ALZHEIMER DISEASE

Cerebrospinal fluid markers for AD change during middle age

According to a new longitudinal study, changes in the levels of various cerebrospinal fluid (CSF) biomarkers for Alzheimer disease (AD) can be detected in many cognitively normal adults throughout middle age. The results might facilitate the early detection of AD.

Anne Fagan and colleagues identified a cohort of participants in the Adult Children Study at Washington University in St Louis, MO, USA. This ongoing longitudinal study focuses on the early pathogenesis of AD, recruiting people between the ages of 45–74 years who have no signs of cognitive impairment, and regularly following up with them to conduct clinical examinations, CSF biomarker assays and neuroimaging.

The investigators identified 169 study participants who had provided at least two CSF samples, each approximately 3 years apart. Participants were stratified into early (45–54 years), intermediate (55–64 years) or late (65–74 years) middle age, and split into groups depending on whether they carried an *APOE*ε4* allele, the strongest genetic risk factor for AD. The investigators then analysed CSF samples for the hallmarks of AD: amyloid- β truncated at amino acid 42 ($A\beta_{1-42}$), total tau and phosphorylated tau protein. The team also assessed levels of visinin-like protein 1 (a marker of neuronal injury) and chitinase-3-like protein 1 (a marker of gliosis).

The investigators observed notable reductions in the level of CSF $A\beta_{1-42}$ in certain individuals from all the age groups. Among the participants with one or two *APOE*ε4* alleles, those in intermediate and late middle age had lower levels of $A\beta_{1-42}$ in CSF than did those in the youngest group. These decreases might reflect the sequestration of $A\beta_{1-42}$ in plaques.

Baseline levels of total tau were elevated in participants in late middle age who did not carry an *APOE*ε4* allele, and these people also showed longitudinal increases in tau levels. For *APOE*ε4* carriers, longitudinal increases in total tau levels were observed when participants were in early and intermediate middle age. Levels of phosphorylated tau and visinin-like protein 1 followed largely similar patterns as total tau.

Expression of chitinase-3-like protein 1 correlated positively with age, and these age-related increases were compounded by the presence of an *APOE*ε4* allele. The authors speculate that this result might reflect an association between neuroinflammation and/or gliosis with the deposition of $A\beta$ plaques in individuals with increased risk of AD.

A subset of the cohort ($n = 74$) also underwent PET with the amyloid tracer Pittsburgh Binding Compound B (PiB). Amyloid burden detected with PiB-PET was associated with decreased $A\beta_{1-42}$ in CSF, though many individuals without increased PiB binding showed comparably low levels of $A\beta_{1-42}$ to the PiB-positive participants. Together, these results suggest that CSF $A\beta_{1-42}$ decreases before plaques in the brain are detectable.

The results of this investigation provide valuable insight into how the levels of AD biomarkers in CSF change during middle age. Continued follow-up with these participants will be essential to determine how these changes relate to the subsequent development of dementia.

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