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Glymphatic Dysfunction Assessed by DTI-ALPS in Neurodegenerative and Cerebrovascular Diseases: Associations with One-Year Gray Matter Atrophy, White Matter Lesions, and Cognitive Decline via Inflammatory and Structural Pathways

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BACKGROUND

Impaired glymphatic clearance has been associated with neurodegenerative diseases causing dementia. The diffusion tensor image analysis along the perivascular space (DTI-ALPS) index has been proposed as a non-invasive measure to assess glymphatic function. The main objective was to examine the association between baseline DTI-ALPS and one-year changes in gray matter (GM) and white matter hyperintensity (WMH) volumes in the Ontario Neurodegenerative Disease Research Initiative (ONDRI) cohort. Secondary objectives were: (1) to assess whether the effect of baseline DTI-ALPS on GM volume change over one year was mediated by plasma glial fibrillary acidic protein (GFAP), and (2) to assess the effect of baseline DTI-ALPS on processing speed change trough the baseline GM volume.

METHODS

A total of 302 ONDRI participants (mean age = 69.7 ± 7.7 years; 61% male) were included in this analysis: patients with Alzheimer's disease/mild cognitive impairment (ADMCI; n = 120), cerebrovascular disease (CVD; n = 139), and frontotemporal dementia (FTD; n = 45). DTI images were preprocessed using the FSL Diffusion Toolbox, and the ALPS indices (mean, left, and right) were calculated from diffusion data in projection and association fiber regions. Lower DTI-ALPS values reflect reduced glymphatic function. WMH, GM, perivascular spaces (PVS), and total intracranial volumes were extracted from MRI. Processing speed change over one year was computed as a z-score from Trail Making Test A and the Symbol Digit Modalities Test. Linear regression models and mediation analyses were used; covariates were selected based on Pearson correlation. Demographics (age, sex, education), vascular risk factors (hypertension, diabetes, hypercholesterolemia, smoking), depressive symptoms, sleep quality, and plasma GFAP levels were also collected.

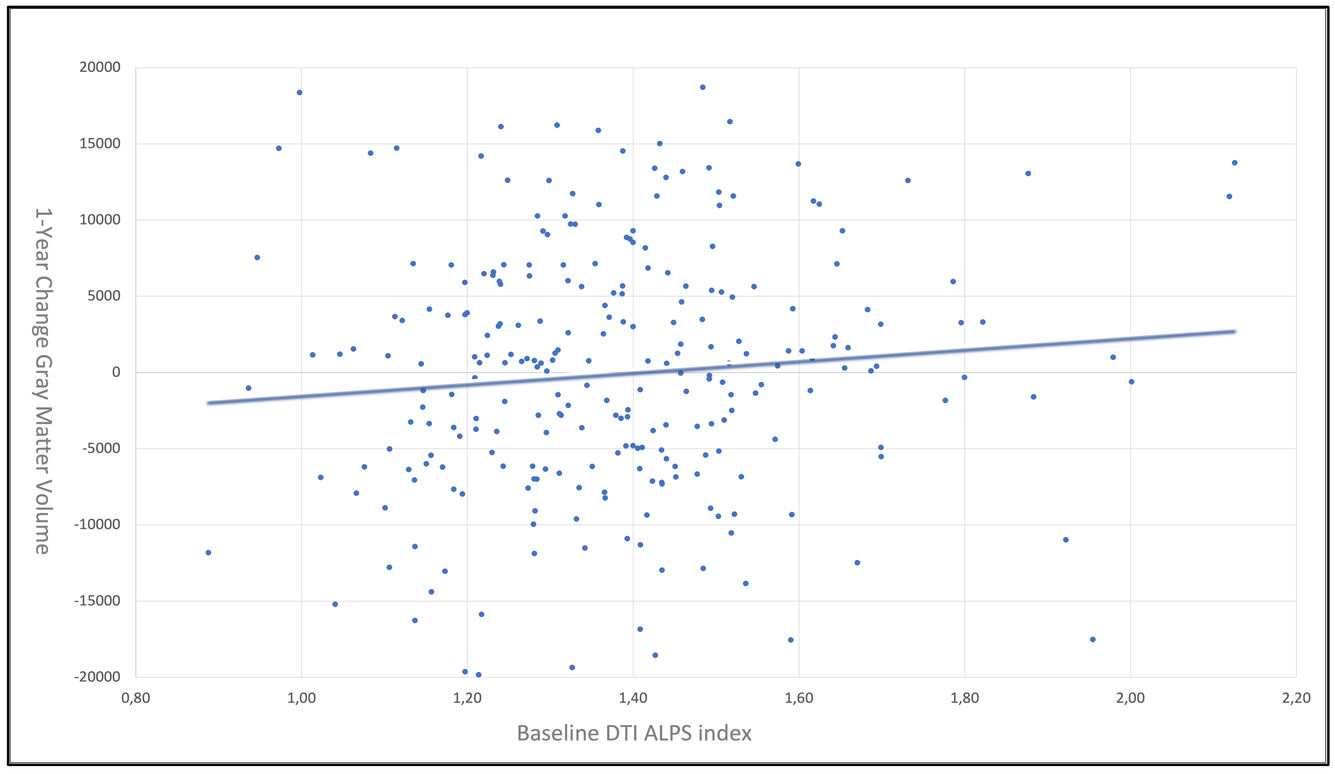

Figure 1: Association of baseline DTI ALPS index with 1-year change of Gray Matter Volume

