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

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Abstract

Objective—To determine the relative contributions of individual pathologic protein deposits associated 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.

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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 [99%]), 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.

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] Studies[10–12] using the in vivo amyloid-imaging agent [^{11}C]–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 study[13] 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) bio-marker data also support the hypothesis that both tauopathy (hyperphosphorylated tau) and reduced Aβ42 herald the onset of cognitive change in AD.[16] Previous studies[3,9,17] relied on the occurrence of Aβ plaques to conclude that AD contributed to dementia in people with PD, but this finding would not meet the most widely used pathologic criteria for AD.

At this point, the relative frequencies of the different pathologic entities that contribute to dementia in people with PD remain unclear. Analysis of individual pathologic changes for individual protein species could help define distinct pathologic subtypes that may relate to pathogenesis or prognosis. Defining such pathologic subtypes is particularly important for designing interventions that target specific pathologic protein species, such as anti-Aβ therapies. To test this hypothesis, we used markers of these 3 pathologic protein deposits and applied previously established lesion staging scales to a cohort of consecutively collected neuropathologic cases of dementia associated with PD. We used immunohistochemical methods to detect the most frequently encountered pathologic protein changes in PD and AD and to determine whether this helps categorize PD patients with dementia.

METHODS

STANDARD PROTOCOL APPROVALS, REGISTRATIONS, AND PATIENT CONSENT

The Human Research Protection Office at Washington University School of Medicine in St Louis, Missouri, gave permission for this analysis.

STUDY DESIGN AND PATIENTS

Sequentially collected autopsy information was obtained from 32 patients with PD and dementia who died between February 24, 2005, and July 25, 2010, and who were evaluated by movement disorders specialists at the Movement Disorders Center at Washington University School of Medicine. All patients had a clinical diagnosis of idiopathic PD based on modified United Kingdom Parkinson Disease Society Brain Bank clinical diagnostic criteria with clear clinical response to levodopa.[18] Age of PD onset was determined based on historical information regarding onset of motor symptoms. Severity of motor symptoms was rated at the last visit before death with the Unified Parkinson Disease Rating Scale motor subscale 3 and Hoehn and Yahr staging.[19,20] Dementia was determined by clinical assessment of cognitive dysfunction sufficiently severe to impair activities of daily living. Cognitive impairment was further evaluated using the AD8[21] and Mini-Mental State 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 calculated for each patient using medical and prescription record data.

NEUROPATHOLOGIC ANALYSIS

Brains were fixed in 10% neutral buffered formalin for 2 weeks and paraffin embedded, and sections were cut at 6 μm. Blocks were taken from the frontal, temporal, parietal, and occipital lobes; thalamus; striatum, including the nucleus basalis of Meynert; amygdala; hippocampus; midbrain; pons; medulla oblongata; and the cervical spinal cord. Histologic stains included hematoxylin-eosin and a modified Bielschowsky silver impregnation. Immunohistochemical analysis was performed using the following antibodies: Aβ (10D5, Elan Pharmaceuticals), phosphorylated tau (PHF-1, supplied by Peter Davies, MD, Albert Einstein Medical School, Bronx, New York), ubiquitin (Dako), and phosphorylated α-synuclein (Wako Chemicals USA Inc). Lewy body stage was assessed using a PD staging scale (range:, 0–6)[4] and the staging scale by McKeith et al.[7,8] The AD pathologic changes were rated using an amyloid plaque stage (range, 0 to A–C)[23] and neurofibrillary tangle (tauopathy) stage (range, 0–VI).[24] Diffuse and neuritic plaques were also assessed, and cases were classified according to the neuropathologic criteria of Khachaturian,[25] the Consortium to Establish a Registry for Alzheimer Disease (CERAD),[26] and NIA-Reagan.[14] The presence of additional conditions, including vascular disease, was also noted.[27–29]

STATISTICAL ANALYSIS

Data were analyzed with PASW, version 18, statistical software (SPSS Inc) and GraphPad Prism Software (GraphPad Inc). Nonparametric tests (χ^2 and Mann-Whitney tests) were used for group comparisons of demographic and clinical data. All tests were 2-tailed, and $P<.05$ was considered significant. Kaplan-Meier survival analyses were used to estimate survival across pathologically defined subtypes for the following dependent measures: years from PD onset until death, years from PD onset until dementia, and years from dementia onset until death. Additional survival analyses used Cox proportional hazard models to include the age-weighted Charlson comorbidity score[30] and sex covariates.

RESULTS

PATIENT CHARACTERISTICS

Table 1 lists the demographic and clinical characteristics of the 32 patients.

