Research Article

Evaluation of Glymphatic System Activity Using Diffusion Tensor Imaging Analysis Along the Perivascular Space (DTI-ALPS) in Alzheimer's Disease

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Abstract

Aim: The glymphatic system is a recently discovered waste drainage system that facilitates the movement of cerebrospinal fluid through the brain's perivascular spaces and aids in removing soluble proteins. The Diffusion Tensor Imaging (DTI-ALPS) index analysis is a modern method used to evaluate the movement of water molecules in these spaces by measuring the diffusion coefficient. This study aimed to examine glymphatic system function in Alzheimer's disease (AD) patients compared to healthy controls (HC) using the DTI-ALPS method and to analyze its relationship with cognitive disorders. **Methods:**DTI data from 59 AD patients and 59 HC were obtained by downloading medical data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) platform. Using DSI Studio software, the diffusivities of the DTI data were extracted, and DTI-ALPS indices were calculated. Correlation analysis evaluated the relationship between the DTI-ALPS index and clinical features. **Results:**The findings indicated that the DTI-ALPS index was significantly lower in AD patients compared to HC ($p = 0.042$). Furthermore, the DTI-ALPS index showed a significant correlation with the Functional Activities Questionnaire (FAQ) ($r = -0.214$, $p = 0.020$) and the Mini-Mental State Examination (MMSE) ($r = 0.225$, $p = 0.014$). **Conclusions:**The study demonstrated that AD individuals have impaired glymphatic system function, as indicated by the DTI-ALPS index, which correlates with worse cognitive performance. These findings support early diagnosis methods for AD. A better understanding of glymphatic system function may provide new perspectives for monitoring AD progression.

Keywords: Alzheimer's Disease, Brain Perivascular Space, Diffusion Tensor Imaging, G-lymphatic System, G-lymphatic Clearance System

Introduction

The g-lymphatic system is a macroscopic waste removal system that employs perivascular tunnels formed by astroglial cells to facilitate the removal of soluble proteins and metabolites from the central nervous system (CNS).[1,2] The glymphatic system derives its name from its functional resemblance to the lymphatic system in peripheral tissues and the crucial involvement of glial AQP4 channels in facilitating convective fluid movement.[2] This system effectively regulates the cerebrospinal fluid (CSF) transport mechanism, facilitating the removal of interstitial fluid (ISF) and metabolic waste from the brain.[3] Two extracellular fluids, the ISF and the CSF, provide support to neural cells in the brain.[4] The ISF, in conjunction with the extracellular matrix, serves as a conduit between the vascular system and neural networks.[5] This fluid envelops the brain parenchymal cells and accounts for approximately 12–20% of the brain's water content.[4] The CSF is in a constant state of interaction with ISF, providing mechanical protection to the brain and regulating homeostasis.[6,7] Despite the fact that ISF is formed in the perivascular and interstitial spaces that constitute the glymphatic pathway and drains predominantly into the subarachnoid CSF compartment, surprisingly little is known about the impact of ISF production on the bulk fluid flow within this system.[4] The genetic deletion of AQP4 has been demonstrated to impede the exchange of the cerebrospinal fluid-intraocular substance (CSF-ISF) by approximately 65%, and to diminish the clearance of β-amyloid by approximately 55%.[1] The findings indicate that age-related changes in perivascular AQP4 polarization, particularly along penetrating arterioles, and the association between AQP4 depolarization and CSF-ISF exchange suggest that the age-related decline in glymphatic function may be attributable, at least in part, to dysregulation of astrocyte water transport.[2] It seems reasonable to posit that a reduction

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in glymphatic activity with advancing age is attributable to a number of factors, including a 66% decline in CSF production and a 27% reduction in CSF pressure.[8-10] A comprehensive grasp of the CSF system is essential for advancing our understanding of CNS diseases.[11] The dysfunction of the glymphatic pathway is characterised by the inability to clear interstitial solutes. This is recognised as an important feature of natural brain ageing as well as CNS diseases, including Alzheimer's disease (AD), traumatic brain injury (TBI), and ischaemic or haemorrhagic stroke.[4,12-14] As a consequence of the physiological changes associated with the ageing process, an increase in connective tissue between the vascular system and epithelial cells may result in a reduction in the secretion of CSF. This has been linked to a decline in the efficiency of the waste clearance system during the progression of neurodegenerative diseases such as AD. AD is an age-related disease, characterised by the accumulation of neurofibrillary tangles, amyloid β peptide and other specific proteins in the brain. It is hypothesised that the waste clearance system plays a pivotal role in the removal of these proteins. However, the reduction in CSF flow from the periarterial spaces to the brain parenchyma via AQP4 may contribute to protein accumulation.[15,16] Indeed, a study of human AD brains revealed that the loss of AQP4, which is located in perivascular astrocytic foot tips, was associated with the development of AD.[17,18] Moreover, evidence indicates that altered AQP4 expression is associated with the formation of edema in the context of CNS injury.[19] This provides a significant insight into the potential impact of the glymphatic system on both neurodegenerative processes and acute CNS injuries. A comprehensive understanding of the CSF system is essential for elucidating the mechanisms underlying CNS diseases.[11]

