Longitudinal pathways of cerebrospinal fluid and positron emission tomography biomarkers of amyloid-β positivity

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Abstract:

Mismatch between CSF and PET amyloid-β biomarkers occurs in up to ≈20% of preclinical/prodromal Alzheimer's disease individuals. Factors underlying mismatching results remain unclear. In this study we hypothesized that CSF/PET discordance provides unique biological/clinical information. To test this hypothesis, we investigated non-demented and demented participants with CSF amyloid-β42 and [18F]Florbetapir PET assessments at baseline (n = 867) and at 2-year follow-up (n = 289). Longitudinal trajectories of amyloid-β positivity were tracked simultaneously for CSF and PET biomarkers. In the longitudinal cohort (n = 289), we found that participants with normal CSF/PET amyloid-β biomarkers progressed more frequently toward CSF/PET discordance than to full CSF/PET positivity ($\chi2(1) = 5.40$; $p < 0.05$). Progression to CSF+/PET+ status was ten times more frequent in cases with discordant biomarkers, as compared to csf−/pet− cases ($\chi2(1) = 18.86$; $p < 0.001$). Compared to the CSF+/pet− group, the csf−/PET+ group had lower APOE-ε4ε4 prevalence ($\chi2(6) = 197$; $p < 0.001$; n = 867) and slower rate of brain amyloid-β accumulation ($F(3,600) = 12.76$; $p < 0.001$; n = 608). These results demonstrate that biomarker discordance is a typical stage in the natural history of amyloid-β accumulation, with CSF or PET becoming abnormal first and not concurrently. Therefore, biomarker discordance allows for identification of individuals with elevated risk of progression toward fully abnormal amyloid-β biomarkers, with subsequent risk of neurodegeneration and cognitive decline. Our results also suggest that there are two alternative pathways ("CSF-first" vs. "PET-first") toward established amyloid-β pathology, characterized by different genetic profiles and rates of amyloid-β accumulation. In conclusion, CSF and PET amyloid-β biomarkers provide distinct information, with potential implications for their use as biomarkers in clinical trials.

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