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Published in:
Alzheimer's Research & Therapy

DOI:
10.1186/alzrt163

2013

Link to publication

Citation for published version (APA):
Zetterberg, H., Wilson, D., Andreasson, U., Minthon, L., Blennow, K., Randall, J., & Hansson, O. (2013). Plasma tau levels in Alzheimer's disease. Alzheimer's Research & Therapy, 5(2), Article 9. https://doi.org/10.1186/alzrt163

Total number of authors:
7

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Plasma tau levels in Alzheimer’s disease

Henrik Zetterberg*1,2, David Wilson3, Ulf Andreasson1, Lennart Minthon4, Kaj Blennow1, Jeffrey Randall3 and Oskar Hansson4

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)*  | 27 (1.6)     | 29 (1.4)         |
| Plasma T-tau, pg/mL | 8.80 (10.1)* | 123 (49.2)*  | 137 (57.6)*      |
| CSF T-tau, pg/mL | 828 (375)* | 550 (421)    | 507 (254)        |
| CSF P-tau, pg/mL | 4.68 (4.25) | 78.1 (28.8)  | 73.4 (20.5)      |
| CSF Aβ42, pg/mL  | 828 (375)* | 550 (421)    | 507 (254)        |

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. *Compared with patients with mild cognitive impairment (MCI) or controls, P < 0.001. *Compared with patients with MCI, P = 0.001. *Compared with controls, P = 0.02. AD, Alzheimer’s disease; MMSE, mini-mental state examination.
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].

**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.

**Acknowledgments**
This study was funded by grants from Swedish Brain Power, the Swedish Research Council, the Wolfson Foundation, the Alzheimer’s Association, the JPND Project BIOMARKAPD, Swedish State Support for Clinical Research, the Swedish Brain Fund, the Alzheimer Foundation of Sweden, and the Dementia Association of Sweden.

**Author details**
1. Clinical Neurochemistry Laboratory, Institute of Neuroscience and Physiology, Department of Psychiatry and Neurochemistry, the Sahlgrenska Academy at the University of Gothenburg, S-431 80 Mölndal, Sweden.
2. UCL Institute of Neurology, Queen Square, London, WC1N 3BG, UK.
3. Quanterix Corporation, 113 Hartwell Avenue, Lexington, MA 02421, USA.
4. Clinical Memory Research Unit, Clinical Sciences Malmö, Lund University, Simrisbanvägen 14, S-212 24 Malmö, Sweden.

**Published:** 28 March 2013

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doi:10.1186/alzrt163

Cite this article as Zetterberg H, et al. Plasma tau levels in Alzheimer’s disease. *Alzheimer’s Research & Therapy* 2013, 5:9.