ELSEVIER

Alzheimer's & Dementia ■ (2018) 1-9

Alzheimer's & Dementia

Featured Article

Plasma phospho-tau181 increases with Alzheimer's disease clinical severity and is associated with tau- and amyloid-positron emission tomography

Michelle M. Mielke[a,b,*], Clinton E. Hagen[c], Jing Xu[d], Xiyun Chai[d], Prashanthi Vemuri[e], Val J. Lowe[e], David C. Airey[d], David S. Knopman[b], Rosebud O. Roberts[a,b], Mary M. Machulda[f], Clifford R. Jack, Jr.[e], Ronald C. Petersen[a,b], Jeffrey L. Dage[d]

[a]*Division of Epidemiology, Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota, USA*
[b]*Department of Neurology, Mayo Clinic, Rochester, MN, USA*
[c]*Division of Biomedical Statistics and Informatics, Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota, USA*
[d]*Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, USA*
[e]*Department of Radiology, Mayo Clinic, Rochester, MN, USA*
[f]*Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN, USA*

Abstract

Introduction: We examined and compared plasma phospho-tau181 (pTau181) and total tau: (1) across the Alzheimer's disease (AD) clinical spectrum; (2) in relation to brain amyloid β (Aβ) positron emission tomography (PET), tau PET, and cortical thickness; and (3) as a screening tool for elevated brain Aβ.

Methods: Participants included 172 cognitively unimpaired, 57 mild cognitively impaired, and 40 AD dementia patients with concurrent Aβ PET (Pittsburgh compound B), tau PET (AV1451), magnetic resonance imaging, plasma total tau, and pTau181.

Results: Plasma total tau and pTau181 levels were higher in AD dementia patients than those in cognitively unimpaired. Plasma pTau181 was more strongly associated with both Aβ and tau PET. Plasma pTau181 was a more sensitive and specific predictor of elevated brain Aβ than total tau and was as good as, or better than, the combination of age and apolipoprotein E (*APOE*).

Discussion: Plasma pTau181 may have utility as a biomarker of AD pathophysiology and as a noninvasive screener for elevated brain Aβ.

Keywords: Plasma tau; Plasma phosphorylated tau; Amyloid PET; Tau PET; Alzheimer's disease; Predicting brain amyloid

Conflicts of interest: M.M.M. served as a consultant to Eli Lilly and Lysosomal Therapeutics, Inc., and receives research support from the National Institutes of Health (R01 AG49704, P50 AG44170, and U01 AG06786 RF1 AG55151), Department of Defense (W81XWH-15-1), and unrestricted research grants from Biogen, Roche, and Lundbeck. J.X., X.C., D.C.A., and J.L.D. are employees of Eli Lilly. V.J.L. consults for Bayer Schering Pharma, Piramal Life Sciences, and Merck Research and receives research support from GE Healthcare, Siemens Molecular Imaging, AVID Radiopharmaceuticals, and the NIH (NIA, NCI). M.M.Ma. receives research support from the National Institutes of Health (U01 AG006786). R.O.R. receives research support from the National Institutes of Health (U01 AG006786) and an unrestricted research grant from F. Hoffman-La Roche. D.S.K. served as a Deputy Editor for *Neurology*®; serves on a Data Safety Monitoring Board for Lundbeck Pharmaceuticals and for the DIAN study; is an investigator in clinical trials sponsored by TauRx Pharmaceuticals, Lilly Pharmaceuticals, and the Alzheimer's Disease Cooperative Study; and receives research support from the NIH (R01 AG011378, P50 AG016574, U01 AG006786, AG029550, AG032306, and U01 HL096917). C.R.J. has provided consulting services for Eli Lilly. He receives research funding from the National Institutes of Health (R01 AG011378, U01 HL096917, U01 AG024904, RO1 AG041851, R01 AG037551, R01 AG043392, and U01 AG006786) and the Alexander Family Alzheimer's Disease Research Professorship of the Mayo Clinic. R.C.P. serves on scientific advisory boards for Roche, Inc., Merck, Inc., Biogen, Inc., and Genentech, Inc.; receives royalties from the publication of *Mild Cognitive Impairment* (Oxford University Press, 2003); and receives research support from the National Institutes of Health (P50 AG016574, U01 AG006786, U01 AG024904, and R01 AG011378). C.E.H. has no disclosures.

