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Presence of Striatal Amyloid Plaques in Parkinson's Disease Dementia Predicts Concomitant Alzheimer's Disease: Usefulness for Amyloid Imaging

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Abstract

Dementia is a frequent complication of Parkinson's disease (PD). About half of PD dementia (PDD) is hypothesized to be due to progression of the underlying Lewy body pathology into limbic regions and the cerebral cortex while the other half is thought to be due to coexistent Alzheimer's disease. Clinically, however, these are indistinguishable. The spread of amyloid plaques to the striatum has been reported to be a sensitive and specific indicator of dementia due to Alzheimer's disease (AD). The purpose of the present study was to determine if the presence of striatal plaques might also be a useful indicator of the presence of diagnostic levels of AD pathology within PD subjects. We analyzed neuropathologically-confirmed cases of PD without dementia (PDND, N = 31), PDD without AD (PDD, N = 31) and PD with dementia meeting clinicopathological criteria for AD (PDAD, N =40). The minimum diagnostic criterion for AD was defined as including a clinical history of dementia, moderate or frequent CERAD cortical neuritic plaque density and Braak neurofibrillary stage III–VI. Striatal amyloid plaque densities were determined using Campbell-Switzer and Thioflavine S stains. Striatal plaque densities were significantly higher in PDAD compared to PDD ($p<0.001$). The presence of striatal plaques was approximately 80% sensitive and 80% specific for predicting AD. In comparison, the presence of cerebral cortex plaques alone was highly sensitive (100%) but had poor specificity (48% to 55%). The results suggest that striatal amyloid imaging may be clinically useful for making the distinction between PDD and PDAD.

Keywords

striatum; Lewy body; diagnosis; autopsy; neuropathology; biomarker

Introduction

When dementia presents at least one year after the onset of motor Parkinson's disease (PD), patients are clinically diagnosed as Parkinson's disease with dementia (PDD) [2,3]. However, if dementia precedes PD or the diagnosis is within 1 year of the onset of motor signs, patients are diagnosed as dementia with Lewy bodies (DLB) [3,4]. The cause of cognitive impairment and dementia in PDD is thought to be due primarily to either PD-

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related pathologic lesions (Lewy bodies and associated neuritic changes) or concomitant AD-type changes (amyloid plaques and neurofibrillary tangles) but other pathologies are also contributory, including vascular lesions, non-AD tauopathies, hippocampal sclerosis and progressive supranuclear palsy [2,5–10].

The presence of concomitant histopathology meeting clinicopathological criteria for AD within the setting of PDD has been reported to range from non-existent to 65% and varies depending on the specific neuropathological criteria used to diagnose AD [2,7,8,11–14]. A recent consensus paper has issued new guidelines for the neuropathological diagnosis of AD in an attempt to reconcile divergent opinions and assimilate new data [15]. The relative importance of AD and Lewy-type histopathology for dementia within PD has been debated but the majority of the research indicates both are significant contributors [13,16–20]. Currently, however, it is not possible to clinically separate PDD from PDAD as the characteristics of the dementia syndrome are very similar [14].

Striatal plaques in AD were first reported in 1984 [21]. It was soon realized that striatal plaques are a later disease development, being infrequent at preclinical stages and frequent when dementia is present [22–24]. The spread of amyloid plaques to the striatum and other brain regions beyond the cerebral cortex was later used as the basis of a staging scheme for AD by Thal and colleagues [22]. In this scheme, amyloid deposition first occurs in the neocortex and then progresses to allocortex, diencephalon and striatum, brainstem and finally cerebellum. We recently demonstrated, in an autopsy sample composed of AD and non-demented elderly control subjects, that striatal plaques have a high predictive value for the presence of clinicopathological AD [25].

Striatal plaques may have similar diagnostic value in the setting of PDD. Striatal plaques have been reported to be present in PDD and DLB [26–30] but their diagnostic value for AD in the context of PDD has not been specifically assessed. The purpose of this study was to determine if striatal plaques could be used to predict, in an autopsy sample of subjects with PDD, the presence of pathologically defined AD.

