CSF biomarkers of neuroinflammation and cerebrovascular dysfunction in early Alzheimer disease

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Study objective
To test the hypothesis that elevated CSF biomarkers for neuroinflammation and cerebrovascular dysfunction are associated with Alzheimer Disease (AD) progression.

What is known and what this paper adds
AD is associated with neuroinflammation and cerebrovascular changes. This study provides evidence that CSF biomarkers for neuroinflammation and cerebrovascular dysfunction are increased at preclinical disease stages and may predict AD pathology.

Participants and setting
This study acquired data for 508 cognitively unimpaired elderly persons, 256 patients with mild cognitive impairment and 57 patients with AD dementia from the Swedish BioFINDER cohort.

Design, size, and duration
All participants underwent baseline clinical assessments, and follow-up assessments were conducted annually for patients with cognitive complaints and biennially for cognitively unimpaired participants. Cognitive decline was measured with the Mini-Mental State Examination and the Clinical Dementia Rating (CDR) scale. CSF samples were analyzed for 11 neuroinflammatory and cerebrovascular biomarkers. The biomarkers for AD pathology examined in this study were CSF β-amyloid (Aβ) and tau levels and cortical thinning in MRI scans.

Main results and the role of chance
Elevated levels of these biomarkers are associated with progression of AD pathology. Increased CSF levels of 5 neuroinflammatory and cerebrovascular biomarkers (YKL-40, ICAM-1, VCAM-1, IL-15 and Flt-1) were detected in the preclinical, prodromal, and dementia stages of AD (p ≤ 0.005) and were associated with the pathologic Aβ status (p < 0.001). The 5 biomarkers interacted with the Aβ status to predict the total tau status (p ≤ 0.043), and 3 of them interacted with the Aβ status to predict the phosphorylated tau status (p ≤ 0.024). Increased CSF levels of the biomarkers were associated with cortical thinning primarily in the precuneus and superior parietal regions. Increased CSF levels of 4 biomarkers were associated with faster CDR-measured cognitive decline (p ≤ 0.015).

Bias, confounding, and other reasons for caution
Past studies in this area have yielded conflicting results.

Generalizability to other populations
The examination of a large, well-characterized cohort favors the generalizability of this study’s results.

Study funding/potential competing interests
This study was funded by European and Swedish government agencies and various Swedish foundations. Some authors report cofounding Brain Biomarker Solutions and receiving research support, consultancy and speaker fees, advisory board appointments, and travel support from various biopharmaceutical companies. Go to Neurology.org/N for full disclosures.

Figure Kaplan-Meier curves for progression to AD among cognitively unimpaired participants and patients with mild cognitive impairment divided into tertiles for CSF YKL-40 levels

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