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Amyloid- β associated clinical decline occurs only in the presence of elevated p-tau

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Abstract

Objective—To elucidate the relationship between the two hallmark proteins of Alzheimer's disease (AD), amyloid- β (A β) and tau, and clinical decline over time among cognitively normal older individuals.

Design—A longitudinal cohort of clinically and cognitively normal older individuals assessed with baseline lumbar puncture and longitudinal clinical assessments.

Setting—Research centers across the United States and Canada.

Patients—We examined one hundred seven participants with a Clinical Dementia Rating (CDR) of 0 at baseline examination.

Main Outcome Measures—Using linear mixed effects models, we investigated the relationship between CSF p-tau_{181p}, CSF A β ₁₋₄₂ and clinical decline as assessed using longitudinal change in global CDR, CDR-Sum of Boxes (CDR-SB), and the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog).

Results—We found a significant relationship between decreased CSF A β ₁₋₄₂ and longitudinal change in global CDR, CDR-SB, and ADAS-cog in individuals with elevated CSF p-tau_{181p}. In the absence of CSF p-tau_{181p}, the effect of CSF A β ₁₋₄₂ on longitudinal clinical decline was not significantly different from zero.

Conclusions—In cognitively normal older individuals, A β -associated clinical decline over a mean of three years may occur only in the presence of ongoing, “downstream” neurodegeneration.

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Disclosure Statement

Dr. Anders M. Dale is a founder and holds equity in CorTechs Labs, Inc, and also serves on the Scientific Advisory Board. The terms of this arrangement have been reviewed and approved by the University of California, San Diego in accordance with its conflict of interest policies.

Dr. Linda K. McEvoy's spouse is CEO of CorTechs Labs, Inc.

INTRODUCTION

The identification of clinically normal older individuals destined to develop Alzheimer's disease (AD) is of increasing clinical importance as therapeutic interventions for the prevention of dementia are developed. Evidence from both genetic at-risk cohorts and clinically normal older individuals suggests that the pathobiological process of AD begins years before the diagnosis of clinical dementia.¹ Based on prior experimental evidence indicating that amyloid- β (A β) deposition triggers the neurodegenerative process underlying AD², a number of recent human studies have primarily focused on the relationship between A β , neurodegeneration, and cognitive decline to identify clinically normal elderly individuals considered to be in the 'preclinical' stage of dementia.³ However, amyloid plaques correlate poorly with memory decline⁴ and immunotherapy-induced plaque removal may not prevent progressive neurodegeneration⁵ suggesting that other entities may be required for AD-related degeneration.

Recent studies using transgenic mouse models show that the presence of tau is required for A β to induce neuronal and synaptic damage.⁶ Reductions in tau protect against A β -induced neuronal dysfunction⁷ while the presence of tau potentiates A β -associated synaptotoxicity.⁸ Recent evidence from our laboratory indicates that in older humans at risk for dementia, A β -associated volume loss occurs only in the presence of phospho-tau (p-tau).⁹ Building upon this work, in this study, using CSF levels of decreased A β_{1-42} and increased p-tau_{181p}, *in vivo* biomarkers of amyloid- β ¹⁰ and p-tau associated neurofibrillary pathology¹¹, we investigated whether A β -associated clinical decline in cognitively normal older individuals occurs only in the presence of p-tau.

SUBJECTS AND METHODS

We evaluated healthy older controls (HC, n = 107) from the Alzheimer's Disease Neuroimaging Initiative (ADNI). The ADNI is a large multi-site collaborative effort launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies and non-profit organizations as a public-private partnership aimed at testing whether serial MRI, PET, other biological markers and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. ADNI is the result of many co-investigators from a broad range of academic institutions and private corporations, with subjects recruited from over 50 sites across the US and Canada. For more information, please see <http://www.adni-info.org>.

Each participant was formally evaluated using eligibility criteria that are described in detail elsewhere (http://www.adniinfo.org/index.php?option=com_content&task=view&id=9&Itemid=43). The institutional review boards of all participating institutions approved the procedures for this study. Written informed consent was obtained from all participants or surrogates. Experienced clinicians conducted independent semi-structured interviews with the participant and a knowledgeable collateral source that included a health history, neurological examination, and a comprehensive neuropsychological battery.

We evaluated participants who were clinically diagnosed at baseline as cognitively and clinically normal. We examined clinical decline (537 longitudinal assessments) using the global Clinical Dementia Rating (CDR) scale, CDR-Sum of Boxes (CDR-SB)¹² and the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog).¹³ We restricted participants to those with baseline CSF data and baseline and follow-up clinical data.

