ORIGINAL ARTICLE

Striatal β-Amyloid Deposition in Parkinson Disease With Dementia

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Abstract

Dementia is common in Parkinson disease (PD), although its anatomic and pathologic substrates remain undefined. Recently, striatal abnormalities in Lewy body diseases have been described, but their clinical relevance is not clear. Thirty PD cases from the United Kingdom Parkinson's Disease Society Tissue Bank were grouped as demented (PDD; n = 16) and nondemented (PD; n = 14) based on a review of clinical records. The extent of α-synuclein, tau, and amyloid β peptide (Aβ) deposition in the caudate nucleus, putamen, and nucleus accumbens was assessed. All cases showed severe dopaminergic striatal terminal denervation based on tyrosine hydroxylase immunohistochemistry. α-synuclein and tau deposition in the striatum were rare in both groups, but the Aβ burden was significantly greater in the striatum of PD cases with dementia than present in the nondemented PD group. Striatal Aβ deposition was type-independent of Alzheimer disease changes in the cortex and was minimal in nondemented PD cases. We conclude that Aβ deposition in the striatum strongly correlates with dementia in PD.

Key Words: Amyloid β deposition, Dementia, Parkinson disease, Striatum.

INTRODUCTION

Parkinson disease (PD) is a common neurodegenerative disorder that is characterized pathologically by the abnormal deposition of α-synuclein (αSN) as Lewy bodies (LBs) and Lewy neurites in the midbrain and other brain regions. Motor deficits are the major clinical features of the disease (1), but nonmotor manifestations are also common (2). Among the most prominent of these is dementia (2–4).

Although most of the classical motor deficits of the disease relate to pathologic alterations in the substantia nigra pars compacta (5) that are associated with dopamine depletion in the striatum, the neuropathologic substrates of dementia in PD remain unclear. Most studies suggest that αSN-type lesions in neocortical and limbic structures are strongly associated with this clinical feature (6–10).

Recently, an increased awareness of striatal pathology in LB diseases has emerged, particularly with Duda et al (11) having shown extensive αSN pathologic findings in the striatum. The greatest density was found in patients with a combination of Alzheimer disease (AD) and dementia with LBs (DLB), followed by cases with DLB alone. Parkinson disease patients also showed mild to moderate abnormalities. Furthermore, Liang et al (12) found abundant Aβ pathology in the striatum of cases with DLB that was more pronounced than in cases of PD with dementia (PDD). Jellinger and Attems (13) confirmed these findings in a larger cohort and point to a morphologic distinction between DLB and PDD on the basis of differences in striatal pathology. Although these reports describe previously underestimated pathologic findings in the striatum in LB diseases, their precise clinical correlates have not been closely studied. In addition, the examination of striatal pathologic findings was limited to the caudate nucleus (CN) and putamen omitting the ventral striatum (i.e. nucleus accumbens [NAcc]), a region that is strongly involved in cognition (14).

In this study, we investigated the relationship between dementia and striatal pathology in PD by assessing the burden of striatal αSN- and AD-type changes in PD patients with and without dementia.

MATERIALS AND METHODS

Neuropathologic Assessment

Neuropathologic diagnoses were based on αSN, tau, and Aβ immunohistochemistry of superior frontal gyrus, hippocampus, and midbrain. Confounding pathologic features were assessed on hematoxylin and eosin–stained slides from 18 brain tissue blocks in each case. Tissue was collected and processed according to an established protocol (15). Neuropathologic diagnoses were made using international consensus criteria for the definite diagnosis of PD (http://www.ICDNS.org). Alzheimer disease pathologic findings in isocortical and/or entorhinal regions were also assessed using the grading system posted at http://www.ICDNS.org and staged according to the scheme of Braak et al (16) using AT8 immunohistochemistry. All cases with a clinicopathologic diagnosis of DLB or the additional diagnosis of AD were excluded from this analysis.

