Relationship Between Platelet-Derived Growth Factor Receptor-β and Alzheimer's Biomarkers in a Racially Diverse, High-Risk Cohort.

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Background: With the increasing prevalence of Alzheimer's disease (AD), there is an increased need for systematic research targeting preclinical pathophysiologic mechanisms of AD development for high-risk, racially diverse, populations. Neurovascular dysfunction and blood brain barrier (BBB) breakdown likely occur early in AD pathology, however their relationship to AD biomarkers in preclinical populations are not well known. Soluble platelet derived growth factor receptor-β (sPDGFRβ), a novel CSF biomarker of BBB-associated capillary pericyte damage, is shed from injured human pericytes and is associated with AD pathology. Here we tested the hypothesis that sPDGFRβ is related to CSF AD biomarkers and CSF markers of vascular dysfunction in a cohort of African American (AA) and non-Hispanic White (NHW) participants.

Methods: Cognitively unimpaired, middle-aged (45-65 years) adults with a parental history of AD were enrolled. CSF was collected at baseline and 2 years for measurement of sPDGFRβ, AD biomarkers (Aβ and tau), and markers of vascular dysfunction (ACE activity, and VCAM-1).

Results: Participants (N=80) were mostly female (69%), well educated (81% college or greater), and 34% identified as AA. Forty-eight percent were ApoEε4 positive. At both baseline and 2 years sPDGFRβ was positively correlated with P-tau (r=.380, p=.003; r=.356, p=.008), T-tau (r=.466, p<.001; r=.485, p<.001), $A\beta_{40}$ (r=.439, p=.001; r=.454, p=.001), ACE-1 activity (r=.363, p=.003; r=.272, p=.041), and VCAM-1 (r=.511, p<.011; r-=.401, p=.002) and negatively correlated with $A\beta_{42/40}$ (r=-.282, p=.024; r=-.399, p=.002), controlling for age, sex, race, and education. At both time points, AAs had lower sPDGFRβ, P-tau, T-tau, and $A\beta_{40}$ and higher $A\beta_{42/40}$ compared to NHWs.

Conclusions: sPDGFRβ was associated with tau hyperphosphorylation (P-tau) and neurodegeneration (T-tau) in a cohort of cognitively normal middle-aged adults at risk for AD. Pericyte loss may relate to disease pathology early in AD development in at-risk individuals, providing a potential mechanistic target for early intervention and prevention strategies. sPDGFRβ was associated with ACE-1 and VCAM-1, suggesting a potential role for endothelial activation in early BBB breakdown. As we found differences in AD biomarkers between AA and NHW participants, reference ranges for these biomarkers may vary by race. More research is needed examining pre-clinical disease pathways in diverse populations.