Pathologic Accumulation of α-Synuclein and Aβ in Parkinson Disease Patients With Dementia

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Objective: To determine the relative contributions of individual pathologic protein deposits associated with dementia in patients with Parkinson disease (PD).

Design: Autopsied patients were analyzed from February 24, 2005, through July 25, 2010, to determine the distribution and severity of individual pathologic protein deposits (α-synuclein, Aβ, and tau) using routine protocols for histologic and immunohistochemical analysis and established neuropathologic staging criteria. Clinical data were extracted from an electronic medical record system used for all patients with PD.

Patients: Thirty-two consecutive autopsied patients treated at the Washington University Movement Disorders Center who had neuropathologic confirmation of PD and a history of dementia, regardless of the timing of the onset of dementia with respect to motor symptoms.

Results: Three pathologic subgroups of dementia associated with PD were identified: (1) predominant synucleinopathy (Braak Lewy body stages 5-6) (12 [38%]), (2) predominant synucleinopathy with Aβ deposition (Braak amyloid stages B-C) but minimal or no cortical tau deposition (19 [59%]), and (3) synucleinopathy and Aβ deposition with at least moderate neocortical tauopathy (Braak tau stages 5-6; 1 [3%]). Kaplan-Meier and Cox regression analyses revealed that patients with synucleinopathy plus Aβ deposition had significantly shorter survival (years from PD onset until death and years from dementia onset until death) than patients with synucleinopathy only.

Conclusions: Dementia associated with PD has 2 major pathologic subgroups: neocortical synucleinopathy and neocortical synucleinopathy with Aβ deposition. Alzheimer disease with neocortical Aβ and tau deposition does not commonly cause dementia with PD. Furthermore, accumulation of Aβ is associated with lower survival rates in PD patients with dementia. Additional studies are needed to prospectively determine the association between α-synuclein and Aβ accumulation and the role of Aβ in the development and progression of cognitive impairment in PD.


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Individuals with Parkinson disease (PD) have an increased risk of dementia.1,2 The 2 major correlates of dementia associated with PD are cortical synucleinopathy (α-synuclein aggregates in Lewy bodies or Lewy neurites) or pathologic changes frequently interpreted as Alzheimer disease (AD).3,9 Studies10-12 using the in vivo amyloid-imaging agent [11C]–Pittsburgh Compound B (PiB) with positron emission tomography have reported elevated cortical PiB binding in patients with PD, supporting the notion that Aβ accumulation commonly accompanies dementia with PD. However, a recent pathologic study13 of PD patients with dementia who had received PiB scans suggests that Aβ accumulation is not necessarily accompanied by neocortical tauopathy in PD. Thus, the relative frequency and extent of tauopathy in the PD population remain unclear. Frequently used clinicopathologic diagnostic criteria (eg, National Institute on Aging and Reagan Institute [NIA-Reagan] criteria) require tauopathy (neocortical neurofibrillary tangles and neuritic plaques) and Aβ plaques to attribute cognitive impairment to dementia from AD.14,15 Cerebrospinal fluid (CSF) biomarker data also support the hypothesis that both tauopathy (hyperphosphorylated tau) and reduced Aβ42 herald the onset of cognitive change in AD.16 Previous studies18,17 relied on the occurrence of Aβ plaques to conclude that AD contributed
Examination.22 As part of their standard clinical care, patients
also were evaluated for hallucinations and excessive daytime
lethargy. An age-weighted Charlson comorbidity score was cal-
culated for each patient using medical and prescription record
information regarding onset of motor symptoms. Severity of
cortical synucleinopathy was accompanied by substantial
neocortical accumulation of Aβ (Braak plaque stages B-C) with
or without substantial neocortical tau (Braak neurofibrillary tangle stage 5-6). Twelve patients had cortical synucleinopathy without substantial Aβ or
tau (synuclein only). Nineteen patients had cortical synucleinopathy plus substantial cortical Aβ but no or minimal
neocortical tau deposition (Braak tangle stages 0–IV; entorhinal and hippocampal tau without significant neocortical deposition) (synuclein plus Aβ). Three patients
met neuropathologic diagnostic criteria for “probable” AD according to CERAD. Only 1 patient had neocorti-
cal synucleinopathy, Aβ, and tau (Braak tangle stage V/VI) deposition (synuclein plus Aβ plus tau) that was suf-
cient to meet CERAD criteria for “definite” AD or NIA-Reagan “high likelihood” criteria for AD contributing to
dementia.

