Amyloid-β–Associated Clinical Decline Occurs Only in the Presence of Elevated P-tau

Rahul S. Desikan, MD, PhD; Linda K. McEvoy, PhD; Wesley K. Thompson, PhD; Dominic Holland, PhD; James B. Brewer, MD, PhD; Paul S. Aisen, MD; Reisa A. Sperling, MD; Anders M. Dale, PhD; for the Alzheimer’s Disease Neuroimaging Initiative

Objective: To elucidate the relationship between the 2 hallmark proteins of Alzheimer disease (AD), amyloid-β (Aβ) 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 107 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 cerebrospinal fluid (CSF) phospho-tau 181 (p-tau181p), CSF Aβ1-42, and clinical decline as assessed using longitudinal change in global CDR, CDR–Sum of Boxes, and the Alzheimer Disease Assessment Scale–cognitive subscale.

Results: We found a significant relationship between decreased CSF Aβ1-42 and longitudinal change in global CDR, CDR–Sum of Boxes, and Alzheimer Disease Assessment Scale–cognitive subscale in individuals with elevated CSF p-tau181p. In the absence of CSF p-tau181p, the effect of CSF Aβ1-42 on longitudinal clinical decline was not significantly different from 0.

Conclusions: In cognitively normal older individuals, Aβ-associated clinical decline during a mean of 3 years may occur only in the presence of ongoing downstream neurodegeneration.


THE IDENTIFICATION OF CLINICALLY NORMAL OLDER INDIVIDUALS DESTINED TO DEVELOP ALZHEIMER 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 PATHOLOGIC PROCESS OF AD BEGINS YEARS BEFORE THE DIAGNOSIS OF CLINICAL DEMENTIA.1 Based on prior experimental evidence indicating that amyloid-β (Aβ) deposition triggers the neurodegenerative process underlying AD,2 a number of recent human studies have primarily focused on the relationship between Aβ, 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 neurodegeneration,5 suggesting that other entities may be required for AD-related degeneration.

CME available online at www.jamaarchivescme.com

Recent studies using transgenic mouse models show that the presence of tau is required for Aβ to induce neuronal and synaptic damage.6 Reductions in tau protect against Aβ-induced neuronal dysfunction,7 while the presence of tau potentiates Aβ-associated synapotoxicity.8 Recent evidence from our laboratory indicates that in older humans at risk for dementia, Aβ-associated volume loss occurs only in the presence of phospho-tau (p-tau).9 Building upon this work, we used cerebrospinal fluid (CSF) levels of decreased Aβ1-42 and increased p-tau181p, in vivo biomarkers of amyloid-β,10 and p-tau–
Table. Demographic, Clinical, and Imaging Data for All Healthy Older Control Subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Aβ-+/p-tau - (n = 46)</th>
<th>Aβ-+/p-tau + (n = 19)</th>
<th>Aβ+/p-tau - (n = 20)</th>
<th>Aβ+/p-tau + (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>74.3 (0.6)</td>
<td>78.0 (1.4)</td>
<td>74.9 (1.1)</td>
<td>78.2 (1.0)</td>
</tr>
<tr>
<td>Female, %</td>
<td>24</td>
<td>29</td>
<td>31</td>
<td>38</td>
</tr>
<tr>
<td>Education, y</td>
<td>15.5 (0.4)</td>
<td>15.5 (0.4)</td>
<td>14.8 (0.8)</td>
<td>16.7 (0.6)</td>
</tr>
<tr>
<td>MMSE</td>
<td>29.1 (0.1)</td>
<td>28.8 (0.3)</td>
<td>29.1 (0.2)</td>
<td>29.3 (0.2)</td>
</tr>
<tr>
<td>Follow-up, y</td>
<td>3.3 (0.1)</td>
<td>3.3 (0.2)</td>
<td>3.0 (0.2)</td>
<td>2.9 (0.2)</td>
</tr>
<tr>
<td>ADAS-cog annualized change, %</td>
<td>–0.13 (0.7)</td>
<td>0.43 (0.6)</td>
<td>0.61 (0.7)</td>
<td>1.6 (0.9)</td>
</tr>
<tr>
<td>CDR-SB annualized change, %</td>
<td>0.03 (0.01)</td>
<td>0.006 (0.01)</td>
<td>–0.03 (0.1)</td>
<td>0.2 (0.1)</td>
</tr>
</tbody>
</table>

Abbreviations: Aβ, amyloid-β; ADAS-cog, Alzheimer Disease Assessment Scale-cognitive subscale; CDR-SB, Clinical Dementia Rating–Sum of Boxes; MMSE, Mini-Mental Status Examination; and p-tau, phospho tau.

