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LETTER

Plasma tau levels in Alzheimer's disease

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Introduction

Efforts to find reliable blood biomarkers for Alzheimer's disease (AD) in a highly warranted clinical laboratory test have met with little success. There is no clear change in plasma β-amyloid in AD, and assays for the axonal injury marker tau have been hampered by a lack of analytical sensitivity for accurate measurement in blood samples [1]. Here, the results of a novel ultra-sensitive assay for tau in peripheral blood are reported.

Findings

We have developed an ultra-sensitive assay for tau in peripheral blood [2]. In brief, the assay is based on digital array technology [3] and uses the Tau5 monoclonal antibody for capture (Covance, Princeton, NJ, USA) and HT7 and BT2 monoclonal antibodies for detection (Pierce, now part of Thermo Fisher Scientific Inc., Waltham, MA, USA). This combination reacts with both normal and phosphorylated tau with epitopes in the mid-region of the molecule, making the assay sensitive to all known tau isoforms. The calibrator was recombinant tau 381 (EMD Millipore Corporation, Billerica, MA, USA). To minimize matrix effects, all samples were diluted 1:4 in phosphate-buffered saline with 2% bovine serum albumin diluent prior to assay. The limit of detection of the assay, which requires 30 μL of plasma, is 0.02 pg/mL [2], which is more than 1,000-fold more sensitive than conventional immunoassays.

Here, we assess the association of plasma tau levels with AD in a cross-sectional study of 54 patients with AD dementia [4], 75 patients with mild cognitive impairment (MCI) [5], and 25 cognitively normal controls (Table 1). All participants were recruited at the specialized memory clinic at Skåne University Hospital in Malmö, Sweden, and underwent extensive clinical evaluation, including cerebrospinal fluid (CSF) sampling by lumbar puncture, in addition to venipuncture and collection of blood in ethylenediaminetetraacetic acid (EDTA) tubes for plasma preparation by centrifugation within 15 minutes from sampling. Plasma samples were aliquoted into cryo tubes and stored at −80°C pending analysis, which was performed on one occasion by using one batch of reagents with an average coefficient of variation of 9.7% for triplicate measurements of each sample. The patients with MCI were cognitively stable for an average of 101 months (n = 36) or developed AD dementia (n = 35) or other types of dementias – vascular dementia (n = 3) and semantic dementia (n = 1) – during follow-up. The study was approved by the regional ethics committee at Lund University and complied with the Declaration of Helsinki. Informed consent was obtained from all study participants.

Table 1. Demographic and biochemical data

	AD (n = 54)	MCI (n = 75)	Controls (n = 25)
Age, years	75 (6.2)	68 (9.3)	74 (6.7)
Gender, male/female	17/37	29/46	6/19
MMSE, score	19 (4.9)[a]	27 (1.6)	29 (1.4)
Plasma T-tau, pg/mL	8.80 (10.1)[b,c]	4.68 (4.25)	4.43 (2.83)
CSF T-tau, pg/mL	828 (375)[a]	550 (421)	507 (254)
CSF P-tau, pg/mL	123 (49.2)[a]	78.1 (28.8)	73.4 (20.5)
CSF Aβ42, pg/mL	380 (87.6)[a]	478 (204)	584 (215)

Quantitative data are presented as mean (standard deviation). Statistical differences were determined by using nonparametric tests. Cerebrospinal fluid (CSF) biomarker concentrations are INNOTEST ELISA-normalized Luminex AlzBio3 (Innogenetics, Gent, Belgium) values. [a]Compared with patients with mild cognitive impairment (MCI) or controls, $P < 0.001$. [b]Compared with patients with MCI, $P = 0.001$. [c]Compared with controls, $P = 0.02$. AD, Alzheimer's disease; MMSE, mini-mental state examination.

Tau levels in plasma were significantly higher in AD patients compared with both controls and MCI patients (Figure 1a). MCI patients who developed AD during follow-up had tau levels similar to those of patients with stable MCI and cognitively normal controls (Figure 1b). There was no correlation between tau levels in plasma and CSF in any diagnostic group (Figure 1c).

The results of this study have several important implications. First, plasma tau levels are elevated in AD but with overlapping ranges across diagnostic groups.