Materials and Methods

Case selection

The study took place at Banner Sun Health Research Institute (BSHRI), with autopsies performed on elderly subjects who had volunteered for the BSHRI Brain and Body Donation Program, a longitudinal clinicopathological study of normal aging, dementia and parkinsonism [31]. The study was approved by the Banner Health Institutional Review Board and all participants or next of kin gave informed consent. The database was queried for cases between the years of 1997–2010 that had clinicopathological diagnoses of PD [32] without dementia (PD, N=31), PDD [3] without pathological AD (PDD, N=31), and PDD with pathological AD (PDAD, N=40). For comparative purposes, subjects from a previously published study [25] with AD without PD (AD, N = 50) as well as non-demented normal control subjects without parkinsonism (NC, N = 62) were also included. For all subjects, those with concomitant clinicopathological diagnoses of other causes of parkinsonism such as corticobasal degeneration and progressive supranuclear palsy were excluded. Subjects (Table 1) were clinically characterized as previously described [31,33] through use of standardized periodic neurological and neuropsychological assessments and/or review of private medical records, self-report and telephone interviews with spouses and/or caregivers. All cases underwent autopsy and a standardized neuropathological assessment, resulting in the assignment of pathological diagnoses according to published recommendations. For clinicopathologic diagnoses, cases received a diagnosis of PD if they had two or more cardinal clinical signs as well as Lewy bodies and pigmented neuron loss in the substantia

nigra. Cases received a diagnosis of AD if they had a clinical history of dementia and were classified as “intermediate” or “high” according to the 1997 NIA-Reagan criteria [34] as well as the revised criteria recently published [15]. Dementia with Lewy bodies was distinguished from PD with dementia according to consensus criteria published by the Dementia with Lewy Bodies Consortium [4]. Subjects with Lewy body-related histopathology were also classified according to the Unified Staging System for Lewy Body Disorders [13].

Tissue processing and histological methods

Tissue processing methods have been previously described [25,31]. Briefly, the cerebrum was cut in the coronal plane at the time of brain removal into 1 cm thick slices and then divided into left and right halves. The slices from the right half were frozen between slabs of dry ice while the slices from the left half were fixed by immersion in neutral-buffered 4% formaldehyde for 48 hours at 4 degrees C. Following cryoprotection in ethylene glycol and glycerol with 0.1 M pH 7.4 phosphate buffer, selected 3 × 4 cm blocks were sectioned at 40 or 80 μm thickness on a sliding freezing microtome. Sections were stained with hematoxylin and eosin (H&E), thioflavine S and enhanced silver methods for amyloid plaques and neurofibrillary tangles, using the Campbell-Switzer and Gallyas methods respectively. The Campbell-Switzer stain has been reported by several groups to be as sensitive as Aβ immunohistochemistry for the detection of all types of senile plaques including diffuse plaques [22]. Thioflavine S is one of the methods recommended and validated for neuritic plaque density grading by the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) [1] while the Braak neurofibrillary tangle staging protocol was originally described using the Gallyas stain [35]. The validity and accuracy of this combination of stains for estimating the density of Aβ deposits has also been established in our laboratory through strong correlations with autoradiographic binding of an imaging ligand, Florbetapir, in postmortem human brain sections (R = 0.95) from AD subjects [36], and with ELISA biochemical measures of Aβ (R = 0.89) in cerebral cortex extracts [37].

Histopathological scoring was performed blinded to clinical and neuropathological diagnosis. Amyloid plaque densities were graded using the CERAD templates, and neurofibrillary tangles were assessed using the original Braak and Braak protocol with the Gallyas stain [35]. All subjects were genotyped for apolipoprotein E (ApoE) using a modification of a standard method [38,39]. In a subset of 41 cases (NC= 20; AD = 3; ADPD = 7, PDD = 5; PDND = 6) striatal tyrosine hydroxylase (TH) concentrations were assessed in the posterior putamen using an ELISA method previously published [40].

