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

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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 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.


See editorial comment see page 691

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 pathobiologic 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.

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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-tau in vivo biomarkers of amyloid-β,10 and p-tau–
associated neurofibrillary pathology to investigate whether Aβ-associated clinical decline in cognitively normal older individuals occurs only in the presence of p-tau.

**METHODS**

We evaluated healthy older control participants (n = 107) from the Alzheimer Disease Neuroimaging Initiative (ADNI). The ADNI is a large multisite 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 nonprofit organizations as a public–private partnership aimed at testing whether serial magnetic resonance imaging, positron-emission tomography, other biological markers, and clinical and neuropsychologic assessment can be combined to measure the progression of mild cognitive impairment and early AD. The Alzheimer Disease Neuroimaging Initiative (http://www.adni-info.org) is the result of the work by many investigators from a broad range of academic institutions and private corporations, with subjects recruited from more than 30 sites across the United States and Canada.

Each participant was formally evaluated using eligibility criteria that are described in detail elsewhere (http://www.adni-info.org). 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 semistructured interviews with the participant, and a knowledgeable collateral source that included health history, neurologic examination, and comprehensive neuropsychologic 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) across all participants, we found that positive CSF Aβ1-42 status significantly correlated with change in global CDR (β1.03; standard error [SE] = 0.01; P = .04), CDR-SB (β = 0.09; SE = 0.05; P < .05), and ADAS-cog (β = 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 = −0.0002; 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 (β = 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 (β = −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 (β = 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 (β = −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 (β = 0.94; SE = 0.32; P = .004) (Figure, B). There was no association between...

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, across all participants, we found that positive CSF Aβ1-42 status significantly correlated with change in global CDR (β = 0.03; standard error [SE] = 0.01; P = .04), CDR-SB (β = 0.09; SE = 0.05; P < .05), and ADAS-cog (β = 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 = −0.0002; 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).
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 = 0.002; 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).

**COMMENT**

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,3 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 dependent36 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 Lumineux), 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 1,21 may also interact with Aβ to predict clinical decline in cognitively normal elderly individuals. Finally, the

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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 A\textsubscript{\beta} and CSF p-tau\textsubscript{181} 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 A\textsubscript{\beta} 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\textsubscript{181} and CSF A\textsubscript{\beta} status of participants because older individuals with increased CSF p-tau\textsubscript{181} and decreased CSF A\textsubscript{\beta} levels are likely to have a different rate of clinical progression than individuals with normal CSF p-tau\textsubscript{181} and decreased CSF A\textsubscript{\beta} levels. These findings also illustrate the need for developing novel therapeu tic approaches that specifically target tau. It is feasible that although A\textsubscript{\beta} 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\textsubscript{\beta}. As such, targeting downstream events, such as tau phosphorylation and aggregation, in older individuals with both decreased CSF A\textsubscript{\beta} and increased CSF p-tau\textsubscript{181} levels may be an additionally beneficial treatment strategy.


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REFERENCES