We first evaluated whether there was a relationship between CSF Aβ1-42 status and longitudinal clinical decline. Consistent with prior studies,13–17 across all participants, we found that positive CSF Aβ1-42 status significantly correlated with change in global CDR (β̂ = 0.03; standard error [SE] = 0.01; P = .04), CDR-SB (β̂ = 0.09; SE = 0.05; P < .05), and ADAS-cog (β̂ = 0.59; SE = 0.23; P = .01). To ensure that our results were not owing to a categorical treatment of variables, we examined CSF Aβ1-42 as a continuous variable and found significant associations between decreased CSF Aβ1-42 levels and change in global CDR (β-coefficient = −0.002; SE = 0.0001; P = .03), CDR-SB (β-coefficient = −0.0009; SE = 0.0004; P = .04), and ADAS-cog (β-coefficient = −0.005; SE = 0.002; P = .02).

We next investigated whether the presence of CSF p-tau181p influenced the relationship between CSF Aβ1-42 and longitudinal clinical decline. We found that positive CSF Aβ1-42 status was associated with change in global CDR only among CSF p-tau181p-positive individuals (β̂ = 0.06; SE = 0.02; P = .01). There was no association between CSF Aβ1-42 status and change in global CDR among CSF p-tau181p-negative individuals (β̂ = −0.02; SE = 0.02; P = .35). Similarly, we found that positive CSF Aβ1-42 status was associated with change in CDR-SB scores only among CSF p-tau181p-positive individuals (β̂ = 0.24; SE = 0.11; P = .04) (Figure, A). There was no association between CSF Aβ1-42 status and change in CDR-SB scores among CSF p-tau181p-negative individuals (β̂ = −0.003; SE = 0.04; P = .94). Consistent with these results, we found that positive CSF Aβ1-42 status was associated with change in ADAS-cog scores only among CSF p-tau181p-positive individuals (β̂ = 0.94, SE = 0.32, P = .004) (Figure, B). There was no association between
CSF Aβ1-42 status and change in CDR-SB scores among CSF p-tau181p–negative individuals (β = 0.41; SE = 0.34; P = .23).

Consistent with the results obtained from categorizing subjects on the basis of cutoff values, we found that decreased CSF Aβ1-42 levels significantly associated with change in global CDR only among CSF p-tau181p–positive individuals (β-coefficient = –0.005; SE = 0.0002; P = .02). Similarly, decreased CSF Aβ1-42 levels significantly associated with change in ADAS-cog scores (β-coefficient = –0.007; SE = 0.002; P = .006) and showed a trend toward significant association with change in CDR-SB scores (β-coefficient = –0.002; SE = 0.001; P = .06) only among CSF p-tau181p–positive individuals. Neither CSF p-tau181p status nor CSF p-tau181p level significantly associated with clinical decline, irrespective of CSF Aβ1-42 status.

Finally, we examined whether the presence of a non-specific form of tau—t-tau—affected the relationship between CSF Aβ1-42 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 Aβ1-42 status did not associate with change in global CDR or CDR-SB either among CSF t-tau–positive or–negative individuals. Positive CSF Aβ1-42 status significantly associated with change in ADAS-cog scores among CSF t-tau–positive individuals (β-coefficient = 1.43; SE = 0.49; P = .005) and showed a trend toward significance among CSF t-tau–negative individuals (β-coefficient = 0.48; SE = 0.27; P = .07).

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

These findings provide important insights into the preclinical stage of AD. Consistent with prior studies,18-21 our results indicate that in clinically normal older individuals, Aβ deposition by itself is not associated with clinical decline; the presence of p-tau represents a critical link between Aβ deposition and accelerated clinical decline. Furthermore, our findings point to p-tau as an important marker of AD-associated degeneration. Elevations in CSF t-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 disorders,22 suggesting that p-tau may represent a more specific marker of the Alzheimer pathologic process than t-tau. When considered together with recent work from our laboratory,13 these data suggest that the combination of p-tau and Aβ likely reflects underlying pathobiology of the preclinical stage of AD.