NEUROPATHOLOGIC ANALYSIS

Histopathologic analysis of the 32 patients with PD and dementia revealed that all had cortical synucleinopathy (Braak Lewy body stage 5 [n = 6] or6 [n = 26] (Table 2). Patients could be assigned to 3 subgroups based on whether 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 neocortical synucleinopathy, Aβ, and tau (Braak tangle stage V/VI) deposition (synuclein plus Aβ plus tau) that was sufficient 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 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 ($U = 81.5$, $z = -1.32$, $P = .19$), age at dementia onset ($U = 74.5$, $z = -1.29$, $P = .20$), age at death ($U = 102.5$, $z = -0.47$, $P = .64$), age-weighted Charlson comorbidity score ($U = 80.50$, $z = -1.41$, $P = .16$), or sex ($\chi^2_1 = 0.09$, $P = .76$). 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 $P \geq .30$). Our PD patients, with dementia include those who would be classified as having dementia with Lewy bodies by the criteria of McKeith et al,[8] 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 analyes (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-set until dementia onset; $P = .14$; HR, 0.62;

95% CI, 0.23–1.23) (Figure, C). Additional Cox proportional hazard models that included variables for sex, age-weighted Charlson comorbidity score, and duration of PD without dementia produced similar differences in post-PD onset survival (adjusted HR, 0.23; 95% CI, 0.07–0.77; $P = .02$) and postdementia onset survival (adjusted HR, 0.27; 95% CI, 0.09–0.81; $P = .02$).

COMMENT

Dementia associated with PD has 2 major underlying pathologic subtypes: neocortical Lewy bodies and Lewy neurite deposition (Braak Lewy body stage V/Vl) 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 tauopathy 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.[13]

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 progression 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,[35] which is supported by a previously observed correlation between cortical Lewy body disease and Aβ plaque scores.[32]

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.[36] 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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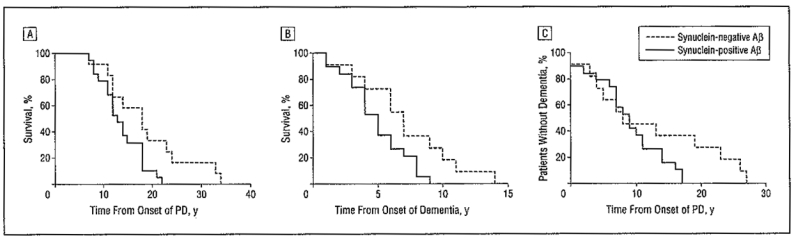

Figure.

Comparison of the synuclein only and synuclein plus Aβ subtypes of dementia associated with Parkinson disease (PD) using Kaplan-Meier survival analysis. Kaplan-Meier survival curves show the percentage of survival with respect to time from the onset of PD (A) and time from the onset of dementia (B), C, The survival curve shows time to the development of dementia after the onset of PD.

Table 1

Clinical Comparison of the 32 Synuclein Only, Synuclein Plus Aβ, and Synuclein Plus Aβ PLUS Tau Patients[a]

Characteristic	Synuclein Only (n=12)	Synuclein Plus Aβ (n = 19)	Synuclein Plus Aβ Plus Tau (n = 1)	*P* Value[b]
Male/female, No.,	10/2	15/4	0/1	.76
Age at PD onset, y	56.7 (11.9)	63.1 (8.4)	70	.19
Age at dementia onset, y	68.1 (7.1)	71.9 (6.5)	71	.32
Age at death, y	75.4 (4.9)	76.8 (6.5)	78	.64
Lowest MMSE score	19.2 (8.5)	17.0 (8.0)	27[c]	.35
Last AD8 score	6.4. (1.6)	5.8 (2.5)	8	.50
Hallucinations, No. (%)	10 (83)	18 (94)	1 (100)	.30
Lethargy (yes/no), No.	4/11	5/19	1/1	.56
Last UPDRS motor subscale score	44.7 (14.9)	50.9 (16.9)	35.5	.31
Last H&Y stage of 1/2/2.5/3/4/5	0/3/0/5/2/2	0/2/0/5/2/10	0/0/0/0/1/0	.06
Duration of motor impairment, y	18.8 (8.5)	13.7 (4.4)	8	.10
Duration of cognitive impairment, y	7.09 (3.7)	4.9 (2.4)	7	.25
Duration between onset of motor and cognitive impairment, y	12.3 (9.9)	8.8 (5.3)	1	.49
Age-weighted Charlson comorbidity index score, y	2.5 (1.24)	3.05 (1.0)	5	.16

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

Characteristic	Synuclein Only (n = 12)	Synuclein Plus Aβ (n = 19)	Synuclein Plus Aβ Plus Tau (n=1)
Braak Lewy body stage for synucleinopathy, mode, (range).	6 (5–6)	6 (5–6)	6
Braak amyloid stage for Aβ deposition, mode (range)	0 (0–1)	3 (2–3)	3
Braak NFT stage for tauopathy, mode (range)	1 (1–4)	3 (1–4)	6
Neuropathologic diagnostic criteria, % of patients[a]			
Khachaturian[b]	0	94.7	100
CERAD[c]	0	15.8	100
NIA-Reagan[d]	0	0	100

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 criteria of McKeith et al,[8] there is a low/intermediate likelihood that the Alzheimer disease causes dementia.