NEUROPATHOLOGIC SUBTYPE COMPARISONS

We compared clinical and demographic characteristics of the neuropathologically defined subtypes (Table 1). Given
Table 1. Clinical Comparison of the 32 Synuclein Only, Synuclein Plus Aβ, and Synuclein Plus Aβ PLUS Tau Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Synuclein Only (n = 12)</th>
<th>Synuclein Plus Aβ (n = 19)</th>
<th>Synuclein Plus Aβ Plus Tau (n = 1)</th>
<th>P Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female, No.</td>
<td>10/2</td>
<td>15/4</td>
<td>0/1</td>
<td>.76</td>
</tr>
<tr>
<td>Age at PD onset, y</td>
<td>56.7 (11.9)</td>
<td>63.1 (8.4)</td>
<td>70</td>
<td>.19</td>
</tr>
<tr>
<td>Age at dementia onset, y</td>
<td>66.8 (7.1)</td>
<td>71.9 (6.5)</td>
<td>71</td>
<td>.32</td>
</tr>
<tr>
<td>Age at death, y</td>
<td>75.4 (4.9)</td>
<td>76.8 (6.5)</td>
<td>78</td>
<td>.64</td>
</tr>
<tr>
<td>Lowest MMSE score</td>
<td>19.2 (8.5)</td>
<td>17.0 (8.0)</td>
<td>27a</td>
<td>.35</td>
</tr>
<tr>
<td>Last ADB score</td>
<td>6.4 (1.6)</td>
<td>5.8 (2.5)</td>
<td>8</td>
<td>.50</td>
</tr>
<tr>
<td>Hallucinations, No. (%)</td>
<td>10 (83)</td>
<td>18 (94)</td>
<td>1 (100)</td>
<td>.30</td>
</tr>
<tr>
<td>Lethargy (yes/no), No.</td>
<td>4/11</td>
<td>5/19</td>
<td>1/1</td>
<td>.56</td>
</tr>
<tr>
<td>Last UPDRS motor subscale score</td>
<td>44.7 (14.9)</td>
<td>50.9 (16.9)</td>
<td>35.5</td>
<td>.31</td>
</tr>
<tr>
<td>Last H&amp;Y stage of 1/2/2.5/3/4/5</td>
<td>0/3/0/5/2/2</td>
<td>0/2/0/5/2/2</td>
<td>0/0/0/1/0/1/0</td>
<td>.06</td>
</tr>
<tr>
<td>Duration of motor impairment, y</td>
<td>18.8 (8.5)</td>
<td>13.7 (4.4)</td>
<td>8</td>
<td>.10</td>
</tr>
<tr>
<td>Duration of cognitive impairment, y</td>
<td>7.09 (3.7)</td>
<td>4.9 (2.4)</td>
<td>7</td>
<td>.25</td>
</tr>
<tr>
<td>Duration between onset of motor and cognitive impairment, y</td>
<td>12.3 (9.9)</td>
<td>8.8 (5.3)</td>
<td>1</td>
<td>.49</td>
</tr>
<tr>
<td>Age-weighted Charlson comorbidity index score, y</td>
<td>2.5 (1.24)</td>
<td>3.05 (1.0)</td>
<td>5</td>
<td>.16</td>
</tr>
</tbody>
</table>

Abbreviations: H&Y, Hoehn and Yahr; MMSE, Mini-Mental State Examination; UPDRS, Unified Parkinson Disease Rating Scale.

a Values are given as mean (SD) unless otherwise indicated.

b P values reflect statistical comparison between the synuclein only and synuclein plus Aβ groups.

c This MMSE score was obtained 6 years before death, before the onset of clinical dementia.

Table 2. Comparison of Neuropathologic Lesions Among 3 Subgroups of Dementia Associated With Patients With Parkinson Disease