Plaque density measures

Amyloid plaque density was graded and staged at standard sites in frontal, temporal and parietal cortex, based on the aggregate impression from the thick sections stained with thioflavine S, Campbell-Switzer and Gallyas methods. Plaque density scores were obtained by assigning values of none (0), sparse (1), moderate (2) and frequent (3), according to the published CERAD templates [1]; representative images are located in Figure 1. Scores for plaque density were derived by considering all types of plaques together (cored + neuritic + diffuse = total plaques) as well as separately for cored and neuritic plaques (NP) considered together, without diffuse plaques (Table 2).

The striatum was assessed within the posterior putamen at the level of the full development of the lentiform nucleus. The caudate nucleus was not assessed. Semi-quantitative grading of striatal plaque density in PD cases was performed by 4 raters (BND, GES, TGB, LIS) blinded to case diagnostic status. In a subset of 29 cases graded by all raters, Spearman correlations between all raters were found to be strong and statistically significant

(Spearman rho ranged between 0.85–0.96; all p values <0.001). After all grading was complete, data were un-blinded for analysis.

Statistical analysis

Kruskal-Wallis non-parametric analysis of variance and chi-square tests were used to analyze clinical and pathologic differences between groups. Dunn's post hoc pairwise analysis was used as appropriate. All statistical analyses were performed with Sigma Plot 12.0 (Systat Software, Inc., San Jose, CA, USA). The significance level for all tests was set at $p < 0.05$. Sensitivity and specificity calculations were performed separately using all three PD groups (PDND, PDD and PDAD) or only the PDD and PDAD groups, in order to simulate possible clinical settings. A diagram of how sensitivity and specificity were calculated is located in Figure 2.

Results

The basic characteristics of the study subjects are shown in Table 1. Seven of the AD cases also met clinicopathological criteria for vascular dementia (VaD) and 3 had the additional diagnosis of hippocampal sclerosis (HS). Subjects with AD alone did not differ significantly in any demographic or AD-related neuropathological measures from those with AD/VaD or AD/HS and therefore all were grouped together for further analysis. There were no differences amongst groups with respect to gender ratios. The normal control group was significantly older than all other groups at the time of death. With respect to Parkinson's disease duration, cases having PDD had significantly longer disease duration when compared to PDAD. With respect to dementia duration PDAD and PDD did not differ but AD cases had a significantly longer duration when compared to either. As expected, Braak neurofibrillary stage and NIA Reagan criteria were significantly greater in any case diagnosed with AD (AD, PDAD) as compared to other groups. The percentage of cases carrying at least one APOE4 allele was greater in the AD and PDAD groups than in PDD, PDND, and NC. With respect to Lewy-type histopathology, cases of PDD and PD were more frequently classified as Unified Stage III (Brainstem and Limbic) while PDAD cases had a higher proportion of stage IV (Neocortical) cases. There were no other significant differences amongst groups with respect to demographics and basic neuropathology.

Table 2 shows scores for plaque densities. As expected, the AD and PDAD cases had significantly higher cerebral cortex total and neuritic plaque density scores when compared to PDD, PDND and NC. Striatal plaques (total, all types) were present in 48/50 AD subjects, 32/40 PDAD, 6/31 PDD, 7/31 PDND and 22/62 NC subjects (Table 3) while striatal neuritic/cored plaques were present in 43/50 AD, 19/40 PDAD, 1/31 PDD, 4/31 PDND, and 14/62 NC subjects. Whether considering only the three PD groups, or only the two PD groups with dementia, thereby simulating possibly relevant clinical settings, the presence of striatal plaques had sensitivities and specificities of approximately 80% (plus or minus 1%) in both group settings for the presence of clinicopathological AD. In comparison, the presence of cerebral cortex plaques was 100% sensitive but only 48% specific (when PDND, PDAD and PDD groups were all included) or 55% specific (when only the PDAD and PDD groups were included). When striatal neuritic and/or cored plaques were used as the diagnostic marker (rather than total plaques as above), the sensitivities were much lower (results not shown). With respect to predicting the presence of dementia in all subjects (PD, PDD, PD/AD, AD and normals), the presence of any striatal amyloid plaques had a sensitivity of 71% and specificity of 69%, while cortical plaques had a sensitivity of 86% and specificity of 35%.

