

Aqueductal CSF Dynamics By DTI Are Linked To Glymphatic Dysfunction And Cognitive Decline In Alzheimer’s Disease



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- CSF dynamics in the cerebral aqueduct are independently linked to cognitive decline
- The glymphatic system acts as the key mediator of this relationship
- Aqueductal DTI is a promising non-invasive functional biomarker

INTRODUCTION	METHODS	RESULTS	CONCLUSIONS
The relationship between cerebrospinal fluid (CSF) dynamics and cognitive function remains inconclusive. CSF plays a pivotal role in the clearance of neurotoxic substances from the brain, suggesting that CSF dynamics may influence cognitive decline in neurodegenerative diseases. This study aims to evaluate the diffusion velocity and direction of CSF water molecules in the cerebral aqueduct using diffusion tensor imaging (DTI), and to investigate its correlation with cognitive function, thereby providing a novel non-invasive approach for the assessment CSF dynamics.	This study enrolled participants (n = 226) from the Ruijin Neurobank cognitive cohort (RJNB). DTI was used to assess CSF in the cerebral aqueduct, and fractional anisotropy (FA), mean diffusivity (MD), and the DTI-ALPS (diffusion tensor image analysis along the perivascular space) index were calculated. Intracranial Aβ and Tau accumulation were quantified using 18F-Florbetapir PET-MR and 18F-MK-6240 PET-MR. Cognitive function was measured using the Mini-Mental State Examination (MMSE) and Auditory Verbal Learning Test (AVLT). Participants were classified into cognitive normal (CN, n = 55), mild cognitive impairment (MCI, n = 71) and Alzheimer’s disease (AD, n=100) according to the 2016 NIA-AA diagnostic criteria. The cohort is registered at ClinicalTrials.gov (ID: NCT05623124).	Among CSF DTI metrics in the aqueduct, significant differences across CN, MCI and AD groups was detected by FA (0.21 ± 0.03 vs. 0.24 ± 0.04 vs. 0.23 ± 0.04, P = 0.001) and Mes-FA (0.15 ± 0.03 vs. 0.17 ± 0.04 vs. 0.17 ± 0.03, P = 0.001). Spearman’s correlation analysis revealed that FA and Mes-FA was significantly associated with Aβ SUVR (FA: ρ = 0.18, P = 0.005; Mes-FA: ρ = 0.15, P = 0.021) and Tau SUVR (FA: ρ = 0.13, p = 0.086; Mes-FA: ρ = 0.10, p = 0.169). When adjusted for age, sex, AV45 SUVR and Tau SUVR, FA and Mes-FA showed negative correlation with cortical thickness (FA: β = -0.54, p = 0.018; Mes-FA: β = -0.54, p = 0.032). After adjustment for age, sex, AV45 SUVR, Tau SUVR and cortical thickness, FA and Mes-FA were independently associated with declined cognitive performance assessed by AVLT (FA: β = -12.35, p = 0.002; Mes-FA: β = -16.32, p < 0.001). Regarding glymphatic function, FA and Mes-FA were correlated with DTI-ALPS (FA: ρ = -0.30, p < 0.001; Mes-FA: ρ = -0.22, p = 0.001). Mediation analysis with adjustment for age showed that DTI-ALPS partially mediated the influence of FA (mediation effect = 24.87%) and Mes-FA (mediation effect = 18.10%) on AVLT, and fully mediated the association between FA (mediation effect = 57.44%), Mes-FA (mediation effect = 41.24%) with MMSE.	CSF dynamics in the cerebral aqueduct is associated with cognitive decline, independent of Aβ and Tau deposition, and this relationship may be mediated by DTI-ALPS.
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