AD is a progressive neurodegenerative disease that typically presents as a clinically isolated amnestic deficit and evolves into a characteristic dementia syndrome. The primary symptoms of AD are memory loss and cognitive impairments, which can impact an individual's ability to engage in social and educational activities.[20] Advances in neuroimaging research have enabled the mapping of various molecular, functional, and structural aspects of AD pathology with increasing temporal and regional detail. The mounting evidence indicates that the disparate imaging irregularities associated with AD adhere to a uniform trajectory throughout the disease's progression. The initial alterations can be discerned years prior to the disease's clinical manifestation. Despite the ongoing uncertainty regarding the pathogenesis of AD, the inability to effectively remove potentially toxic molecules from the interstitium of the aging brain may be a contributing factor.[13] Despite the potential for a tracer method to assess the g-lymphatic system in humans, tracer studies of the g-lymphatic system are currently limited by the time required to track the distribution of the tracer in the brain.[21] Furthermore, it is not possible to monitor the activity of the g-lymphatic system in real time. It is therefore evident that alternative monitoring methods, beyond those employed in tracer studies, are required in order to assess the g-lymphatic system.[21]

The Diffusion Tensor Image Analysis Along the Perivascular Space (DTI-ALPS) method was developed for the purpose of evaluating the brain's g-lymphatic function or ISF dynamics.[7,22] Since the introduction of the g-lymphatic system hypothesis, there has been a growing number of studies attempting to describe the fluid dynamics within the brain parenchyma.[1,3,12,23-25]

Taoka et al. (2017)[22] proposed DTI-ALPS, a DTI-based index designed to measure diffusion along the perivascular space (ALPS) and assess the function of the g-lymphatic system.

The movement of water molecules within the perivascular space is evaluated through the measurement of the diffusion coefficient, employing the DTI-ALPS method.[7,26] The ALPS index has been proposed as an indirect indicator of glymphatic function status, as it measures the diffusion in the direction of the perivascular space in the periventricular white matter.[7,21,22,27] The diffusion tensor imaging index method (DTI-ALPS), which was employed in the present study, utilizes diffusion images that can be obtained in a relatively short period of time. This method may have the potential to monitor the status of the glymphatic system over time.[22] In the present study, we investigated the glymphatic function by applying the DTI-ALPS method and comparing patients with AD and healthy controls. Furthermore, we examined the correlations between the DTI-ALPS index and cognitive function in different areas.

Materials And Methods

The ethics committee approval has been obtained from Uskudar University. Non Interventional Research Ethics Committee report number of 61351342/MAY 2023-12. (29 May 2023).

Imaging Data

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu) [28]. The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessments can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD).

The current study utilized neuroimaging data obtained specifically from the ADNI database. This dataset represents a comprehensive and multi-modal collection that has been widely used in AD research, particularly concerning disease progression, diagnostic evaluation, and treatment development. The utilized data included diffusion tensor imaging (DTI) from 59 patients with Alzheimer's disease and 59 healthy controls. In addition to structural and molecular brain imaging, the dataset encompasses cognitive assessments (e.g., NINCDS/ADRDA), genetic information (e.g., APOE4), demographic characteristics, and biofluid biomarkers such as plasma isoprostanes and CSF profiles. The Clinical Dementia Rating (CDR) scale was employed to determine the severity of dementia in participants.

Diffusion Tensor Imaging (DTI) Acquisition

Diffusion tensor imaging was conducted using the same scanner (3.0 T, 32-channel head coil, AchievaTx, Phillips Healthcare, Best, The Netherlands). It was performed using spin-echo single-shot echo-planar pulse sequences with a total of 32 different diffusion directions (repetition time/echo time = 8,620/85 ms, flip angle = 90°, slice thickness = 2.25 mm, acquisition matrix = 120 × 120, field of view a = 240 × 240 mm2, and b-value = 1,000 s/mm2).

