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Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring 1 (2015) 403-411

Alzheimer's & Dementia

CSF Biomarkers

Longitudinal cerebrospinal fluid biomarker measurements in preclinical sporadic Alzheimer's disease: A prospective 9-year study

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Abstract

Introduction: Ascertainment of the pattern and temporal change of biomarkers in preclinical (asymptomatic) sporadic Alzheimer's disease (AD) will increase knowledge about early pathogenesis and facilitate interventional therapeutic trials.
Methods: In this prospective longitudinal study, repeated cerebrospinal fluid (CSF) collections and cognitive evaluations were performed in cognitively healthy elderly individuals during a 9-year period.
Results: Low CSF β-amyloid $(A\beta)_{42}$ levels predicted subsequent development of clinical AD 9 years later. Noteworthy, one-third of individuals with pathologically low baseline $A\beta_{42}$ levels remained cognitively intact during follow-up. No further decrease in $A\beta_{42}$ was seen in those with low levels already at baseline.
Discussion: CSF $A\beta_{42}$ predicts sporadic AD at least 9 years before dementia onset and has plateaued already at this time. However, many individuals can harbor brain amyloid accumulation over a decade without signs of cognitive deterioration, which could implicate how CSF biomarkers are used to identify preclinical AD in future interventional therapeutic trials.

Keywords: Dementia; Alzheimer's disease; Cognitive aging; Cerebrospinal fluid; Cohort studies; β-Amyloid$_{1-42}$; Tau protein

1. Introduction

The slowly progressive nature of Alzheimer's disease (AD) implies a long preclinical phase before onset of cognitive symptoms. Increasing evidence suggests that cerebral accumulation of β-amyloid (Aβ) can be detected 5–20 years before dementia onset in AD, when using cerebrospinal fluid (CSF) $A\beta_{42}$ or amyloid positron emission tomography (PET) imaging [1–4]. Important evidence comes from studies evaluating asymptomatic individuals with autosomal dominant forms of AD [1,5]. To determine the temporal evolution of AD biomarkers during the early phases of sporadic AD, we need longitudinal studies with repeated biomarker assessments over 5–15 years covering the preclinical phases of AD. A few studies with repeated longitudinal biomarker assessments in cognitively healthy individuals have been published [6–8], but studies over extended periods, of >4 years, are still lacking.

Several studies imply that CSF can identify cognitively healthy elderly individuals that are at increased risk of subsequent development of cognitive decline [9–14]. However, the frequency of false positive cases is still unclear. To address this, we need long-term follow-up cognitively healthy individuals with deviant CSF biomarkers.

E.S., L.M., H.Z., and O.H. report no disclosures. K.B. is on the advisory board for Roche Diagnostics and for IBL International. All authors declare that they have no conflict of interest related to this study.

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http://dx.doi.org/10.1016/j.dadm.2015.09.002

In this prospective and longitudinal study, we investigated CSF biomarkers repeatedly over 9–10 years in individuals, who all were cognitively healthy at baseline. The cognitive performance and development of dementia were determined during the clinical follow-up. Great care was taken to minimize drop-out during the study.

2. Methods

2.1. Study design

The objective of this study was to model within-person neurodegenerative biomarker trajectories in preclinical AD using repeated assessments of CSF biomarkers and cognitive performance as well as to investigate the predictive ability of CSF biomarkers to identify future development of clinical dementia. It is a prospective, longitudinal, observational study on initially cognitively healthy elderly volunteers recruited through advertisement in year 2002 in the city of Malmö, Sweden [13], for the purpose to constitute a healthy control group in dementia studies. Individuals who responded were included in the study unless they fulfilled any of the prospectively set exclusion criteria. Baseline exclusion criteria were (1) subjective cognitive decline, (2) presence of mild cognitive impairment (MCI) or dementia, (3) mini-mental state examination (MMSE) [15] score of <27, and (4) presence of other morbidities possibly affecting cognitive status such as major depressive episode, ongoing alcohol abuse, and severs disorders of the central nervous system. Treatable and reversible diseases that could affect cognition were treated and did not lead to exclusion. Included participants were then followed longitudinally in approximately every third year with focus on cognitive performance and CSF measurements.