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Clinical Assessment and Selection of Cases

Clinical data were compiled retrospectively from hospital records by a neurologist with expertise in movement disorders (R.K.B.P.). Only subjects that had been evaluated by a clinician within 2 years prior to death and for whom there were complete clinical histories were included. The clinical diagnoses of PD, PDD, and DLB were based on published criteria (10, 17, 18). Parkinson disease was considered present if the patient had at least 2 of the 4 cardinal signs (rigidity, hypokinesia, resting tremor, and postural instability) and exhibited a positive response to levodopa (17). Patients with PD who developed late dementia (>2 years after motor signs) were classified as PDD (10). The diagnosis of DLB was made when dementia preceded extrapyramidal signs by 2 years or when they developed within a 12-month period (18). On the basis of these guidelines, all cases that fulfilled the clinical criteria for DLB were excluded. Thus, all cases studied initially presented with motor deficits, while cognitive and psychiatric complications developed later in the disease course (range, 2–34 years). The diagnosis of dementia satisfied *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (19) and *International Statistical Classification of Diseases, 10th Revision* clinical criteria. Because the study was based on retrospective data, the clinical severity of dementia was measured using a semiquantitative global impression scale (0, absent; 1, mild; 2, moderate; and 3, severe). Retrospective analyses by specialists in movement disorders are well-accepted methods of case ascertainment and have been frequently used in clinicopathologic studies involving both dementia and parkinsonism (20–22).

Two PD case groups were identified, that is, 14 PD cases without dementia and 16 PD cases with dementia (Table 1). All but possibly 1 patient had responded to levodopa (Table 1). The severity of motor signs was rated on a semiquantitative global impression scale (0 to 3+, absent to severe) (Table 1).

Immunohistochemistry

Immunohistochemistry was performed using standard protocols (23). The primary antibodies used in this study were (against) αSN for identification of LBs and Lewy neurites (Becton-Dickinson, Oxfordshire, UK, at a dilution of 1:1000), tau for visualization of neurofibrillary changes (Autogen Bioclear, Wiltshire, UK, PHF-Tau [clone AT8] at a dilution of 1:800), 1E8 for visualization of Aβ plaques (Aβ) (courtesy of GlaxoSmithKline, Middlesex, UK, at a dilution of 1:1000), and tyrosine hydroxylase for examination of nigrostriatal fibers (Vector, Peterborough, UK, at a dilution of 1:30).

Semiquantitative Assessment of αSN and AD Lesions

For each study case, 3 representative sections from the CN, putamen, and NAcc were assessed for the occurrence of αSN, Aβ, and tau immunoreactivity, respectively. The NAcc was defined as the roughly triangular portion of the striatum at the ventral edge of the internal capsule, as examined in Brilliant et al (24). The slides were scored semiquantitatively using a scale ranging from 0 to 3 (absent to frequent; Fig. 1).

Examination of αSN and AD pathologic findings was also conducted in the temporal and entorhinal cortices, CA2 sector of the hippocampus, and superior frontal gyrus and assessed semiquantitatively from 0 to 3 (absent to frequent). Sections were graded by 2 investigators (M.E.K. and S.M.G.).

Statistical Analysis

Statistical analysis was performed using the SPSS program version 15.0 for Windows XP (SPSS, Inc., Chicago, IL) and GraphPad Prism 4 (GraphPad Software, Inc., San Diego, CA). The differences in αSN, tau and Aβ burden, age at death, and onset and duration of disease among the PD and PDD groups were analyzed by the nonparametric Mann-Whitney U test. The Kruskal-Wallis test was applied, followed by Dunn post hoc multiple group comparisons to detect differences in severity of tremor, gait-balance, akinetic-rigid, and hemiparkinsonism signs among the groups. Cohen κ statistic was used to test interrater reliability for the αSN, tau, and Aβ semiquantitative assessment between the 2 investigators. Intrarater reliability was also examined by measuring the striatum of 5 randomly selected subjects on 5 occasions at least a week apart. On each occasion, all operator-dependent processes (i.e. region of interest semiquantitative assessment) were performed blinded to previous values. High intrarater reliability was observed. Correlations were calculated with Spearman 2-tailed correlation analysis (nonparametric). p values less than 0.05 were considered significant.

The diagnostic performance of Aβ deposition in the striatum in predicting dementia was calculated with measures of sensitivity, positive predictive value (PPV), specificity, and negative predictive value (NPV) following the methodology of Harding and Halliday (9). Briefly, sensitivity refers to the probability of having moderate to severe Aβ deposition with high clinical scores for dementia. Specificity refers to the probability of not having high scores for dementia if moderate to severe Aβ burden is not reached. Positive predictive value refers to the probability of having high scores for dementia with moderate to severe Aβ deposition. Negative predictive value refers to the probability of not having high scores for dementia without a moderate to severe Aβ burden.