*Corresponding author. Tel.: 507-293-1069; Fax: 507-284-1516.
E-mail address: mielke.michelle@mayo.edu

https://doi.org/10.1016/j.jalz.2018.02.013
1552-5260/

1. Introduction

Blood-based biomarkers of Alzheimer's disease (AD) pathology (e.g., amyloid β [Aβ] or tau) will be essential for screening the general population, and in low- or middle-income countries, as the first step in a multistep process to determine which nondemented individuals are at greatest risk of AD dementia [1–3]. Because elevated brain Aβ is necessary for a diagnosis of AD dementia, and a requirement for some ongoing secondary prevention trials, a blood-based marker for predicting elevated brain Aβ would have great benefits. Several studies have examined either plasma or serum Aβ1-40 and Aβ1-42 peptides, but these measures have not consistently differed between AD dementia patients and cognitively unimpaired (CU) controls or were associated with cortical Aβ positron emission tomography (PET) deposition [4,5].

Studies examining the clinical utility of plasma total tau have consistently reported that higher levels are associated with cognitive decline and risk of mild cognitive impairment (MCI) [6,7], but this relationship is independent of brain Aβ [7]. Phosphorylated tau is thought to be more specific to AD pathogenesis than total tau [8]. Although blood measures of pTau have been difficult to measure to date due their low levels, recent studies have demonstrated that it may be possible [9]. The goals of the present study using a novel assay for pTau were to: (1) examine and compare levels of plasma phospho-tau181 (pTau181) and plasma total tau by clinical diagnosis across the AD spectrum; (2) examine the associations between plasma pTau181 and total tau with Aβ PET, tau PET, and cortical thickness; and (3) determine the clinical utility of plasma pTau181 or total tau as a screening tool for elevated brain Aβ. Given the specificity of CSF pTau to AD pathophysiology [8], we hypothesized that plasma pTau181 would be a more precise marker than total tau for AD-specific patterns of Aβ PET, tau PET, and cortical thickness.

2. Methods

2.1. Participants

Mayo Clinic data were pooled from two sources: the Mayo Clinic Study of Aging (MCSA) and the Alzheimer's Disease Research Center (ADRC). The MCSA is a population-based epidemiological cognitive aging study of Olmsted County, MN, residents [10,11], who were initially sampled using the Rochester Epidemiology Project medical records linkage system. Beginning in 2004, the MCSA enrolled residents aged 70–89 years; in 2012, enrollment was extended to include residents aged ≥50 years. The ADRC recruits and follows selected patients initially seen in the referral behavioral neurology practice at Mayo Clinic. All CU in this study were enrolled in the MCSA. Those with MCI or AD dementia were enrolled in either the MCSA or the ADRC. For both studies, same day imaging of both Aβ and tau PET began in 2016. The present analyses included the first individuals enrolled in the MCSA or ADRC with a diagnosis of CU, MCI, or AD and with Aβ PET, tau PET, magnetic resonance imaging (MRI), and blood (for total tau and pTau181 assays) at the same study visit. The study protocols were approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards. All participants provided written informed consent.

2.2. MCI and dementia diagnostic determination

For each participant, the clinical diagnosis was determined by a consensus committee including the neurologist, neuropsychologist, and the nurse who evaluated each participant. For MCSA participants, performance in a cognitive domain was compared with the age-adjusted scores of CU individuals previously obtained using Mayo's Older American Normative Studies [12]. This approach relies on prior normative work and extensive experience with the measurement of cognitive abilities in an independent sample of subjects from the same population. Subjects with scores around 1.0 SD below the age-specific mean in the general population were considered for possible cognitive impairment. The operational definition of MCI was based on clinical judgment including a history from the patient and informant. The following published criteria were used for the diagnosis: cognitive complaint, cognitive function not normal for age, essentially normal functional activities, and no dementia [13]. A final decision about impairment in a cognitive domain was made after considering education, occupation, visual or hearing deficits, and reviewing all other participant information. The diagnosis of dementia [14] and AD dementia [15] were based on the published criteria. Participants who performed in the normal range and did not meet criteria for MCI or dementia were deemed CU. Imaging was not considered in determining the clinical diagnosis.

2.3. Imaging methods

Aβ PET imaging was performed with Pittsburgh compound B [16] and tau PET with AV1451 [17] on the same day. Participants also completed computed tomography for attenuation correction. Late uptake Aβ PET images were acquired from 40–60 minutes and tau PET from 80–100 minutes after injection. All PET images were analyzed with our in-house fully automated image processing pipeline [18], where image voxel values are extracted from automatically labeled regions of interest (ROIs) propagated from an MRI template. An Aβ PET standardized update value ratio (SUVR) was formed from the voxel number weighted average of the median uptake in the prefrontal, orbitofrontal, parietal, temporal, anterior and posterior cingulate, and precuneus ROIs normalized to the cerebellar crus gray median. Based on previous work, elevated Aβ PET was defined as SUVR >1.42 [19]. Our primary tau PET ROI was the median uptake in the entorhinal cortex normalized to the