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Widespread Cerebrovascular Dysfunction in Alzheimer's Disease: A Preliminary Study of Brains in the Multi-omics Atlas Project

Daniel Asby, Scott Miners, Laura Palmer, Johanna Jackson, Paul Matthews, Seth Love.

Cerebral vascular dysfunction, including cerebral hypoperfusion and blood-brain barrier (BBB) leakiness, are major contributors to cognitive decline in both vascular dementia and Alzheimer's disease (AD). In this study, we have measured and explored the relationship between markers of vascular dysfunction and disease pathology in brains from the Multi-omics Atlas project, an open resource dedicated to the comprehensive, multi-omic mapping of the cellular pathology of AD over representative stages in its evolution.

We studied 7 pure Alzheimer's disease (AD) cases with minimal co-pathologies, and 3 age-matched controls. Markers of chronic and more recent cerebral hypoperfusion (MAG:PLP1, VEGF-A level), BBB leakiness (haemoglobin-adjusted fibrinogen level), pericyte (PDGFRβ level) and endothelial (CD31) content, and insoluble Aβ42, were measured by ELISA in frontal, temporal, entorhinal, cingulate, calcarine and parahippocampal cortex, trigonal white matter and putamen.

We found widespread reduction in MAG:PLP1 and elevated VEGF-A in AD. Brain fibrinogen was increased and PDGFRβ reduced (and both remained so following adjustment for CD31 level), indicating widespread BBB leakiness and pericyte marker loss in AD. MAG:PLP1 ratio and VEGF-A correlated strongly with Aβ42 level. Fibrinogen and PDGFRβ correlated with markers of cerebral hypoperfusion as well as Aβ42. The relationships were strongest in brain regions with more pronounced cerebral hypoperfusion and higher Aβ42.

Our findings show widespread cortical and subcortical cerebrovascular dysfunction in AD, in which cerebral hypoperfusion and BBB breakdown are associated with pericyte damage and elevated Aβ42.