The effect of pathophysiologic protein accumulation in preclinical Alzheimer's disease on white matter integrity

Billy Chien[1], Salman Shahid[2], Rhea Thukral[2], Yu-Chien Wu[2]
[1]Indiana University School of Medicine; [2]Indiana University School of Medicine, Department of Radiology & Imaging Sciences

Background:
Traditionally, the accumulation of amyloid beta peptides (Aβ) and tau proteins are considered the main pathological hallmarks of AD due to their impact on cortical microstructural organization, which leads to dendritic deficit and neuronal loss. Additionally, it is hypothesized that these pathophysiological processes may induce axonal and oligodendrocyte dysfunction exacerbating myelin impairment. The objective of this cross-sectional study is to estimate the degree of alterations in white matter (WM) microstructural organization associated with pathological proteins at the pre-clinical stage of AD.

Methods:
To achieve this, diffusion magnetic resonance imaging (dMRI) data and cerebrospinal fluid (CSF) samples were obtained from 84 patients determined to be cognitively normal using neurophysiological tests. CSF samples were analyzed for levels of CSF total tau (T-tau), phosphorylated tau (p-tau$_{181}$), and Aβ_{42}. The participants were then divided into two groups based on their biomarker (BM) levels (BM+: T-tau/A$\beta_{42} \geq 0.18$, and BM-: T-tau/A$\beta_{42} < 0.18$). The level of WM integrity was determined through Free Water Eliminating Diffusion Tensor Imaging (FWEDTI) and Neurite Orientation Dispersion and Density Imaging (NODDI) analysis of the dMRI data.

Results:
Comparisons of WM integrity between the two groups showed a significant reduction in diffusivity in BM+ participants, relative to the BM- group. Additionally, region of interest (ROI)/cluster-based analysis displayed significant associations between levels of CSF biomarkers (T-tau, T-tau/Aβ_{42}, and p-tau/Aβ_{42}) with sophisticated diffusion metrices in multiple regions. CSF Aβ_{42} alone lacked significant association with white matter alterations.

Conclusion:
These results suggest that the processes behind pathological protein accumulation influence WM integrity in pre-symptomatic AD, and are primarily driven by tau proteins. Therefore, CSF models which include both measures of tau and Aβ_{42} are better indicators of AD in its non-dormant stages.