RESULTS

Clinical Data and Tyrosine Hydroxylase Immunohistochemistry

No statistically significant differences were identified in the severity of tremor, gait-balance, akinetic-rigid, and hemiparkinsonian signs between the groups (Table 1). Tyrosine hydroxylase immunohistochemistry was performed in all cases, and overall patterns of cell staining in the CN, Put, and NAcc were assessed. All showed severe dopaminergic terminal denervation compared to a control (data not shown).

αSN in the Striatum

Most cases in the nondemented PD group had mild αSN abnormalities (i.e. LBs and Lewy neurites) in all striatal regions. From 21% to 35% of cases (depending on region) showed no αSN pathology. No αSN staining was seen in the

Table 1. Clinical Data for the PD Groups

Case No.	Sex	Age at Onset, yrs	Age at Death, yrs	Duration of Disease, yrs	Neuropathologic Diagnosis (www.ICDNS.org)	ICDNS AD GRADE (www.ICDNS.org) Isocortical	Entorhinal	Braak AD, Stages	Clinical Severity of Dementia	Scores of Presenting Motor Deficits (within first 2 yrs) T	G-B	A-R, S	H-P	Scores of Motor Deficits (after 2 yrs) T	G-B	A-R, S	H-P	L-Dopa Responsiveness
PD group (n = 14)																		
1	F	52	58	6	PD	0	I	I-II	0	1-2	0	0	0	2	0	1-2	0	±
2	M	76	85	9	PD	II	0	I-II	0	1-2	0	0	1-2	1	1	1	0	+
3	M	47	74	27	PD	I	0	I-II	0	1	0	1	1-2	1	1	2-3	1-2	+
4	M	75	82	7	PD	I	II	I-II	0	0	1-2	0	0	0	1	2-3	0	+
5	M	68	78	10	PD	NA	NA	I-II	0	0	1	1	0	1	0	1-2	0	+
6	F	65	75	10	PD	0	0	0	0	0	0	2	1-2	1	0	1	1	+
7	M	70	77	7	PD	0	I	I-II	0	1	0	1-2	1	1-2	2	1	1	+
8	M	86	89	3	PD	0	I	I-II	0	1	0	1	0	1-2	1-2	1	0	+
9	M	67	77	10	PD	0	I	I-II	0	0	0	0	0	0	1	1	0	+
10	F	67	80	13	PD	0	I	I-II	0	2	1	0	0	1	1	0	0	+
11	F	59	79	20	PD	0	0	I-II	0	0	1	0	0	0	1-2	3	0	+
12	M	42	62	20	PD	0	0	0	0	1	0	0	1	1-2	1	0	1-2	+
13	M	41	75	34	PD	I	II	I-II	0	2	0	2	1-2	0	0	0	1	+
14	M	48	76	28	PD	0	I	I-II	0	2	0	2	2	0	2	0	0	+
Mean		62	76	14														
PDD group (n = 16)																		
15	F	57	80	23	PD	II	III	I-II	2	1	0	1	1	1	0	1-2	1	+
16	M	77	82	5	PD	I	II	0	2-3	0	1	0	0	0	1	0	0	+
17	M	56	70	14	PD	IV	III	III	2-3	0	1	1-2	0	0	0	1	0	+
18	M	72	81	9	PD	0	I	I-II	2-3	1-2	1-2	0	0	0	1-2	2	0	+
19	M	57	73	16	PD	I	II	I-II	2	1	0	0	1	2	1	1	1-2	+
20	M	71	82	11	PD	I	II	I-II	2	1	1	1-2	1	1	1-2	1-2	1-2	+
21	M	75	84	9	PD	0	I	0	2	0	0	1	1-2	2	1-2	1-2	1-2	+
22	F	67	85	18	PD	II	I	I-II	2-3	1-2	0	1	1	2	0	0	0	+
23	M	74	87	13	PD	I	II	I-II	2	1	0	1	1	1	1	1	1	+
24	M	54	78	24	PD	0	I	I-II	2-3	0	0	0	0	1	2	1	0	+
25	F	73	84	11	PD	IV	III	III	3	1-2	0	0	1-2	1	1-2	0	1-2	+
26	M	78	84	6	PD	II	II	I-II	2	0	0	1-2	1-2	0	0	2	0	+
27	M	62	71	9	PD	III	III	I-II	2	1-2	0	0	1	2	0	1-2	1	+
28	M	61	80	19	PD	0	III	III	2-3	0	0	1	1	0	0	1-2	0	+
29	M	35	54	19	PD	0	I	0	2	1	1-2	1-2	1-2	1	1	1	1	+
30	M	67	79	12	PD	IV	III	I-II	3	2-3	0	0	0	1	0	1	0	+
Mean		65	78	14														