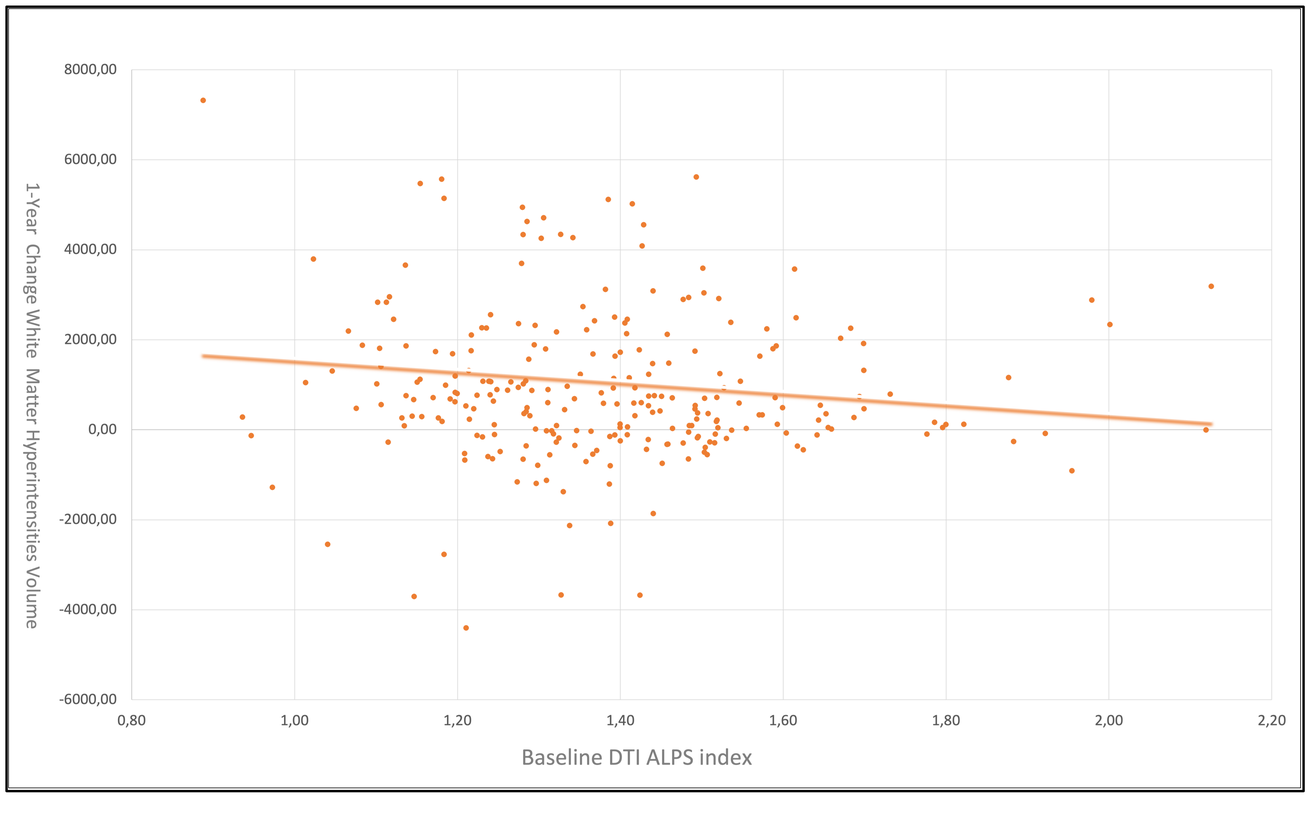

Figure 2 : Association of baseline DTI ALPS index with 1-year change of White Matter Hyperintensities Volume

RESULTS

In the linear regression model ($R^2 = 0.285$, $p < 0.0001$), the baseline mean DTI-ALPS index was significantly associated with one-year changes in GM volume ($\beta = 0.111$, $p = 0.048$) (Figure 1) and WMH volume ($\beta = -0.148$, $p = 0.013$) (Figure 2), as well as with baseline total intracranial volume ($\beta = -0.350$, $p < 0.0001$) and diabetes ($\beta = -0.144$, $p = 0.010$), other demographic and vascular factors were not significantly associated.

In the mediation analysis, the effect of baseline mean DTI-ALPS on one-year GM volume change was significant (total effect: 6572.73 ± 3030.26; 95% bootstrap CI [606.18, 12539.29]; c = 0.1455, p = 0.0310) and was mediated by baseline plasma GFAP levels (indirect effect: 845.94 ± 863.52; 95% CI [73.89, 3370.62]).

The left DTI-ALPS index had a significant effect on one-year change in processing speed z-score (total effect: 0.3787 ± 0.1877; 95% CI [0.0090, 0.7484]; c = 0.1233, p = 0.0447), with a significant mediation by baseline GM volume (indirect effect: 0.1385 ± 0.0757; 95% CI [0.042, 0.3016]).

CONCLUSION

As a potential marker of glymphatic clearance along the perivascular space, baseline DTI-ALPS was associated with one-year changes in WMH and GM volumes in patients with neurodegenerative and cerebrovascular diseases. The effect of DTI-ALPS on GM volume change was partially mediated by plasma GFAP, and its effect on processing speed change was mediated by baseline GM volume. These findings support the hypothesis that glymphatic dysfunction contributes to structural brain changes and cognitive decline, and highlight the role of inflammation, as reflected by GFAP, in these processes. Future longitudinal studies are needed to confirm these results.