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Synuclein Only (n = 12)</th>
<th>Synuclein Plus Aβ (n = 19)</th>
<th>Synuclein Plus Aβ Plus Tau (n = 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Braak Lewy body stage for synucleinopathy, mode (range)</td>
<td>6 (5-6)</td>
<td>6 (5-6)</td>
<td>6</td>
</tr>
<tr>
<td>Braak amyloid stage for Aβ deposition, mode (range)</td>
<td>0 (0-1)</td>
<td>3 (2-3)</td>
<td>3</td>
</tr>
<tr>
<td>Braak NFT stage for tauropathy, mode (range)</td>
<td>1 (1-4)</td>
<td>3 (1-4)</td>
<td>6</td>
</tr>
<tr>
<td>Neuropathologic diagnostic criteria, % of patientsa</td>
<td>0%</td>
<td>94.7%</td>
<td>100%</td>
</tr>
<tr>
<td>Khachaturianb</td>
<td>0</td>
<td>15.8</td>
<td>100%</td>
</tr>
<tr>
<td>CERADc</td>
<td>0</td>
<td>0%</td>
<td>100%</td>
</tr>
<tr>
<td>NIA-Reagand</td>
<td>0</td>
<td>0%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Abbreviations: CERAD, Consortium to Establish a Registry for Alzheimer’s Disease; NFT, neurofibrillary tangle; NIA, National Institute on Aging.

a Additional pathologic changes: 4 patients had TDP-43 inclusions in the medial temporal lobe,27,31 1 patient had argyrophilic grain disease,27 1 patient had a lacunar infarct in the hippocampus, and 1 patient had a lacunar infarct in the thalamus.

b Percentage of patients who met Khachaturian criteria for Alzheimer disease.

c Percentage of patients who met criteria for probable or definite Alzheimer disease by CERAD criteria.

d Percentage of patients who met the NIA-Reagan criteria for a high likelihood that the dementia syndrome is due to Alzheimer disease; in the combined Alzheimer disease and dementia with Lewy bodies study of McKeith et al,3 there is a low/intermediate likelihood that the Alzheimer disease causes dementia.

that there was only 1 patient in the synuclein plus Aβ plus tau subtype, we only compared the synuclein only and the synuclein plus Aβ subtypes statistically. No significant differences were found between the 2 groups based on age at PD onset (U = 102.5, z = −0.47, P = .64), age-weighted Charlson comorbidity score (U = 80.50, z = −1.41, P = .16), or sex (χ² = 0.09, P = .76). Other than a trend-level difference in Hoehn and Yahr stage (U = 69.5, z = −1.90, P = .06), no significant differences were found between these 2 subtypes for any of the clinical features (hallucinations, lethargy, last Unified Parkinson Disease Rating Scale score, lowest Mini-Mental State Examination score, and AD8 score; all P ≥ .30). Our PD patients with dementia include those who would be classified as having dementia with Lewy bodies by the criteria of McKeith et al,9 defined as dementia onset within 1 year of motor symptoms. Although this distinction from other PD patients with later-onset dementia may be useful for some research purposes, we included PD patients with dementia regardless of the timing of the onset of dementia to avoid biasing analyses of progression or survival. However, only 4 patients had onset of dementia within 1 year of PD onset: 1 in the synuclein only Aβ group, 2 in the synuclein plus Aβ group, and 1 in the synuclein plus Aβ plus tau group. We avoided using the term Parkinson disease dementia to describe our cohort because we did not exclude patients based on the timing of the onset of dementia with respect to motor manifestations of PD.

SURVIVAL ANALYSIS

We compared survival between the 2 primary neuropathologic subtypes of PD with dementia (synuclein only vs synuclein plus Aβ) using Kaplan-Meier survival analyses (Figure). The synuclein only subtype group lived significantly longer after PD onset (years from PD onset until death; P = .03; hazard ratio [HR], 0.51; 95% CI, 0.17-0.90) (Figure, A) and lived significantly longer after dementia onset (years from dementia onset until death; P = .04; HR, 0.52; 95% CI, 0.17-0.95) (Figure, B). However, the onset of dementia was not significantly more rapid in the synuclein plus Aβ group compared with those with only synucleinopathy and no Aβ (years from PD on-
Dementia associated with PD has 2 major underlying pathologic subtypes: neocortical Lewy bodies and Lewy neurite deposition (Braak Lewy body stage V/VI) or neocortical synucleinopathy associated with substantial pathologic accumulation of Aβ (Braak amyloid stage B-C). Only a single person (1 of 32 [3%]) had a combination of neocortical synucleinopathy, abnormal Aβ deposition, and significant neocortical tau (Braak tangle stage V/VI) deposition. The combination of synuclein plus Aβ but not widespread neocortical tau disease comprises the largest subgroup (19 [59%]), compared with 12 (38%) with synucleinopathy only. The relatively low frequency of neocortical tau deposition suggests that tautopathy associated with AD is not a major contributor to dementia associated with PD. In the context of PD, Aβ deposition alone does not necessarily indicate AD or an early stage of AD. This finding also has important implications for interpretation of positive PiB positron emission tomographic scan results in those with PD. A positive PiB scan result likely reflects pathologic Aβ only, rather than a combination of Aβ and tauopathy that occurs in those with dementia due to AD.33