Semiquantitative clinical severity scores: 0, absent; 1, mild; 2, moderate; 3, severe; +, yes; −, no; ±, possible. A-R, S, akinesia-rigidity and stiffness; F, female; G-B, gait-balance problems; H-P, hemiparkinsonism; ICDNS, *International Statistical Classification of Diseases, 10th Revision*; M, male; PD, Parkinson disease; PDD, PD cases with dementia; T, tremor.
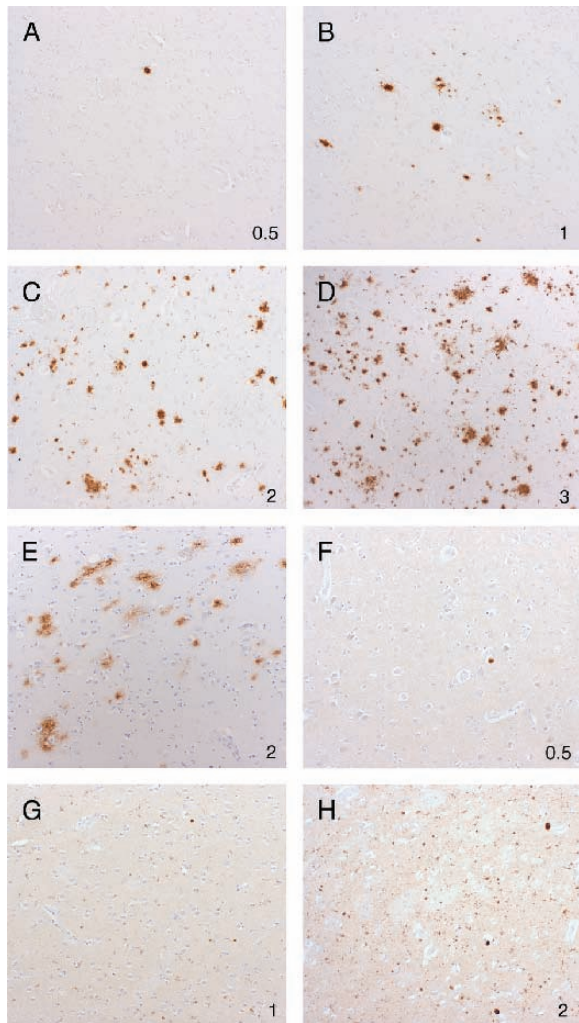
FIGURE 1. Semiquantitative ratings of pathology. Assessment of amyloid β deposits (Aβ) pathology in the striatum was performed using a Consortium to Establish a Registry for Alzheimer's Disease-based (45) visual impression of the numerical density of plaques ranging from 1 to 3 (**B**, **C**, **D**) corresponding to sparse, moderate, and frequent. A value of 0.5 was assigned to those fields where only a single lesion was present (**A**). In a few cases, where the density did not clearly fit into 1 of the main categories, intermediate values were assigned. Similar ratings were performed on the Aβ pathologic findings in the neocortex (**E**) and on the extent of α-synuclein pathology in the striatum (**F**, **G**, **H**). The score for each representative field is indicated in the lower right of each panel. Magnification: 100×.

CN and Put in 40% to 50% of PDD cases; the NAcc was negative in 19% (Fig. 2). When present, most αSN lesions in the CN were in the lateral portions toward the internal capsule; the caudatolenticular gray bridges were also involved. Cohen κ statistic revealed an interrater reliability of 0.75 for αSN ratings between investigators.

Tau in the Striatum

Tau pathologic findings (neurofibrillary tangles and neuropil threads) in the nondemented PD group were mild in

the CN (5/14 cases; 35.7%), the Put (7/14 cases; 50%), and NAcc (10/14 cases; 71.4%), and was otherwise absent in this group. Tau pathology was also mild or absent in the PDD cases with the exception of 1 case in which there were moderate tau pathologic changes in NAcc (Fig. 2). Statistical analysis demonstrated high intrarater reliability (0.8) for semiquantitative assessment of tau.