Methods for CSF acquisition and biomarker measurement using the ADNI cohort have been reported previously.¹⁴ In brief, CSF was collected and stored at -80°C at the University of Pennsylvania ADNI Biomarker Core Laboratory. Amyloid- β from peptides 1-42, tau phosphorylated at threonine 181, and total tau was measured using the multiplex xMAP Luminex platform (Luminex Corp, Austin TX) with Innogenetics (INNOBIA AlzBio3, Ghent, Belgium) immunoassay kit-based reagents.

Using recently proposed CSF cutoffs¹⁴, we classified all participants based on high (>23 pg/ml, “positive”) and low (<23 pg/ml, “negative”) p-tau_{181p} levels and based on low (<192 pg/ml, “positive”) and high (>192 pg/ml, “negative”) A β ₁₋₄₂ levels (Table 1). We investigated the relationship between CSF A β ₁₋₄₂ status and clinical decline using a linear mixed effects model, controlling for the effects of age and sex. Specifically, $\Delta c = \beta_0 \times \Delta t + \beta_1 + \beta_1 \text{CSF_A}\beta_{1-42_status} \times \Delta t + \text{covariates} \times \Delta t + \epsilon$ Here, Δc = global CDR, CDR-SB or ADAS-cog score and Δt = change in time from baseline clinical assessment (years).

RESULTS

We first evaluated whether there was a relationship between CSF A β ₁₋₄₂ status and longitudinal clinical decline. Consistent with prior studies¹⁵⁻¹⁷, across all participants, we found that positive CSF A β ₁₋₄₂ status significantly correlated with change in global CDR ($\beta_1 = 0.03$, Standard Error (SE) = 0.01, $p = 0.04$), CDR-SB ($\beta_1 = 0.09$, SE = 0.05, $p = 0.048$), and ADAS-cog ($\beta_1 = 0.59$, SE = 0.23, $p = 0.0098$). To ensure that our results were not due to a categorical treatment of variables, we examined CSF A β ₁₋₄₂ as a continuous variable and found significant associations between decreased CSF A β ₁₋₄₂ levels and change in global CDR (β -coefficient = -0.0002, SE = 0.0001, $p = 0.030$), CDR-SB (β -coefficient = -0.0009, SE = 0.0004, $p = 0.041$), and ADAS-cog (β -coefficient = -0.005, SE = 0.002, $p = 0.016$).

We next investigated whether the presence of CSF p-tau_{181p} influenced the relationship between CSF A β ₁₋₄₂ and longitudinal clinical decline. We found that positive CSF A β ₁₋₄₂ status was associated with change in global CDR only among CSF p-tau_{181p} positive individuals ($\beta_1 = 0.06$, SE = 0.02, $p = 0.01$). There was no association between CSF A β ₁₋₄₂ status and change in global CDR among CSF p-tau_{181p} negative individuals ($\beta_1 = -0.02$, SE = 0.02, $p = 0.35$). Similarly, we found that positive CSF A β ₁₋₄₂ status was associated with change in CDR-SB scores only among CSF p-tau_{181p} positive individuals ($\beta_1 = 0.24$, SE = 0.11, $p = 0.036$) (Figure 1a). There was no association between CSF A β ₁₋₄₂ status and change in CDR-SB scores among CSF p-tau_{181p} negative individuals ($\beta_1 = -0.003$, SE = 0.04, $p = 0.94$). Consistent with these results, we found that positive CSF A β ₁₋₄₂ status was associated with change in ADAS-cog scores only among CSF p-tau_{181p} positive individuals ($\beta_1 = 0.94$, SE = 0.32, $p = 0.0043$) (Figure 1b). There was no association between CSF A β ₁₋₄₂ status and change in CDR-SB scores among CSF p-tau_{181p} negative individuals ($\beta_1 = 0.41$, SE = 0.34, $p = 0.23$).

Consistent with the results obtained from categorizing subjects on the basis of cutoff values, we found that decreased CSF A β ₁₋₄₂ levels significantly associated with change in global CDR only among CSF p-tau_{181p} positive individuals (β -coefficient = - 0.005, SE = 0.0002, $p = 0.02$). Similarly, decreased CSF A β ₁₋₄₂ levels significantly associated with change in ADAS-cog scores (β -coefficient = -0.007, SE = 0.002, $p = 0.0064$) and showed a trend towards significant association with change in CDR-SB scores (β -coefficient = -0.002, SE = 0.001, $p = 0.06$) only among CSF p-tau_{181p} positive individuals. Neither CSF p-tau_{181p} status nor CSF p-tau_{181p} level significantly associated with clinical decline, irrespective of CSF A β ₁₋₄₂ status.

