Clinical Markers for Small Vessel Pathology in Alzheimer's Disease

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Background:

White matter hyperintensities (WMH) and cerebral microhemorrhages (MH) are common small vessel pathologies that often co-occur with hallmarks of Alzheimer's Disease (AD) including amyloid-β and tau deposition, neurodegeneration, and decreased cognition. We investigated the relationship among these pathologies to better understand their roles in AD pathogenesis.

Methods:

A sample from the AD Neuroimaging Initiative (ADNI) with baseline WMH volume WMHV), MH counts, and serum lipids measurements using the Nightingale Health metabolomics platform included cognitively normal, mild cognitive impairment, and AD participants. Spearman rank correlations coefficient and rank regression models were generated to assess the relationship between vascular pathology and mean arterial pressure (MAP), history of hypertension, and serum biomarkers. Models were covaried for age, sex, APOE status, BMI, and years of education. Further analysis was conducted by dividing participants based on APOE status. False discovery rate was controlled by the Benjamini-Hochberg method.

Results:

WMHV and MH were weakly positively associated ($\rho=0.197$, $p<1*10^{-10}$). MH and MAP were positively correlated ($p<.05$), but MH was not related to history of hypertension, or serum lipids. WMHV was negatively associated with serum VLDL cholesterol ($p<1*10^{-12}$), LDL cholesterol ($p<.0001$), and remnant cholesterol ($p<1*10^{-11}$). In APOE4 carriers only, WMHV was negatively associated with triglycerides ($p<.001$) and total fatty acids ($p<.001$), and positively associated with HDL cholesterol ($p<.002$). WMHV was not related to MAP or history of hypertension.

Conclusion:

Vascular imaging markers have distinct risk factors with lipid profiles most associated with WMH burden, whereas MAP was predictive of MH. Counterintuitively, lipids associated with higher risk of systemic vascular pathology appeared protective against WMH in the ADNI sample. This phenomenon was particularly notable in APOE4 carriers. Further investigation should be conducted to better understand the relationship between serum lipids and small vessel pathology, and how these contribute to AD pathogenesis.