Longitudinal amyloid PET changes by cerebrospinal fluid amyloid and tau profiles in individuals with normal cognition: Role of APOE ε4

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Abstract:

Background: Identifying factors associated with early progression of cortical amyloid deposition is crucial for understanding Alzheimer's disease (AD) pathophysiology, yet these remain unclear.

Objective: To investigate the associations of AD cerebrospinal fluid (CSF) biomarkers with early longitudinal amyloid deposition on positron emission tomography (PET), and the impact of APOE ε4 carriership.

Methods: We selected cognitively unimpaired participants with baseline data on CSF amyloid and p-tau181, APOE ε4 carriership, and ≥ 2 consecutive amyloid PET assessments from the AMYPAD-PNHS cohort. Linear mixed models were used to investigate the associations of combinations of amyloid abnormality (A+) and tau abnormality (T+) in CSF (A+T+, A+T-, A-T+, A-T-), without and with stratification for APOE ε4 carriership, with longitudinal global cortical amyloid deposition on PET, measured in Centiloids.

Results: We included 329 individuals (mean age 63.5 [SD 6.1], 58% female, 49% APOE ε4 carriers). Longitudinally, CSF profiles with abnormal amyloid levels (A+T+, A+T-) showed greater increases in cortical amyloid deposition than profiles with normal amyloid levels (A-T+, A-T-), irrespective of CSF tau abnormality (all $p < 0.001$). Only for CSF profiles with normal amyloid levels, longitudinal amyloid deposition depended on APOE ε4 carriership, with both A-T+ and A-T- showing increased deposition among APOE ε4 carriers (carriers versus non-carriers: A-T+ $p = 0.006$, A-T- $p = 0.016$).

Conclusions: In cognitively unimpaired individuals, longitudinal increase in cortical amyloid deposition was mainly associated with abnormal baseline CSF amyloid rather than tau. APOE ε4 carriership was associated with increased longitudinal cortical amyloid deposition only in individuals with normal baseline CSF amyloid. These findings inform early AD pathological progression and trial design.

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