Aβ Immunohistochemistry in the Striatum

Four types of Aβ deposits were found in the striatal regions as follows: 1) large plaques that resemble diffuse cortical plaques; 2) smaller, more intensely stained deposits of a diffuse type that outnumbered the larger plaques by a factor of approximately 3:1; 3) small, presumably extracellular, deposits (i.e. approximately the size of a glial cell nucleus); and 4) even smaller dot-like aggregates (Fig. 1). Overall, Aβ lesions were more frequent and more severe than αSN and tau pathologic findings in demented PD cases. Amyloid β peptide was absent in 11 of 14 PD cases (78.5%) and only minimal in the remaining 3 cases (21.5%) in CN, Put, and NAcc. In contrast, PDD cases demonstrated moderate to severe Aβ pathologic findings (Fig. 2). A significantly higher burden of Aβ pathology in each striatal region in demented compared with nondemented cases was observed (CN [$p = 0.0007$], Put [$p = 0.0005$], and NAcc [$p = 0.002$]; Fig. 2). These differences cannot be attributed to age because correlation analysis revealed that Aβ burden did not correlate with age at death. Comparison of overall striatal pathology between nondemented and demented PD cases revealed a significantly greater Aβ burden in the latter group ($p = 0.001$; Fig. 3). Similarly, cortical Aβ load was significantly higher in demented than in nondemented PD cases ($p = 0.006$; Fig. 3). Interestingly, however, demented PD cases showed a significantly higher Aβ load in the striatum compared with cortex ($p = 0.03$; Fig. 4). Specifically, Aβ burden was greater in the striatum than in the entorhinal region ($p = 0.04$), superior frontal gyrus ($p = 0.03$), and the CA2 sector of the hippocampus ($p = 0.0007$) (Fig. 4). No statistically significant difference was detected between
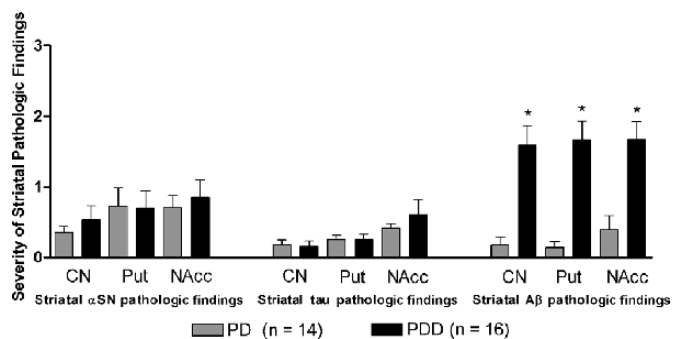

FIGURE 2. Severity of α-synuclein (αSN), tau, and amyloid β (Aβ) pathology in the striatum of Parkinson disease (PD) and PD cases with dementia (PDD) patients. The columns represent mean values ± SEM. Representative images that were used to derive the data points are shown in Figure 1. *, Denotes significant differences in each striatal region for Aβ (caudate nucleus [CN] [$p = 0.0007$], putamen [Put] [$p = 0.0005$], and nucleus accumbens [NAcc] [$p = 0.002$]).
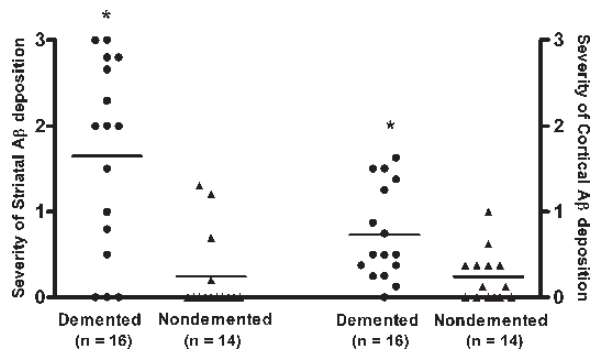
FIGURE 3. Scatter plot showing the extent of Aβ deposition in the striatum and cortex of demented Parkinson disease (PD) subjects (n = 16) and nondemented PD subjects (n = 14). Each data point represents the averaged amyloid β (Aβ) severity score for all striatal and cortical regions assessed. *, Denotes significant difference (Mann-Whitney U test; $p < 0.05$).