Finally, we examined whether the presence of a nonspecific form of tau, total tau (t-tau), affected the relationship between CSF A β ₁₋₄₂ and longitudinal clinical decline. We classified all participants based on high (“positive”, n = 22) and low (“negative”, n = 85) t-tau levels using a CSF cutoff value of 93 pg/ml.¹⁴ We found that positive CSF A β ₁₋₄₂ status did not associate with change in global CDR or CDR-SB either among CSF t-tau positive or negative individuals. Positive CSF A β ₁₋₄₂ status significantly associated with change in ADAS-cog scores among CSF t-tau positive individuals (β -coefficient = 1.43, SE = 0.49, p = 0.005) and showed a trend towards significance among CSF t-tau negative individuals (β -coefficient = 0.48, SE = 0.27, p = 0.067).

DISCUSSION

Here, we show that in clinically normal older individuals A β -associated longitudinal clinical decline occurs only in the presence of elevated p-tau. In the absence of p-tau, the effect of A β on longitudinal clinical decline is not significantly different from zero.

These findings provide important insights into the preclinical stage of Alzheimer's disease. Consistent with prior studies^{18-19, 22-23}, our results indicate that in clinically normal older individuals A β deposition by itself is not associated with clinical decline; the presence of p-tau represents a critical link between A β deposition and accelerated clinical decline. Furthermore, our findings point to p-tau as an important marker of AD-associated degeneration. Elevations in CSF total tau are seen in a number of neurologic disorders characterized by neuronal and axonal death whereas increased CSF p-tau correlates with increased neurofibrillary pathology and can distinguish AD from other neurodegenerative disorders²⁰ suggesting that p-tau may represent a more specific marker of the Alzheimer's pathologic process than total tau. When considered together with recent work from our laboratory⁹, these data suggest that the combination of p-tau and A β likely reflects underlying pathobiology of the preclinical stage of AD.

Recent experiments using transgenic mice illustrates that the presence of tau potentiates A β -associated neurodegeneration. Postsynaptic A β toxicity is tau dependent^{6,8} and tau reduction prevents premature mortality and memory deficits in APP23 mice.⁷⁻⁸ Our human data are consistent with these experimental findings.

This study has limitations. One concern is that CSF biomarkers provide an indirect assessment of amyloid and neurofibrillary pathology and may not fully reflect the biological processes underlying Alzheimer's disease. Another concern is that though our findings indicate that CSF A β ₁₋₄₂, in combination with CSF p-tau_{181p}, may better predict clinical decline than CSF A β ₁₋₄₂, in combination with CSF t-tau, prior studies have shown that CSF p-tau and t-tau, when combined with CSF A β ₁₋₄₂, are equally predictive of decline.^{18-19, 22-23} This difference maybe related to slight differences in CSF measurement assays (ELISA vs. Luminex), the nature of the participant population or other factors. A third limitation is that we primarily focused on CSF biomarkers of the two pathologic hallmarks of AD. Additional markers, such as CSF levels of YKL-40²² or Visinin-like protein-1 (VILIP-1)²³, may also interact with A β to predict clinical decline in cognitively normal elders. Finally, the individuals examined here may represent a group of highly selected, generally healthy older adults who are motivated to participate in research studies. As such, these findings need to be further validated on an independent, community-based cohort of older individuals that would be more representative of the general older population.

From a clinical perspective, these results are consonant with the three stage preclinical AD framework recently proposed by the National Institute on Aging-Alzheimer's Association

workgroup³ and indicate that a biomarker profile consisting of both CSF A β ₁₋₄₂ and CSF p-tau_{181p} levels may better identify those older individuals who are at an elevated risk of progressing to eventual AD dementia than either biomarker by itself. Given that A β accumulation is 'necessary but not sufficient' to express the clinical manifestations of AD dementia³, early intervention trials should take into account both the CSF p-tau_{181p} and CSF A β ₁₋₄₂ status of participants since older individuals with increased CSF p-tau_{181p} and decreased CSF A β ₁₋₄₂ levels are likely to have a different rate of clinical progression than individuals with normal CSF p-tau_{181p} and decreased CSF A β ₁₋₄₂ levels. These findings also illustrate the need for developing novel therapeutic approaches that specifically target tau. It is feasible that though A β initiates the degenerative cascade, elevated levels of tau may represent a second phase of the AD pathologic process where neurodegenerative changes occur largely independent of A β .²¹ As such, targeting 'downstream' events, such as tau phosphorylation and aggregation, in older individuals with both decreased CSF A β ₁₋₄₂ and increased CSF p-tau_{181p} levels may be an additionally beneficial treatment strategy.

