Alzheimer's disease normative cerebrospinal fluid biomarkers validated in PET amyloid-β characterized subjects from the Australian Imaging, Biomarkers and Lifestyle.

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

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Background: The cerebrospinal fluid (CSF) amyloid-β (Aβ)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) Aβ 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 Aβ amyloid ligands. Methods: Aβ 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 (Aβ1-42 >544 ng/L, T-tau <407 ng/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 Aβ1-42 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 Aβ1-42 provided greater accuracy, predicting MCI/AD with Aβ pathology with 92% sensitivity and specificity. Cross-validated accuracy, using all three biomarkers or the ratio of P-tau or T-tau to Aβ1-42 to predict MCI/AD, reached 92% sensitivity and specificity. Conclusions: CSF Aβ1-42 levels and analyte combination ratios demonstrated very high correlation with PET Aβ 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-β, cerebrospinal fluid biomarkers, positron emission tomography Aβ imaging, tau

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