Aβ burden in the striatum and temporal cortex, although a trend toward higher Aβ deposition was apparent in the former (Fig. 4). Furthermore, an application of a diagnostic grading to Aβ pathology in the striatum and cortex revealed that 70% of the cases had abundant Aβ deposition in the striatum that was not coexistent with comparably severe cortical AD pathologic findings (data not shown). κ statistics revealed a high interrater reliability of 0.84 for Aβ lesions ratings between investigators.
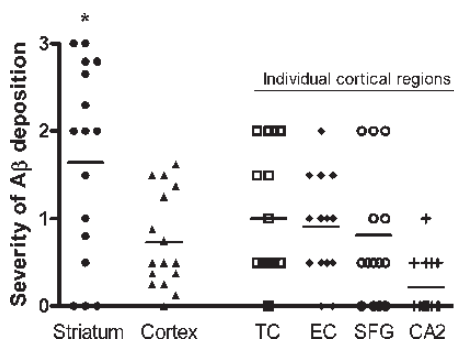

FIGURE 4. Scatter plot showing the overall extent of amyloid β (Aβ) deposition in the striatum and cortex of Parkinson disease (PD) patients with dementia (PD cases with dementia [PDD]; n = 16) (left side of graph). A significantly greater deposition of Aβ burden is observed in the striatum than in the cortex (p = 0.03) (indicated with an *). Each data point for the striatum represents the averaged Aβ severity score for all striatal regions assessed (caudate nucleus, putamen, and nucleus accumbens). Each point for the cortex corresponds to the semiquantitative averaged Aβ severity score across the temporal and entorhinal cortices, CA2 sector of the hippocampus, and superior frontal gyrus. The extent of Aβ deposition in the striatum is also significantly greater than in the entorhinal cortex (p = 0.04), superior frontal gyrus (p = 0.03), and CA2 sector of the hippocampus (p = 0.0007) (right side of graph). Each data point for the individual cortical regions corresponds to the semiquantitative Aβ severity score for each case. EC, entorhinal cortex; SFG, superior frontal gyrus; TC, temporal cortex. *, Denotes significant differences (Mann-Whitney U test; $p < 0.05$).

TABLE 2. Contingency Table (2 × 2) for Calculation of Sensitivity, PPV, Specificity, and NPV for Aβ Burden in the CN, Put, and NAcc in Demented PD Cases

CN, Put, and NAcc Aβ Burden	Clinically Demented		Total No. Cases
	Yes	No	
2–3	9	1	10
0–1	7	13	20
Total cases	16	14	30

Sensitivity of demented PD cases (9 / 16 × 100) = 56%; PPV for demented PD cases (9 / 10 × 100) = 90%. Specificity for cases without dementia (13 / 14 × 00) = 92.8%; NPV for cases without dementia (13 / 20 × 100) = 65%.

Aβ, amyloid β; CN, caudate nucleus; NAcc, nucleus accumbens; NPV, negative predictive value; PD, Parkinson disease; PPV, positive predictive value; Put, putamen.

Because Aβ striatal deposition was most severe in the demented PD group, the sensitivity, PPV, specificity, and NPV in all striatal regions were also calculated to test the accuracy of striatal Aβ pathologic finding assessment in predicting dementia (Table 2). The sensitivity (i.e. the probability of having moderate to severe Aβ deposition with high clinical scores for dementia) was 56%, whereas the PPV (the probability of having high clinical scores for dementia on reaching moderate to severe Aβ deposition) was 90%. Furthermore, the specificity and NPV for cases without dementia was high (in the range of 65% to 93%; Table 2).

DISCUSSION

Recent pathologic studies point to LB-type pathology in limbic and neocortical regions as a determinant of cognitive impairment/dementia in PD (6–10, 25, 26), whereas others have found no clear relationship (23). The literature is further confounded by the presence of AD-type changes that often coexist with αSN pathologic findings. Despite extensive anatomic surveys in the literature, striatal pathology has not been examined in detail. We have observed mild striatal αSN deposition in all striatal regions under investigation, with no statistical differences between the different PD clinical phenotypes. Furthermore, both demented and nondemented PD cases showed minimal or absent tau pathologic findings. Our results demonstrate no evident association between αSN and tau pathology in the striatum with dementia. This result implies that LBs in neocortical and limbic structures are more likely responsible for the development of dementia in PD.

