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## Investigation of Association between Alzheimer Disease and Glymphatic System

Ayşe Cigel

Dokuz Eylül University

Huseyin Avni Eroglu

Canakkale Onsekiz Mart University

**Abstract:** Novel studies indicated that brain metabolic derivatives clearance is provided by a system called glymphatic (glia+lymphatic) system. Glymphatic system drainage works thanks to arterial pulsation and clear out brain wastes via AQP4 channels localized at astrocytes endfeet. Dysfunction of this system associated with senescence and several pathologies. One of those disease is Alzheimer's Disease. This study objected to determine the relation between glymphatic system and Alzheimer's Disease in accordance with previous studies. Method: Data was collected from "Google Scholar" and "Pubmed" publishments drafted by related professionals between 2011-2023 years. Results: Our results indicated that Alzheimer's Disease and glymphatic system tightly associated each other. It was observed that during Alzheimer's Disease glymphatic flux diminished and AQP4 expression levels were decreased, and localization disrupted. Thus, we suggest that glymphatic system inducing treatment or methods might be beneficial for preventive of Alzheimer's Disease.

**Keywords:** Glymphatic system, Alzheimer disease, Aquaporin 4, Amyloid beta

### Introduction

Brain is one of the highest-level energy consuming organs of the body. Due to this type of highest require, blood brain barrier limits the efflux of ultrafiltrate of the plasma. Thus, clearance of the parenchymal tissue of brain becomes harder than other tissues. In addition, brain tissue doesn't contain traditional lymphatic system which provides fluid flux and waste clearance. A new system called glymphatic system avoids this challenge supporting cerebrospinal fluid for cleansing toxins and metabolic waste (Hablitz & Nedergaard, 2021).

The glymphatic system, combination of glia + lymph, is a structure, originates from astrocytes feet, which is tightly related with transportation of cerebrospinal and intracerebral fluid. Considering that, glymphatic system is commonly accepted as pseudolymphatic system of the central nervous system. Glymphatic system provides a counterpart flux between blood system and periarterial cerebrospinal flux. Arterial pulsation supports the movement of cerebrospinal fluid to the parenchymal field and integrate both interstitial and cerebrospinal fluid. The process occurs via Aquaporin 4 (AQP4) channels which localized to vascular astrocytic endfeet. Moreover, the flux of blood brain barrier fluid or cerebrospinal fluid extracted from extrachoroidal supports the glymphatic system. Following the influx of plasma, the fluid of parenchymal tissue moves opposite. Then the mixture of cerebrospinal and intracerebral fluid efflux from the brain via perivenous space and cranial or spinal nerves. Afterwards traditional lymphatic channels located in meninges and soft tissue of cranium remove the final fluid from the area (Mestre et al., 2020).

One of the most effective activators of glymphatic system flux, is non-REM sleep, which is the no eye movement and slow wave activity phase (1-4 Hz, Delta waves). Besides, sleep posture contributes the effective flux (Mestre et al., 2020; Mogensen et al., 2021). On the other hand, aging and various pathologies suppress the

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flux of the glymphatic system depending on disruption of the expression of AQP4 channels at astrocytes endfeet. Especially neurodegenerative diseases, more likely Alzheimer's disease, are crucial for this disruption (Mogensen et al., 2021). From this point of view, the relationship between the Alzheimer's disease and glymphatic system was investigated in the study.

## **Methods**

For this purpose, related publications between 2011-2023 published in "Google Scholar" and "Pubmed" databases released by professionals were searched. The investigated articles were full-text and written in English and Turkish. References of selected articles were determined for related articles which do not exist in search list. Alzheimer's disease, amyloid beta, tau glymphatic system and AQP4 were used as keywords. Best match articles were examined in the line with our aim and counted in the present review.

## **Results**

The accumulation of amyloid beta and tau protein is one of the underlying mechanisms of the relationship of Glymphatic system and Alzheimer's disease. Previous studies claimed that this interaction is tightly related with AQP4 channels which take part in transportation of water and solutes, contributing to glymphatic system (Si et al., 2023). In an Alzheimer's model study with AQP-knock out mice, Iliff et al. (2011) reported that brain might be cleansing through intracerebral AQP4 channels (Iliff et al., 2012). Another study was established this relationship by immunofluorescent and Western blot analysis. They clarified that not only expression of AQP4 channels but also their localisation is important for the underlying mechanism of Alzheimer's disease. They also claimed that AQP4 channels loss by ageing allows amyloid beta accumulation, so this might be an inducing factor of Alzheimer's disease (Zeppenfeld et al., 2017). In one of tau protein induced Alzheimer's disease model animal study, demonstrated that glymphatic system remove tau proteins from parenchymal brain tissue. Further, it was reported that accumulation of tau proteins reduces the AQP4 channels polarisation. Based on this information they suggested that this mechanism has potential for treatment of Alzheimer's disease (Harrison et al., 2020). Chandra and colleagues (2021) investigated the effects of AQP4 channels polymorphism in spectrum of Alzheimer's disease aspect on amyloid burden and clinical situation. Over 800 patients who had mild and moderate cognitive impairment or Alzheimer's disease participated to the study. Results indicated that genetic variations in AQP4 channels caused to amyloid beta accumulation, and it was suggested that mild cognitive impairment contributes to risk of progression of Alzheimer's disease. Also, the results indicated that there was a correlation with the cognitive regression rates. (Chandra et al., 2021). Kamagata et al. (2022) examined the perivascular network by non-invasive magnetic resonance (MRI) of patients with Alzheimer disease or mild cognitive impairment. They investigated the correlation between cerebrospinal fluid markers, PET and cognitive scores. The results of this study indicated that disruption of cognitive and arrangement of daily activities in Alzheimer's disease depend on neuronal loss and glymphatic system disorders (Kamagata et al., 2022).

## **Discussion and Conclusion**

In accordance with the results of aforementioned literatures, there is a tightly relationship between Alzheimer's disease and glymphatic system. It is clear from the previous studies that glymphatic system clear amyloid beta and tau proteins from brain parenchyma. Interestingly, AQP4 channels seem to be important actors of this system. The adequate and regular localised expression of these channels are principal of healthy flux in parenchymal tissue. It could be suggested that triggering glymphatic system activation and providing AQP4 channels polarisation might be potential preventing treatment method of Alzheimer's Disease. Also, it is possible to achieve the goals by cleansing parenchymal tissue. Due to substantial evidence about this interaction, further studies are required to eliminate the risk of Alzheimer's disease.

## **Scientific Ethics Declaration**

The authors declare that the scientific ethical and legal responsibility of this article published in EPHELS journal belongs to the authors.

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### Author Information

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**Ayşe Cigel**  
Dokuz Eylül University  
Izmir, Turkey

**Huseyin Avni Eroglu**  
Canakkale Onsekiz Mart University  
Canakkale, Turkey  
Contact e-mail: hareoglu@comu.edu.tr

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