Recent experiments using transgenic mice illustrate that the presence of tau potentiates Aβ–associated neurodegeneration. Postsynaptic Aβ toxicity is tau dependent19 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 AD. Another concern is that although our findings indicate that CSF Aβ1-42 in combination with CSF p-tau181p may better predict clinical decline than CSF Aβ1-42 in combination with CSF t-tau, prior studies have shown that CSF p-tau and t-tau when combined with CSF Aβ1-42 are equally predictive of decline.18-21 This difference may be related to slight differences in CSF measurement assays (enzyme-linked immunosorbent assay vs Luminesx), the nature of the participant population, or other factors. A third limitation is that we primarily focused on CSF biomarkers of the 2 pathologic hallmarks of AD. Additional markers, such as CSF levels of YKL-4020 or visinin-like protein 1,20 may also interact with Aβ to predict clinical decline in cognitively normal elderly individuals. Finally, the
individuals we examined 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 3-stage preclinical AD framework recently proposed by the National Institute on Aging–Alzheimer Association workgroup and indicate that a biomarker profile consisting of both CSF Aβ 1-42 and CSF p-tau 181p levels may better identify those older individuals who are at an elevated risk for progressing to eventual AD dementia than either biomarker by itself. Given that Aβ accumulation is necessary but not sufficient to express the clinical manifestations of AD dementia, early intervention trials should take into account both the CSF p-tau 181p, and CSF Aβ 1-42 status of participants because older individuals with increased CSF p-tau 181p and decreased CSF Aβ 1-42 levels are likely to have a different rate of clinical progression than individuals with normal CSF p-tau 181p and decreased CSF Aβ 1-42 levels. These findings also illustrate the need for developing novel therapeutic approaches that specifically target tau. It is feasible that although Aβ 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 Aβ. As such, targeting downstream events, such as tau phosphorylation and aggregation, in older individuals with both decreased CSF Aβ 1-42 and increased CSF p-tau 181p levels may be an additionally beneficial treatment strategy.


Correspondence: Rahul S. Desikan, MD, PhD, Department of Radiology, University of California–San Diego, 8950 Villa La Jolla Dr, Ste C101, La Jolla, CA 92037-0841 (rdesikan@ucsd.edu).

Author Contributions: Study concept and design: Desikan, Brewer, and Dale. Analysis and interpretation of data: Desikan, McEvoy, Thompson, Holland, Brewer, Aisen, Sperling, and Dale. Drafting of the manuscript: Desikan, McEvoy, and Dale. Critical revision of the manuscript for important intellectual content: Desikan, McEvoy, Thompson, Holland, Brewer, Aisen, Sperling, and Dale. Statistical analysis: Desikan, Thompson, and Dale. Obtained funding: Dale. Administrative, technical, and material support: Desikan and Dale. Study supervision: Desikan, McEvoy, Brewer, Sperling, and Dale.


Financial Disclosure: Dr McEvoy’s spouse is the chief executive officer of CorTechs Labs. Dr Aisen serves on a scientific advisory board for NeuroPhage as well as serves as a consultant to Elan, Wyeth, Eisai, Bristol-Myers Squibb, Eli Lilly, NeuroPhage, Merck, Roche, Amgen, Abbott Laboratories, Pfizer, Novartis, Bayer, Astellas Pharma, Dainippon, Biomarin, Solvay, Otsuka, Daiichi Sankyo, AstraZeneca, Janssen Pharmaceuticals, Medivation, Tervance, Carderis, and Anavex. He also receives research support from Pfizer, Baxter International, and the National Institutes of Health (grants 01-AG10483, U01-AG024904, R01-AG030048, and R01-AG16381 from the National Institute on Aging). He has also received stock options from Medivation. Dr Dale is a founder and holds equity in CorTechs Labs and also serves on the company’s 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.

Funding/Support: This study was supported by grants R01AG031224, K01AG029218, K02 NS067427, T32 EB005970, P01 AG036694, and K24 AG033007 from the National Institutes of Health and a Young Scholar Award from the Alzheimer’s Association San Diego/Imperial Chapter. Data collection and sharing for this study was funded by the Alzheimer’s Disease Neuroimaging Initiative (grant U01 AG024904 from the National Institute of Health). The Alzheimer’s Disease Neuroimaging Initiative (ADNI) is funded by the National Institute on Aging; the National Institute of Biomedical Imaging and Bioengineering; and contributions from Abbott Laboratories, AstraZeneca, Bayer Schering Pharma, Bristol-Myers Squibb, Eisai Global Clinical Development, Elan, Genentech, GE Healthcare, GlaxoSmithKline, Innogenetics, Johnson & Johnson, Eli Lilly, Medpace, Merck, Novartis, Pfizer, F. Hoffman-La Roche, Schering-Plough, Synarc, and Wyeth, as well as non-profit partners the Alzheimer’s Association and Alzheimer’s Drug Discovery Foundation, with participation from the US Food and Drug Administration. Private sector contributions to ADNI are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer’s Disease Cooperative Study at the University of California–San Diego. Alzheimer’s Disease Neuroimaging Initiative data are disseminated by the Laboratory for Neuro Imaging at the University of California–Los Angeles. This research was also supported by grants P30 AG010129 and K01 AG030514 from the National Institutes of Health and the Dana Foundation.

Additional Information: Data used in the preparation of this article were obtained from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu/). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this article.

REFERENCES


©2012 American Medical Association. All rights reserved.