Although striatal αSN and tau pathology did not differ between PD demented and nondemented groups, we found that Aβ deposition in the striatum distinguished PD patients with dementia from those without. More specifically, we found increased Aβ burden in demented PD patients in all striatal regions, and this increase was independent of comorbid cortical AD pathology. Our results indicate that Aβ burden in the striatum can differentiate cases with dementia from those without high sensitivity and specificity, further supporting a primary role of striatal Aβ deposition in the pathologic processes associated with cognitive dysfunction in PD and pointing to the striatum as an important focus of damage in PD. The clinical severity of motor deficits was

similar among the PD groups, suggesting that the pathologic findings observed were not related to motor manifestations. Altogether, our results demonstrate a greater Aβ striatal pathology in PD cases with cognitive impairment/dementia in the absence of prominent cortical Aβ deposition. Earlier reports had found no clear abnormality of the striatum in PD (27), but 2 recent studies identified an abundant Aβ burden in the striatum of DLB cases that was more pronounced than in PDD, pointing to a morphologic distinction between these disease states (12, 13). Herein, we confirm the existence of PD cases with extensive striatal Aβ pathology and show for the first time a clinical relevance of Aβ deposition in the striatum in PD patients with a higher likelihood of dementia when this pathology is present.

The presence in PDD patients of prominent Aβ deposition within the striatum that is dissociated from appreciable AD comorbidity offers a firm pathologic substrate for subcortical dementia in these individuals giving rise to a distinctive clinical presentation. Although this finding leads to further acknowledgement of a molecular link between PD and AD with respect to Aβ deposition, the topography of involvement in subcortical regions seems distinctive for PDD, independent of the formal additional diagnosis of AD in the brains of these patients.

There is considerable diversity of opinion regarding the significance of neocortical plaque formation to the etiopathogenesis of both AD and PD (6, 8, 28–30). For example, there have been inconsistent reports on the correlation between Aβ burden and various measures of clinical deficits in both diseases (31). Furthermore, in elderly subjects without overt dementia, plaques are found in the neocortex and viewed as part of normal aging (32). In contrast, Aβ deposition in the striatum is universally found in AD brains but is rarely observed in nondemented elderly individuals (33, 34). Furthermore, according to phases of β-amyloidosis in the human brain proposed by Thal et al (35), Aβ deposition in the striatum occurs in Phase 3 with associated clinical dementia, and thus, it seems to reflect a disease-specific pathologic change in clinically proven AD subjects. This suggests that the striatum is an important region that is closely related to dementia in AD. The present study confirms these previous reports and shows for the first time that striatal pathology in the PD brain is strongly correlated with clinical dementia.

A dopaminergic deficit is regarded as the main neurochemical impairment in PD. In our cohort, we found a universal severe dopaminergic denervation of the striatum, demonstrating that loss of striatal monoaminergic terminals is severe in all PD cases with or without cognitive impairment. Our results are in agreement with imaging studies that show that the rate of striatal dopaminergic loss does not seem to increase as dementia develops (36). Furthermore, the daily clinical experience that dementia does not improve or worsens with levodopa treatment suggests that the dopaminergic deficit is not the main neurochemical impairment responsible for dementia in PD.

In addition to being part of the motor loop, the striatum plays a major role in cognition and behavior (14). The CN contributes to memory (37), learning (38, 39), and behavior,

and lesions lead to apathy and decreased recent memory (40). The NAcc receives input from prefrontal and limbic regions (14), and its efferents primarily pass to extrapyramidal centers but also to a number of limbic-related structures, including the septum and the bed nucleus of the stria terminalis (41). Deposition of Aβ plaques would disrupt striatal function by interrupting limbic connections and, thus, directly or indirectly contribute to dementia in PD. Recent studies suggest an interaction between Aβ pathologic findings and αSN lesions (42). In DLB brains, the presence of Aβ deposits in the neocortex was associated with increased αSN lesions and higher levels of insoluble Aβ (42). These data suggest a synergistic reaction between Aβ and αSN, as has been suggested for tau and αSN (43, 44), although evidence of synergism between these abnormally aggregated proteins awaits further clarification.

We have studied a relatively large number of cases (n = 30), used state-of-the-art immunohistochemistry, and evaluated detailed clinical information, but there are limitations germane to all retrospective clinicopathologic studies. Although clinical details were available for all cases, incomplete and inaccurate observations may have introduced an ascertainment bias into the clinical scores. For example, some patients may have had cognitive impairment or dementia that was not recorded in the clinical notes and was therefore underestimated. A selection bias that typically operates in brain bank samples (e.g. patients with more severe or rapidly progressive disease) also cannot be excluded.

In summary, we report the novel finding of a significantly greater deposition of Aβ in the striatum of PD patients with dementia compared with nondemented PD patients that is independent of the extent of cortical AD pathology.

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