Diffusion Tensor Imaging Processing

We utilized the DSI Studio software (version May 2021, http://dsi-studio.labsolver.org) for preprocessing brain MRI data. This process involved open-source imaging, correction of eddy current and phase distortion artifacts, the establishment of a mask through thresholding, smoothing, and defragmentation, as well as reconstruction using the DTI method.

Neuropsychological Assesment

In this study, two well-established instruments from the Alzheimer's Disease Neuroimaging Initiative (ADNI) - the Mini-Mental State Examination (MMSE)[29] and the Functional Activities Questionnaire (FAQ)[30] - were employed to assess cognitive function and functional abilities. These tools provide complementary insights into participants' cognitive status and ability to maintain independence in daily activities, both of which are essential for detecting and monitoring the progression of cognitive decline.

Diffusion Data Processing in MATLAB

In this study, MATLAB was employed for the processing and preparation of DTI data for analysis. Following the selection of ROIs and the determination of fiber orientations in DSI Studio, the data were imported into MATLAB, and diffusivity values were obtained. This approach enabled the efficient extraction of diffusion measurements from specific brain regions. Furthermore, this step facilitated the accurate calculation of the ALPS index by ensuring that the data were structured correctly for subsequent statistical analyses.

DTI-ALPS Index

We defined a rectangular region of interest (ROI) within which the lateral projections of the medullary veins were traced orthogonally to the primary diffusion directions. Subsequently, we extracted the fiber orientations and diffusivities along the x-, y-, and z-axes at the voxel level within the ROI. From the voxel set, the voxel showing maximum orientation for each fiber type (projection and association fibers) along the x-axis was selected. (Supplementary Materıal)

The DTI-ALPS index was calculated using the following formula.[7,21]

ALPS index = mean (Dxxproj, Dxxassoci) / mean (Dyyproj, Dzzassoci)

Dxxproj: diffusivity along the x-axis in the projection fiber, Dxxassoci: diffusivity along the x-axis in the association fiber, Dyyproj: diffusivity along the y-axis in the projection fiber, Dzzassoci: diffusivity along the z-axis in the association fiber.

Statistical Analysis

Statistical analyses were performed using SPSS software (version 27; IBM-SPSS). Descriptive statistics (mean, standard deviation, minimum, maximum, frequency, and percentage) were used to evaluate the data. The Shapiro–Wilk test assessed normality. Categorical variables were compared using the chi-square test, and continuous variables with normal distribution were analyzed using the independent samples t-test. For non-normally distributed data, the Mann-Whitney U test was applied. Pearson's correlation coefficient was used for normally distributed data with a linear relationship, while Spearman's correlation coefficient evaluated non-linear relationships and data without normal distribution. Statistical significance was defined as $p < 0.05$, with a 95% confidence interval applied in the analysis.

Results

Clinical Characteristics of Patients With AD and HC

Table 1 shows the clinical characteristics of patients with AD and HCs. In total, 59 patients with AD (39 men and 20 women; mean age, 74.05±6.1 years; range, 61-83 years) and 59 HC (26 men and 33 women; mean age, 74.56±6.3 years; range, 66-87 years) were finally included in this study. Participant demographic and cognitive data are summarized in Table 1. A power analysis was conducted using the G*Power 3.1 software. A preliminary power analysis determined the effect size (Cohen's d)) to be 0.5, the alpha level to be 0.05 and the desired power to be 0.80. Accordingly, it was calculated that a minimum of 51 participants should be included in each group. Therefore, the study was designed to recruit a total of 102 participants. To account for potential losses during data collection, an additional eight participants were included in each group, resulting in a total of 118 participants, with 59 in each group. The total number of medications used by individuals in both the Alzheimer's patient group and the healthy control group is presented. It was found that 8.5% of Alzheimer's patients do not use any medications. Additionally, 20.3% use one type of medication, 40.7% use two types, 23.7% use three types, and 6.8% use four types of medications. In contrast, 83.1% of individuals in the healthy control group do not use any medications, while 11.9% use one type and 5.1% use two types of medications. A statistically significant difference was identified in the comparison between the groups with regard to the number of medication uses ($p < 0.001$). The presence of the ε4 genotype allele is recognized as a risk-increasing factor. Among 59 individuals in the AD, 44 have the ε4 allele, while 15 do not. In the HC of 59 individuals, 22 have the ε4 allele, and 37 do not. A statistically significant difference in the presence of the ε4 allele exists between AD and HC ($p < .001$). Compared with HCs, patients with AD performed significantly worse in all neurological tests ($p < 0.001$).

