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Featured Article

Plasma concentrations of free amyloid β cannot predict the development of Alzheimer's disease

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Abstract

Introduction: Biomarkers that identify individuals at risk of Alzheimer's disease (AD) development would be highly valuable. Plasma concentration of amyloid β (Aβ)—central in the pathogenesis of AD—is a logical candidate, but studies to date have produced conflicting results on its utility.

Methods: Plasma samples from 339 preclinical AD cases (76.4% women, mean age 61.3 years) and 339 age- and sex-matched dementia-free controls, taken an average of 9.4 years before AD diagnosis, were analyzed using Luminex xMAP technology and INNOBIA plasma Aβ form assays to determine concentrations of free plasma $A\beta_{40}$ and $A\beta_{42}$.

Results: Plasma concentrations of free $A\beta_{40}$ and $A\beta_{42}$ did not differ between preclinical AD cases and dementia-free controls, in the full sample or in subgroups defined according to sex and age group (<60 and ≥ 60 years). The interval between sampling and AD diagnosis did not affect the results. Aβ concentrations did not change in the years preceding AD diagnosis among individuals for whom longitudinal samples were available.

Discussion: Plasma concentrations of free Aβ could not predict the development of clinical AD, and Aβ concentrations did not change in the years preceding AD diagnosis in this sample. These results indicate that free plasma Aβ is not a useful biomarker for the identification of individuals at risk of developing clinical AD.

Keywords: Plasma amyloid β; Aβ; Alzheimer's disease; Dementia; Preclinical Alzheimer's disease; Biomarker

1. Introduction

Several possibly disease-modifying treatments for Alzheimer's disease (AD) are currently being tested in phase 3 clinical trials. The identification of persons at risk of developing AD before symptom onset may thus soon become clinically relevant [1].

Amyloid pathology is present several years before the clinical onset of AD [2]. The analysis of peptide amyloid-β (Aβ) 1–42 in cerebrospinal fluid (CSF) has good diagnostic properties for AD in the clinical and prodromal disease stages, as has the measurements of amyloid burden with positron emission tomography (PET) [3,4]. These two measures are highly concordant [4], and new AD criteria highlight their importance in directly reflecting amyloid

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Table 1
Conditional logistic regression of plasma concentrations of free Aβ and Alzheimer's disease

Group	Alzheimer's disease cases	Dementia-free controls	Odds ratio	95% CI	*P*-value
$pA\beta_{42}$, mean ± SD (ng/L)	43.6 ± 13.1	44.6 ± 12.5	0.994	0.982–1.006	.316
$pA\beta_{40}$, mean ± SD (ng/L)	142.3 ± 36.3	143.9 ± 41.0	0.999	0.994–1.003	.525
$pA\beta_{42}$:$A\beta_{40}$ ratio, mean ± SD	0.325 ± 0.131	0.331 ± 0.129	0.664	0.190–2.325	.522

Abbreviations: CI, confidence interval; pAβ, free plasma amyloid-β peptide; SD, standard deviation.

pathology in AD [5]. However, neither CSF sampling through lumbar puncture nor amyloid PET investigation is feasible for screening to identify individuals at risk of developing AD in the general population. A blood test would be much practical in this context.

Plasma Aβ can be measured reliably using current assays, and given the firm relation between CSF Aβ and AD pathology, it has been investigated as a possible biomarker for AD [6–10]. Findings, however, are conflicting. Results of some studies have indicated that lower $A\beta_{42}$ concentrations or $A\beta_{42}$:$A\beta_{40}$ ratios are associated with a significantly increased risk of AD, whereas other studies have found the reverse relation or failed to identify any association [7–10]. Funnel plots from a meta-analysis suggest the presence of publication bias toward studies showing a relationship between $A\beta_{42}$ and AD [7].

The aim of the present nested case-control study was to investigate the association between free plasma Aβ and AD in a large sample of persons with preclinical AD and closely matched dementia-free controls, using plasma samples taken several years before AD diagnosis.

2. Methods

2.1. Participants

This nested case-control study is part of the Consortium on Health and Aging: Network of Cohorts in Europe and the United States project [11]. Participants were selected using a computerized procedure. Individuals diagnosed with AD at the University Hospital Memory Clinic, Umeå, Sweden, for whom stored EDTA plasma samples collected before clinical disease onset were available in the Medical Biobank of Umeå (The Northern Sweden Health and Disease Study Cohort) [12] were identified. Samples were selected when suitable age-, sex-, cohort-, and sampling date-matched dementia-free controls could be identified.

2.2. Confirmation of AD diagnoses

All AD cases had been examined and diagnosed at the University Hospital Memory Clinic in Umeå, Sweden. These diagnoses were the result of regular clinical investigations and were not related to participation in any study cohort. The diagnosis of AD was supported by typical symptoms of progressive cognitive failure; physical examination findings; results of cognitive screening tests, such as the Mini-Mental State Examination [13]; results of standard blood tests; and findings of examination using at least one brain imaging technique (X-ray computed tomography, magnetic resonance tomography, ^{99m}Tc single-photon emission computed tomography, and/or fluorodeoxyglucose PET). In many cases, the diagnoses were further supported by findings from neuropsychological examination and CSF analysis. An experienced specialist in psychogeriatric medicine assessed the accuracy of AD diagnoses by thorough review of medical records before the final inclusion of cases in the data set. All AD cases were diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition criteria [14], and clinical diagnoses were also compatible with the National Institute of Neurological and Communicative Disorders and Stroke—Alzheimer's Disease and Related Disorders Association criteria [15].

The dementia-free status of matched controls was checked using Swedish diagnosis registries, and persons were excluded when the diagnosis of any dementia disorder was found. The Swedish Death Registry was used to confirm that all controls were alive on the date of AD diagnosis for corresponding cases.

2.3. Plasma analyses

Plasma $A\beta_{40}$ and $A\beta_{42}$ concentrations were measured using Luminex xMAP technology and the INNOBIA plasma Aβ forms assays (Innogenetics, Ghent, Belgium), as described previously [16]. As the measurements were performed on neat EDTA plasma without any pretreatment, we measured the pool of Aβ for which epitopes were available to the antibodies (free Aβ). Plasma Aβ concentrations are presented in nanograms per liter. The measurements were performed in one round of experiments using one batch of reagents by board-certified laboratory technicians who were blinded to clinical data.

Table 2
Multiple linear regression of plasma concentrations of free Aβ

	Free plasma Aβ 1–42		Free plasma Aβ 1–40	
	β	*P*-value	β	*P*-value
Alzheimer's disease cases				
Age (years)	0.275	.041	0.341	.358
Female sex	0.910	.605	8.597	.079
Dementia-free controls				
Age (years)	0.128	.317	0.357	.400
Female sex	3.838	.023	5.100	.360