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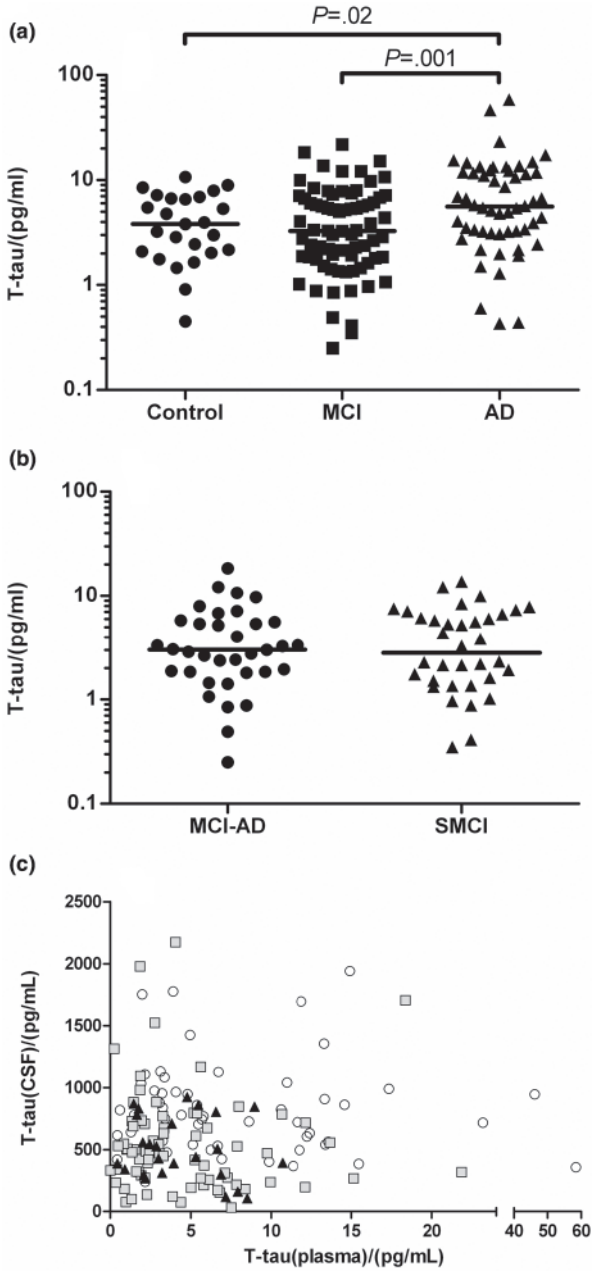

Figure 1. Elevated tau levels in plasma from patients with Alzheimer's disease (AD). (a) Plasma levels of tau are elevated in patients with AD compared with cognitively normal controls and patients with mild cognitive impairment (MCI). **(b)** MCI patients who developed AD (MCI-AD) during follow-up had baseline tau levels similar to those of patients with stable MCI (SMCI). **(c)** There was no correlation between tau levels in plasma and cerebrospinal fluid (CSF) in any diagnostic group. Thin horizontal lines in panels (a) and (b) indicate medians. A nonparametric Kruskal-Wallis test followed by Mann-Whitney was performed to test for statistical significance. Spearman's rank correlation coefficient was used to assess the relationship between plasma and CSF tau concentrations in panel (c), where open circles, gray squares, and black triangles represent AD, MCI, and controls, respectively.

This overlap diminishes the utility of plasma tau as a diagnostic test. However, further studies are needed to evaluate plasma tau as a first-in-line screening tool (for example, in the primary care setting and perhaps together with other markers in a biomarker panel). Second, normal plasma tau levels in the MCI stage of AD suggest that plasma tau is a late marker, requiring substantial axonal injury before increasing to abnormal levels. In this context, other neurodegenerative diseases (for example, Creutzfeldt-Jakob disease) as well as acute conditions (for example, stroke and brain trauma) should be tested. Third, the lack of correlation of tau levels in plasma and CSF suggests that steady-state concentrations of tau in these two body fluids are differentially regulated. In our earlier study of patients with hypoxic brain injury following cardiac arrest, tau was rapidly (within 24 hours) cleared from blood in patients with good neurological outcome [2], indicating potent clearance mechanisms for this marker in the bloodstream. This may obscure any correlation with CSF tau levels, which stay elevated for weeks following an acute neurological insult [6].

This article is part of a series on *Peripheral Biomarkers*, edited by Douglas Galasko. Other articles in this series can be found at http://alzres.com/series/biomarkers

Abbreviations
AD, Alzheimer's disease; CSF, cerebrospinal fluid; MCI, mild cognitive impairment.

Competing interests
DW and JR, who are employees of Quanterix Corporation (Lexington, MA, USA), and HZ and KB are listed as inventors on a US patent application for plasma tau as a brain injury marker. The other authors declare that they have no competing interests.

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