatic system and its possible impairment in AD is essential for identifying innovative therapeutic strategies and improving the preventive approach to the condition.

There is growing evidence that dysfunction of the glymphatic system may be associated with the pathogenesis of AD. In animal models of Alzheimer's, glymphatic dysfunction has led to accelerated accumulation of Aβ and tau, worsening disease progression. Furthermore, studies in humans using advanced neuroimaging techniques have revealed a reduction in glymphatic circulation efficiency in patients with AD compared to healthy controls [5,6].

The underlying mechanisms of glymphatic dysfunction in AD are not yet fully understood. However, it is believed that a combination of factors, including chronic inflammation, vascular changes, and sleep disorders, may contribute to reduced glymphatic clearance efficiency. Inflammation, in particular, is a well-documented factor in the pathogenesis of AD and may directly affect glymphatic function by altering blood vessel permeability and cerebrospinal fluid dynamics [7].

The therapeutic implications of modulating the

glymphatic system for AD are promising but still in the early stages of exploration. Interventions aimed at improving glymphatic function, such as therapies that induce deep sleep or medications that increase CSF flow, have shown encouraging preliminary results in preclinical models. These strategies could potentially slow the progression of AD by facilitating the efficient removal of Aβ and tau from the brain [5].

In addition to direct interventions on the glymphatic system, there is growing interest in understanding how lifestyle factors, such as sleep quality and physical activity, may influence glymphatic function and, by extension, the risk of developing AD. Improvements in sleep patterns and increased physical activity have been associated with better glymphatic function, suggesting that non-pharmacological interventions may also play an important role in the prevention or treatment of AD [7,8].

This integrative review aims to synthesize current evidence on the role of the glymphatic system in AD, exploring the fundamental biology of the system, its dysfunctions in AD, and potential therapeutic interventions. Through a comprehensive analysis of recent literature, we seek to provide a clear and updated view on how modulating glymphatic function could contribute to new approaches in the treatment and prevention of AD, offering valuable insights for future research and clinical practice.

2. Metodology

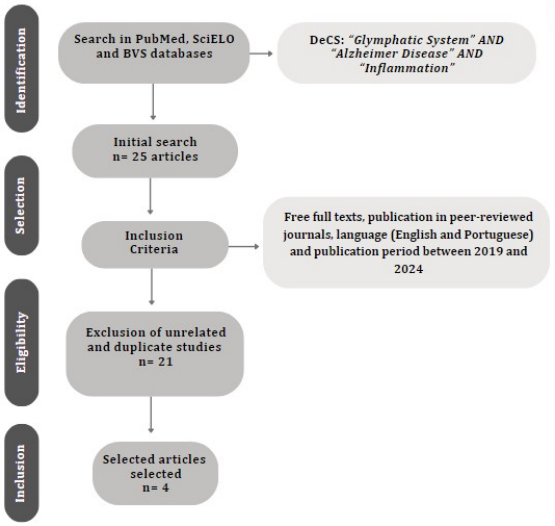
This is an integrative review, a systematic methodology for gathering secondary data. Recognized for its comprehensiveness in synthesizing knowledge, this approach facilitates the integration of various perspectives on a specific topic, making extensive use of available evidence. It is particularly valued for its ability to include a variety of studies, providing a substantial contribution to evidence-based practice [9]. The methodological process was carried out in six distinct stages: first, the topic of interest was identified and the research question was formulated. Next, relevant databases were selected and the inclusion and exclusion criteria for the studies were established. Subsequently, the categories of information to be extracted were defined, and the methodological quality of the studies was assessed. Finally, the results were interpreted, and the review was presented with the synthesis of the acquired knowledge.

The first step involved defining the central research question using the PICO acronym. The target population was elderly individuals diagnosed with AD. The intervention focused on studies related to the glymphatic system. Comparison included patients with AD and healthy individuals. The outcome assessed the impact on the progression of AD [10]. The guiding question resulting from this was: "In patients with AD (P), how does the modulation of glymphatic function (I) compared to healthy individuals (C) impact the progression of the disease (O)?" The objective was to synthesize and evaluate studies to analyze the relationship of the glymphatic system in AD. Based on this question, eligibility criteria were established to search for and select studies published in the last five years (2019-2024), available in English and Portuguese, peer-reviewed, and with free full text.

The exclusion criteria were established to include studies specifically addressing the glymphatic system and AD. Articles without available full text, not peer-reviewed, or published before 2019 were excluded. The search for articles used keywords indexed in the Health Sciences Descriptors (DeCS) and Medical Subject Headings (MeSH), combined with the Boolean operator "AND." The general search key was ((Glymphatic System) AND (Alzheimer Disease)) AND (Inflammation), adapted for specific databases such as PubMed, SciELO, and BVS. The bibliographic search was conducted on July 27, 2024. Initially, 25 articles were identified, of which 4 were selected after reviewing titles and abstracts, excluding one duplicate study. After a complete analysis, the 4 studies were included in this review, meeting the study's objectives.

The studies were selected following the flowchart (Figure 1) according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [11]. Due to the secondary nature of this study, it was not necessary to submit it to the Research Ethics Committee (CEP). However, all ethical principles were strictly adhered to in order to ensure the legitimacy of data collection, analysis, and discussion.

