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Journal Club Neurology

Biomarker Changes 20 Years Preceding AD

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Background

Alzheimer's disease evolves over a period of several years before clinical signs appear. In this preclinical stage, neuropathologic abnormalities and changes in biomarker levels have been reported many years before clinical manifestations. Changes in cerebrospinal fluid (CSF) biomarkers such as levels of amyloid-beta ($A\beta$), total tau, phosphorylated tau 181, and neurofilament light chain (NfL) are indicators of preclinical Alzheimer's disease.

Results

This longitudinal study, spanning 20 years and assessing changes in CSF biomarkers, included 648 people who ultimately received a diagnosis of Alzheimer's disease and an equal number of matched people who remained cognitively normal. $A\beta_{42}$ levels

and the ratio of $A\beta_{42}$ to $A\beta_{40}$ diverged 18 years and 14 years before clinical signs appeared, respectively. The level of phosphorylated tau 181 increased eleven years before onset, while the level of NfL, a marker of neurodegeneration, increased nine years before the diagnosis.

Conclusion

While this study clearly demonstrates the sequence of changes in brain amyloid and CSF biomarkers in sporadic Alzheimer's disease, providing clinicians with useful starting points for prevention and therapeutic strategies, many questions remain for daily practice. Amyloid positron emission tomography imaging is expensive and not always covered by insurance. Lumbar punctures for CSF are not well tolerated by asymptomatic people at

risk. The use of blood-based biomarkers, which is not included in this study, is more acceptable, but results can be ambiguous. Diagnosing Alzheimer's disease and discussing treatment requires a significant investment from all stakeholders, including primary care physicians and memory specialists.

Jia J, Ning Y, Chen M, Wang S, Yang H, Li F, et al. Biomarker Changes during 20 Years Preceding Alzheimer's Disease. *N Engl J Med.* 2024 Feb;390(8):712-22. doi: 10.1056/NEJMoa2310168. PMID: 38381674.