2.2. Subjects

In total, 62 individuals could be recruited of which 54 performed baseline lumbar puncture and CSF collection. All participants also underwent comprehensive examination including physical, neurologic, and psychiatric evaluation, computed tomography (CT) of the brain, and cognitive testing at baseline. Cognitive follow-up was offered after 3, 5, and 9–10 years with renewed lumbar puncture after 5 and 9–10 years. Individuals with baseline CSF values and clinical cognitive follow-up after 9 years (n = 44) were included in the main analyses of the present study (Fig. 1). Only a handful of participants were evaluated after closer to 10 years at the last follow-up, whereas the overwhelming majority was evaluated after 9 years.

In the subgroup of participants who were not available for the 9-year follow-up visit (n = 10, Fig. 1), medical record was collected and antemortem cognitive follow-up performances in the study were evaluated in nine cases. In this subgroup, we found one individual who had developed MCI and the rest were cognitively normal at the last observation.

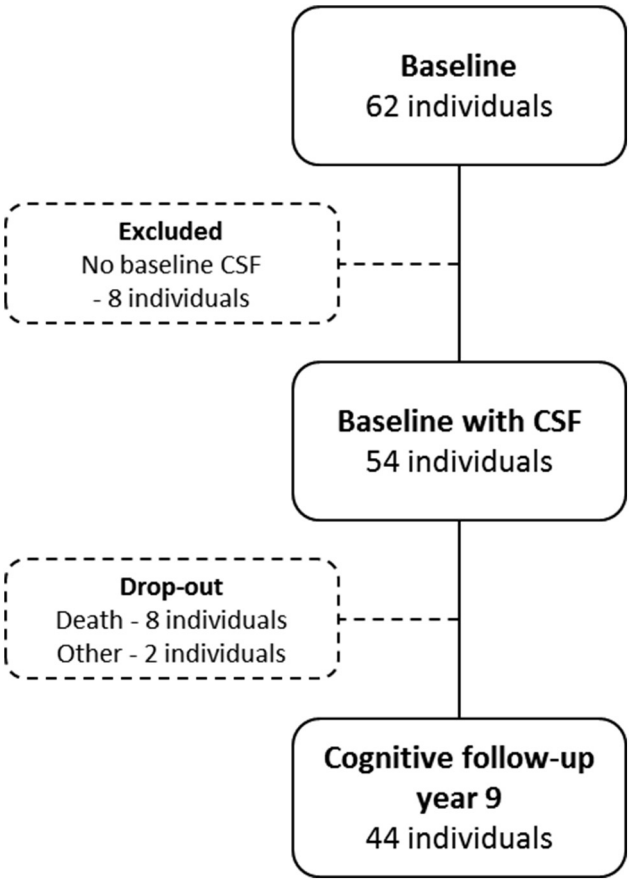

Fig. 1. Flowchart of inclusion and drop-out in the study sample. Abbreviation: CSF, cerebrospinal fluid.

2.3. Cognitive evaluation

Cognitive testing included MMSE (all visits) [15], clock drawing test (all visits) [16], cube drawing (all visits) [17], delayed memory in Alzheimer's disease assessment scale cognitive subscale (ADAS-cog; baseline, follow-up years 5 and 9) [17], and a quick test (follow-up years 3, 5, and 9) [18]. At follow-up after 9 years, Stroop test [19], trail making test A and B [20], symbol digit modalities test [21], letter S fluency test (phonemic fluency) [22], animal fluency test (semantic fluency) [22], and month naming test (the task of naming the months backward as fast as possible starting with December) were also added. Delayed memory was scored as number of correctly recalled words, which gives higher scores when better delayed memory function.

Cognitive diagnosis was based on clinical evaluation by a physician experienced in dementia disorders and was later confirmed by a consensus group of experienced physicians. The consensus group was blinded to biomarker values and had only access to medical history, cognitive test results, and CT scan results. Diagnosis criteria used in regular clinical settings were applied, i.e. MCI [23], Alzheimer's dementia [24], vascular dementia [25], dementia with Lewy body (DLB) [26], and other dementia (OD) [27]. DLB and AD participants are studied together in this study because