Table 1: Demographic data and cognition among AD and HC groups

	AD (n=59)	Range	HC (n=59)	Range	p value
Age, years, mean± SD	**74.05±6.1**	**61-83**	**74.56±6.3**	**66-87**	**0.659**
Sex, male/female, n	39/20		28/42		0.016 *
Number of Drugs Used, n (%)					<.001 *
No medicine	5 (8.5%)		49 (83.1%)		
1 types of medicine	12 (20.3%)		7 (11.9%)		
2 types of medicine	24 (40.7%)		3 (5.1%)		
3 types of medicine	14 (23.7%)				
4 types of medicine	4 (6.8%)				
APOE ε4 Allele	44 (74.6%)		22 (37.3%)		<.001 *
Neurological Tests, mean±SD					
MMSE	23.05±2.5	15-28	29.17±1.1	26-30	<.001 *
FAQ	14.59±6.3	1-30	0.69±1.8	0-9	<.001 *

AD, Alzheimer Disease; HC, Healty Control; MMSE, Mini Mental State Examination; FAQ Functional Activities Questionnaire

*p value less than 0.05 indicate statistical significance.

DTI-ALPS Index

There were significant differences in the DTI-ALPS index between patients with AD and HCs. The DTI-ALPS index in patients with AD was lower than that in HCs ($p = 0.042$). In addition, there were differences in the diffusivity along the x-axis, y-axis, and z-axis of the fibers, as shown in Table 2.

Table 2: DTI-ALPS index AD and HC groups

Diffusivity	AD (N=59)	HC(N=59)	p value
Dxxproj	6.01±1.47	6.27 ±1.70	0.385
Dyyproj	5.21±1.57	5.29±1.76	0.785
Dxxassoc	5.92±3.34	6.76± 2.84	0.143
Dzzassoc	5.63±2.13	5.72±1.68	0.797
DTI-ALPS-index	1.15±0.29	1.27±0.28	0.042*

Dxx: diffusion along x-axis, Dyy: diffusion along y-axis, Dzz: diffusion along z-axis, ALPS: analysis along perivascular space

*p value less than 0.05 indicate statistical significance.

Correlation Analysis

Patients with AD dementia exhibited a significantly lower DTI-ALPS index across the whole brain compared to healthy controls (HCs) ($p = 0.022$). A positive correlation was observed between the DTI-ALPS index and MMSE scores ($r = 0.225$, $p = 0.014$), while a negative correlation was found between the DTI-ALPS index and FAQ scores ($r = -0.214$, $p = 0.020$). Additionally, MMSE and FAQ scores were strongly and negatively correlated ($r = -0.796$, $p < 0.001$). Moreover the number of medications used demonstrated a significant positive correlation with FAQ scores ($r = 0.634$, $p < 0.001$), whereas MMSE scores exhibited a significant negative correlation ($r = -0.675$, $p < 0.001$). However, the DTI-ALPS index did not show significant correlations with other clinical characteristics, including age ($r = -0.041$, $p = 0.662$) and the number of medications used ($r = -0.159$, $p = 0.085$). Lastly, there was no significant correlation between age and MMSE scores ($r = -0.065$, $p = 0.486$), nor between age and FAQ scores ($r = 0.037$, $p = 0.694$).

Discussion

The principal aim of this study was to examine the function of the glymphatic system in the brains of patients with Alzheimer's disease (AD) by utilising diffusion tensor imaging (DTI) and the DTI-ALPS index calculation method. The study evaluated the movement of water molecules towards the perivascular space by measuring water diffusion through the DTI-ALPS approach. A significant finding was the identification of glymphatic system dysfunction in AD patients when compared to healthy controls.

The DTI-ALPS index method, developed and implemented in 2017, was used to evaluate the glymphatic system function in AD using small sample sizes. The results indicated that lower diffusivity was observed along the perivascular space in relation to the severity of AD.[22] In another study evaluating cognitive functions, lower diffusivity was detected by the DTI-ALPS index method and was found to be associated with cognitive impairment.[31]

