CSF biomarkers in Alzheimer’s disease: are the hypotheses more dynamic than the biomarkers?

Abbreviated title: CSF biomarker dynamics in AD

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Biomarkers for Alzheimer's disease (AD) such as hippocampal atrophy and abnormal concentrations of cerebrospinal fluid (CSF) amyloid $\beta_{42}$ (A$\beta_{42}$), phosphorylated tau$_{181}$ (p-tau) and total tau (t-tau) have become established tools in the diagnostic work-up of patients suspected of dementia. Recently, AD research has seen a shift in focus towards the prodromal and preclinical stages of this disease, at the same time creating a shift in emphasis from clinical criteria towards biomarkers that represent core features of AD. The CSF biomarkers A$\beta_{42}$, p-tau and t-tau are promising candidates, as they reflect the neuropathologic features of AD and research indicates they become abnormal early in the disease process. However, data are currently lacking regarding the exact timing of these biomarkers becoming abnormal, and the order in which these events happen. Longitudinal studies to elucidate the dynamics of this process are still ongoing, but several hypothetical models have been proposed. These models are relevant in providing a framework for further research, for example to establish a paradigm in which biomarker changes over time could become surrogate end-points in disease modification trials. In addition, biomarker dynamics might provide information on disease stage and progression once these models have been confirmed.

An interesting feature that these models have in common is that they make a clear distinction between the moment that CSF A$\beta_{42}$ becomes abnormal and the moment that CSF tau becomes abnormal. Amyloid deposition (resulting in reduced levels of CSF A$\beta_{42}$) is suggested to be the earliest event, occurring long before cognitive symptoms are apparent, and plateauing early in the disease. Tau on the other hand is suggested to become abnormal much later, when clinical symptoms are already present, and to continue to increase in patients who progress from mild cognitive impairment (MCI) to moderate and severe dementia.$^{1,2}$

We question this distinction in timing between amyloid and tau. To illustrate that these models can be challenged by empirical data, we present a case of early-onset AD with the
longest follow-up of CSF biomarkers reported in the literature. During the nine years between
the earliest clinical manifestation and advanced dementia, we noted no essential changes in
CSF Aβ42, p-tau and t-tau. At age 53, this man presented with a mild memory disorder
objectified by neuropsychological testing. Neuroimaging (CT cerebrum) was normal, but CSF
analysis showed abnormal results: 294 pg/ml (reference value >500 pg/ml), phosphorylated
tau181 (p-tau) 141 pg/ml (<85 pg/ml), and t-tau 660 pg/ml (<350 pg/ml).3 No interference with
activities of daily living was established and MCI was diagnosed. Over the next four years he
gradually progressed – confirmed by repeated neuropsychological evaluation – to a diagnosis
of probable AD, Clinical Dementia Rating (CDR) 1. Nine years after first contact, we re­
evaluated this patient, now progressed to CDR 2, with marked brain atrophy on CT. Lumbar
puncture showed Aβ42 399 pg/ml, p-tau 108 pg/ml, t-tau 655 pg/ml.

This case suggests that either there is no delay between changes in CSF Aβ42, p-tau
and t-tau, or that the change in tau occurs much earlier than suggested, that is, already in the
preclinical stage. Studies in MCI patients support this by showing that both CSF Aβ42 and tau
are already abnormal in those patients who progressed to AD at follow up.4 We observed no
further decrease in Aβ42 or increase in p-tau or t-tau during disease progression in this case.
This observation is supported by the few longitudinal studies performed so far in MCI and
AD patients – albeit with a much shorter follow up of 2 years – that show a remarkable
stability of CSF Aβ42 and t-tau concentrations.4,5 This argues against the assumption that a
change in pathological direction of these biomarkers could be of use as surrogate markers to
reflect progression of disease.

This case questions models built largely on cross-sectional data. Inter-individual
differences in progression rate and disease duration at diagnosis make cross-sectional studies
unsuitable for inferences about the timing and order of events. Longitudinal studies covering
the full spectrum of the disease, with measurement of imaging and biochemical markers, will
be needed before a valid temporal model can be constructed. We speculate, however, that such studies will fail to demonstrate a clear distinction between the timing of Aβ42 and tau becoming abnormal. Likely, they will demonstrate a lack of relevant CSF Aβ42, p-tau and t-tau changes over time in the transition from early MCI to AD.
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Conflicts of Interest

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Author’s Contributions

Concept and design: Petra Spies and Jurgen Claassen; data collection: Petra Spies and Marcel Verbeek; analysis and interpretation of data: all authors; preparation of the manuscript: all authors. All authors approved the final version.

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References


