Alzheimer's Disease Normative Cerebrospinal Fluid Biomarkers Validated in PET Amyloid-☒ Characterized Subjects from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study

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Abstract: Background: The cerebrospinal fluid (CSF) amyloid-⊠ (A⊠)1-42, total-tau (T-tau), and phosphorylated-tau (P-tau181P) profile has been established as a valuable biomarker for Alzheimer's disease (AD). Objective: The current study aimed to determine CSF biomarker cut-points using positron emission tomography (PET) A⊠ imaging screened subjects from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging, as well as correlate CSF analyte cut-points across a range of PET A⊠ amyloid ligands. Methods: A⊠ pathology was determined by PET imaging, utilizing 11C-Pittsburgh Compound B, 18F-flutemetamol, or 18F-florbetapir, in 157 AIBL participants who also underwent CSF collection. Using an INNOTEST assay, cut-points were established (A⊠1-42 >544ng/L, T-tau <407ng/L, and P-tau181P <78 ng/L) employing a rank based method to define a "positive" CSF in the sub-cohort of amyloid-PET negative healthy participants (n=97), and compared with the presence of PET demonstrated AD pathology. Results: CSF A⊠1-42 was the strongest individual biomarker, detecting cognitively impaired PET positive mild cognitive impairment (MCI)/AD with 85% sensitivity and 91% specificity. The ratio of P-tau181P or T-tau to A⊠1-42 provided greater accuracy, predicting MCI/AD with A⊠ pathology with ⊠92% sensitivity and specificity. Cross-validated accuracy, using all three biomarkers or the ratio of P-tau or T-tau to A⊠1-42 to predict MCI/AD, reached ⊠92% sensitivity and specificity. Conclusions: CSF A⊠1-42 levels and analyte combination ratios demonstrated very high correlation with PET A⊠ imaging. Our study offers additional support for CSF biomarkers in the early and accurate detection of AD pathology, including enrichment of patient cohorts for treatment trials even at the pre-symptomatic stage.

Keywords: Alzheimer's disease, amyloid-⊠, cerebrospinal fluid biomarkers, positron emission tomography A⊠ imaging, tau

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