To determine whether distinct combinations of pathologic protein deposits define clinically distinct subtypes of PD with dementia, we analyzed subgroups based on whether neocortical α-synuclein accumulation was accompanied by substantial accumulation of Aβ. Our analysis of the 2 subgroups provides novel insight into whether the presence of Aβ accumulation is associated with distinct clinical features in dementia with PD. We found that many of the demographic and clinical features are similar among the subgroups but that the synuclein plus Aβ group has significantly shorter survival than the synuclein only group. There was also a trend toward earlier dementia onset in the synuclein plus Aβ group. The shorter survival identified by Kaplan-Meier and Cox regression analysis for those with the combination of synuclein and Aβ deposition suggests that this classification is clinically meaningful and that further prospective studies are needed to characterize the distinct clinical characteristics of the 2 subgroups.

Our findings are consistent with previous observations that Aβ accumulation occurs commonly in people with dementia and PD.1,3,5,9,10,17,32,33 However, because widespread neocortical tau deposition (Braak stage V-VI) rarely accompanied Aβ deposition in our cohort, we conclude that Aβ accumulation may represent pathologic processes in PD that are distinct from those occurring in AD. Thus, definition of subgroups based on individual pathologic protein deposits, as done in this study, may provide a less ambiguous classification scheme than the application of terms such as AD-like pathology. Clearly, our interpretation overlaps with previous classifications and relies on NIA-Reagan criteria for pathologic diagnosis of coexisting AD in someone with PD. Higher CERAD Aβ plaque scores have been associated with shorter time to onset of dementia in PD.3 Furthermore, PD patients with low CSF Aβ levels, a measure highly correlated with Aβ plaque deposition, experience a faster rate of cognitive decline in 2 years.33 These observations are consistent with the decreased survival and trend toward shorter time to onset of dementia observed for the synuclein plus Aβ group in our analysis. This finding also supports others who report that Aβ accumulation shortens survival regardless of the timing of the onset of dementia with respect to motor symptoms in PD.34 Thus, the results from our study and previous studies support a primary association between Aβ plaque deposition and increased disease progression in people with PD and dementia. More important, our results suggest that the association with Aβ is independent of tau and therefore does not include the full pathologic spectrum (neurofibrillary tangles and neuritic plaques) associated with a diagnosis of “definite” AD according to NIA-Reagan criteria. However, our analysis does not exclude the possibility that tau accumulation limited to entorhinal cortex and medial temporal lobe (Braak stage I-IV) also could contribute to pro-
gession in either the synuclein only or synuclein plus Aβ groups, which will require additional studies with larger numbers of patients.

The mechanisms responsible for Aβ accumulation in PD and the associations between Aβ accumulation and other pathogenic processes in PD remain unclear. Impaired protein homeostasis may be one mechanism by which the accumulation of Aβ is linked to pathologic α-synuclein accumulation. Primary pathways that promote intraneuronal accumulation of α-synuclein may be distinct from those that promote extracellular accumulation of Aβ, but progressive accumulation of one protein could further impair protein homeostasis pathways in ways that predispose individuals to the accumulation of the other misfolded protein,33 which is supported by a previously observed correlation between cortical Lewy body disease and Aβ plaque scores.34

Imaging agents to monitor α-synuclein accumulation, when available and combined with Aβ imaging and Aβ CSF measurements, could clarify the temporal relationship between neocortical α-synuclein accumulation and Aβ accumulation.35 Other mechanisms, potentially influenced by age or APOE ε4 genotype, may impair neuronal and nonneuronal function in PD and promote Aβ accumulation. It remains unknown whether fibrillar Aβ accumulation directly impairs cognitive function and survival or whether Aβ accumulation positively correlates with other factors that affect the rate of disease progression. Larger, prospective studies using PiB-amyloid imaging, CSF Aβ measurements, and postmortem tissue analysis are needed to clarify the association between Aβ accumulation and clinical features of PD. Further support for the role of Aβ accumulation in promoting disease progression for PD would provide rationale for testing the therapeutic effects of one or more evolving approaches for reducing Aβ accumulation that, so far, have focused on AD.

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