Fig.1 - Flowchart of the Scientific Article Search Process



Source – Literary Research Process - Prepared by the author.

3. Results and Discussion

The results of the studies suggest that glymphatic dysfunction, neuroinflammation, and vascular changes are interconnected and play critical roles in the pathology of neurodegenerative diseases, including AD, as shown in Table 1.

Tab. 1 - Presentation of the articles included in the review

Author / Year	Objectives	Methods	Results
Mehta, R. I., & Mehta, R.	Review the pathogenesis of	Literature review	AD is pathologically heterogeneous,

I. (2023)	Alzheimer's disease (AD) and discuss the influence of mixed pathologies, vascular changes, and immunologic al alterations.		with vascular lesions and complex inflammation influencing the progression of the disease.
Shirola-pov I. *et al*., 2023	Analyze how neuroinfla-mmation, microglia activation, and glymphatic dysfunction contribute to brain aging and dementia.	Literature review	Dysfunction of the glymphatic system and the accumulation of pathological proteins are key factors in the development of Alzheimer's dementia.
Chen *Z. et al*., 2024	Analyze the role of cytokines in AD.	Literature review	Dysfunction of the glymphatic system and neuroinfla-mmation are interrelated and contribute to neurodegene-ration.
Szlufik S. *et al*., 2024	To explore the relationship between neuroinflam mation and dysfunction of the glymphatic system in neurodegene ration.	Literature review	Neuroinfla-mmation and dysfunction of the glymphatic system interact and influence neurodegene-ration.

Source - Studies included in the review - prepared by the author.

AD reveals a pathological complexity that goes beyond the simple accumulation of β-amyloid (Aβ) and tau, evidenced by vascular changes and brain inflammation that often coexist with typical neuropathological lesions, such as Aβ plaques and neurofibrillary tangles (NFTs). Studies show that vascular and inflammatory lesions can lower the threshold for clinical dementia, suggesting that AD is a multifactorial and heterogeneous disease. Additionally, the presence of mixed pathologies in some individuals may explain variability in disease progression, with some patients showing resistance to AD despite the presence of brain pathology [12].

Cellular and molecular processes, including neuroinflammation, microglial activation, and glymphatic dysfunction, are interconnected and play crucial roles in brain aging and neurodegeneration. The overproduction and inadequate clearance of metabolites and aberrant proteins, combined with disturbances in brain architecture and sleep patterns, significantly contribute to the development of neurodegenerative diseases such as AD. While the amyloid-beta and tau hypotheses provide a crucial foundation for understanding AD pathology, it is essential to advance in identifying predictive biomarkers and effective therapeutic interventions, especially in the early stages of the disease. Current research highlights the importance of the glymphatic pathway and glia-mediated clearance, offering new perspectives on the etiology and progression of neurodegeneration [13].

The neuroimmune system, which includes immune cells, cytokines, and the glymphatic system, is crucial in the pathogenesis and progression of AD. Cytokines such as IL-1β, IL-17, IL-12, IL-23, IL-6, and TNF-α play a central role in neuroinflammation associated with AD, exacerbating neuronal damage. However, anti-inflammatory cytokines like IL-2, IL-3, IL-33, and IL-35 are also secreted and have a protective effect against neuroinflammation [14].

A comprehensive understanding of the pathomechanism of neurodegenerative disorders is crucial for developing effective treatments. Neurodegeneration and neuroinflammation are interrelated processes that mutually reinforce each other, with glymphatic system dysfunction exacerbating pathological progression. Glial cells, especially astrocytes and the AQP4 protein, are key in modulating inflammation and maintaining glymphatic function. Additionally, the gut-brain axis and the microbiome may influence these processes, offering new perspectives for understanding the pathomechanism of neurodegeneration and potentially guiding therapeutic interventions [13].

4. Conclusion

Understanding the interaction between the glymphatic system and neuroinflammation is essential for unraveling the complex mechanisms of neurodegeneration, particularly in AD. This review highlighted that glymphatic system dysfunction, associated with inflammatory processes and accumulation of pathological proteins, plays a central role in disease progression. AQP4, a protein essential for glymphatic function, emerges as a key factor in modulating inflammatory responses and clearing metabolites in the brain. Additionally, the gut-brain axis and the microbiome were identified as potential influences on neuroinflammation and glymphatic function, underscoring the need for a holistic approach in investigating these interactions.

Although advances in research have enhanced our understanding of these processes, significant gaps remain in fully elucidating the pathological mechanisms and translating this knowledge into effective therapeutic strategies. Future studies should focus on deepening the understanding of the specific roles of different cytokines and proteins, exploring new approaches for modulating the glymphatic system, and investigating the interaction between the microbiome and the CNS. Additionally, it is essential to develop reliable biomarkers for early diagnosis and monitoring of disease progression, as well as preventive and

therapeutic strategies to slow or halt the progression of AD. The integration of new discoveries and the application of emerging technologies could lead to significant advancements in the treatment and quality of life for patients affected by neurodegenerative disorders.

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