The mechanism proposed in 2012 for waste clearance, based on the principles of the glymphatic system, suggests that a reduction in the efficiency of Aβ and tau clearance is associated with increased aggregation of these proteins, which is a hallmark of Alzheimer's disease.[1] This indicates that dysfunction of the glymphatic system may result in the accumulation of extracellular proteins related to cognition prior to the onset of dementia and AD.[1,14] A recent study examined the relationship between glymphatic system function, as measured by DTI-ALPS, and other commonly used biomarkers in the assessment of AD progression. These included amyloid accumulation, hippocampal atrophy, and cognitive function. The results demonstrated a significant linear correlation between all biomarkers and the ALPS index. This indicates a close relationship between alterations in glymphatic system function in the brain and neurodegenerative changes.[32] Furthermore, cerebral grey matter acts as a mediator between the glymphatic system and cognitive processes.[33] The results of the exploratory analysis indicated that the relationship between the ALPS index and cognition was fully mediated by cerebral grey matter reserve in the amygdala, superior frontal gyrus, thalamus, and hippocampus in patients with AD.[33] Moreover, a positive correlation was identified between the ALPS index and a number of additional cognitive measures, including the MMSE, CASI, short-term memory, drawing skills and language scores, in the AD group.[33]

It has been observed that sleep disorders in AD result in the accumulation of brain metabolic wastes and Aβ plaques, perivascular reactive astrocytosis, and mislocalisation of astrocyte AQP4. The glymphatic system is involved in the clearance of brain fluid and the removal of waste products during sleep, with the assistance of glial cells and perivascular channels.[34] In patients with obstructive sleep apnoea (OSA), the DTI-ALPS index demonstrated a statistically significant difference between the groups, and evidence of dysfunction in the glymphatic system was identified.[26] In consideration of these findings, it can be proposed that obstructive sleep apnoea (OSA) may exert an influence on the elevated risk of dementia development. Furthermore, the disruption of glymphatic system activity, which is associated with sleep, and the DTI-ALPS results demonstrate these effects.[26] It is well documented that traumatic brain injury (TBI) represents a significant risk factor for the early development of dementia, including Alzheimer's disease. In the aftermath of such trauma, the brain frequently exhibits the presence of neurofibrillary tangles, which are composed of protein tau aggregates.[31] In a study investigating the relationship between G-lymphatic function and white matter damage and cognitive impairment in patients with TBI using DTI-ALPS, significant correlations were identified between lower DTI-ALPS and executive functions.[30] These findings provide support for the hypothesis that the "G-lymphatic system" and "DTI-ALPS index" methodologies, as described in the existing literature, can be employed as a unified approach for the early diagnosis of a range of neurodegenerative disorders, particularly AD. A comparison of MMSE scores between the groups within the scope of the study yielded statistically significant results. Furthermore, a statistically significant correlation was identified between DTI-ALPS index data and MMSE scores. In other studies that align with the research findings, a notable positive correlation was observed between the spread through perivascular spaces, as indicated by the ALPS index, and the MMSE score.[22,32-35] A further study indicated that g-lymphatic dysfunction was linked to impaired performance in cognitive domains, including language, attention, and application.[36]

The disease has a progressive impact on an individual's capacity for independent functioning and the quality of their daily life.[37] As the disease progresses, activities such as eating, dressing, basic hygiene, shaving, and eventually using the toilet will likely be neglected as routines are forgotten and skills deteriorate.[38] The objective of the FAQ is to evaluate the essential competencies and capacities that individuals must possess in order to maintain their autonomy and quality of life. A comparison of the FAQ scores between the groups within the scope of the study yielded statistically significant results. In alignment with the findings documented in a comparable study within the existing literature, a statistically significant inverse correlation was identified between DTI-ALPS index values and FAQ scores.[35]

It has been proposed that the relatively modest sample sizes of the studies may be a contributing factor to the observed variations in the results.[39] As this requires further validation on larger datasets, it is hypothesised that this parameter may serve as a useful imaging biomarker for identifying individuals with dementia or at risk of dementia.[39] In recent studies on the ALPS index, the relatively small sample size represents a limitation of the research.[7,36] A review of the sample sizes used in previous studies in light of the existing literature indicated that a larger sample size would be preferable in the current study, in accordance with the recommendations. The present study included a total of 59 individuals diagnosed with AD and 59 HC. Moreover, discrepancies in the study populations may be a contributing factor to the observed findings. It is recommended that further studies employing larger and more diverse populations be conducted.[36,39]

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Patient informed consent

There is no need for patient informed consent.

Ethics committee approval

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Conflict of interest

The authors declare no conflict of interest.

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Author contribution subject and rate

- Beyza Aslı Bilsel (40%): Conceptualization, investigation, data collection, formal analysis, methodology, and writing – original draft.
- Barış METİN (40%): Project administration, conceptualization, investigation, methodology development, supervision of data analysis and interpretation, and writing – review & editing.
- Murat AŞIK (20%): Conceptualization, methodology, and writing – review & editing.

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