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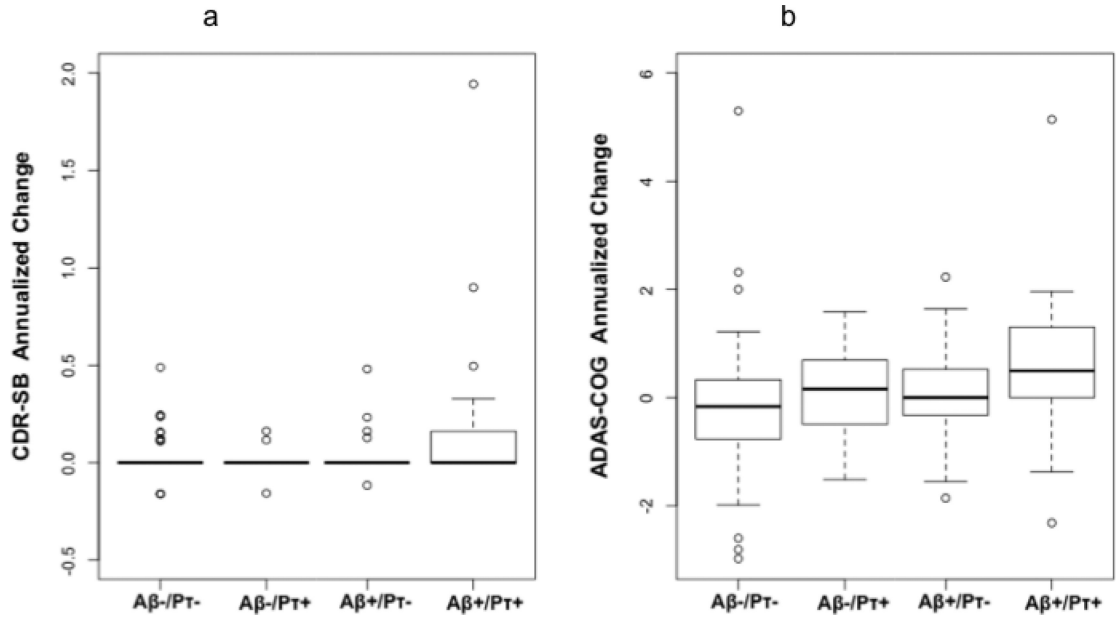


Figure 1. Box and whisker plots for all participants illustrating change in (a) CDR-SB and (b) ADAS-cog scores, measured as annualized percent change (APC), based on CSF Aβ₁₋₄₂ (Aβ) and CSF p-tau_{181p} (pτ) status. For each plot, thick black lines show the median value. Regions above and below the black line show the upper and lower quartiles, respectively. The dashed lines extend to the minimum and maximum values with outliers shown as open circles. As illustrated, the Aβ +/pτ + individuals demonstrated the largest change in CDR-SB and ADAS-cog scores.

Table 1

Demographic, clinical, and imaging data for all healthy older controls (HC) in this study. MMSE = Mini-mental status exam, CDR-SB = CDR-Sum of Box Scores, ADAS-cog = Alzheimer's Disease Assessment Scale-cognitive subscale, APC = Annualized Percent Change, SE = Standard error of the mean

	Aβ -/P-tau - (n = 46)	Aβ -/P-tau + (n = 19)	Aβ +/P-tau - (n = 20)	Aβ +/P-tau + (n = 21)
Age, Mean (SE)	74.3 (0.6)	78.0 (1.4)	74.9 (1.1)	78.2 (1.0)
Female, %	24	29	31	38
Education Years, Mean (SE)	15.5 (0.4)	15.5 (0.4)	14.8 (0.8)	16.7 (0.6)
MMSE, Mean (SE)	29.1 (0.1)	28.8 (0.3)	29.1 (0.2)	29.3 (0.2)
Years Follow-up, Mean (SE)	3.3 (0.1)	3.3 (0.2)	3.0 (0.2)	2.9 (0.2)
ADAS- cog APC, Mean (SE)	-0.13 (0.7)	0.43 (0.6)	0.61 (0.7)	1.6 (0.9)
CDR-SB APC, Mean (SE)	0.03 (0.01)	0.006 (0.01)	-0.03 (0.1)	0.2 (0.1)