Analysis of the subset of cases with available putamen TH concentrations showed no significant differences based on the presence (N= 19) or absence (N=22) of striatal plaques.

However, when comparing only those with PD (ADPD, PDND, or PDD), cases with striatal plaques (N=9) had a higher mean TH concentration than those without (N=9) (mean TH concentration 18.25 vs. 2.9 ng/mg; P = 0.042).

Discussion

We sought to determine if the presence, density or type of striatal plaques was predictive of the presence of the clinicopathological diagnosis of AD in subjects with PD and dementia. We defined clinicopathological AD as requiring dementia as well as NIA-Reagan or NIA-Alzheimer's Association "intermediate" or "high" probability ratings. The NIA-Alzheimer's Associations guidelines are a recently published revision of the NIA-Reagan criteria [15]. The presence of any type (diffuse, neuritic or cored) of striatal plaques predicted the clinicopathological diagnosis of AD with 80% sensitivity and 80% specificity. Requiring the presence of neuritic or cored striatal plaques or requiring higher densities of striatal plaques resulted in less diagnostic accuracy. The higher striatal TH concentrations in subjects having striatal plaques, as compared to subjects without, are somewhat surprising but may indicate that PDAD has similarities with DLB/AD, as the latter group has been repeatedly shown to have less severe degeneration of the nigrostriatal dopaminergic system than what is seen in PD [13]. Additional studies with larger numbers of cases will be needed to confirm this finding.

The results presented here suggest that, with the use of amyloid imaging, the presence of striatal plaques could clinically distinguish PDD from PDAD. Previously, imaging reports of striatal amyloid plaques have been primarily concerned with their presence in subjects with early-onset, autosomal dominant inheritance of AD [41–44]. Few studies have documented striatal amyloid in late-onset sporadic AD [45–47]; one of these found the striatal amyloid signal in late-onset subjects to be equivalent to that in early-onset disease [47]. Most imaging studies in PD have been restricted to estimates of cortical amyloid load [48–51]. Cortical amyloid, however, is a relatively non-specific finding due to the presence of cortical amyloid plaques in a large proportion of neurologically normal elderly subjects [24,52–60], and this is further supported by the low specificity found in our study for cortical plaques.

There has been some debate as to the specificity of amyloid imaging ligands for Aβ amyloid. It is probable that, like their parent histological staining compounds, these ligands will bind with any β-pleated sheet structures. However, amyloid ligands may not appreciably bind to in-situ Lewy bodies. Previous literature has shown that one amyloid ligand (Pittsburgh compound B or PiB) does not produce a significant autoradiographic signal within sections of PD amygdala with frequent Lewy bodies [61] and a case study of pathologically confirmed DLB showed no correlation between Lewy body densities and PiB retention [62]. This agrees with histological knowledge that Lewy bodies are only weakly fluorescent with amyloid stains such as thioflavine S. Previous studies have found that PiB does produce an autoradiographic signal co-localized with neurofibrillary tangles [61,63] but the signal was so weak as to be unlikely to affect the much stronger signal associated with amyloid plaques. It also appears likely, based on postmortem autoradiography studies with antemortem amyloid imaging, that all types of Aβ amyloid, including diffuse, cored and neuritic plaques as well as amyloid angiopathy, will elicit strong amyloid imaging signals [61,63,64]. Additionally one autopsy case study showed clear correspondence between the striatal amyloid imaging signal and striatal diffuse plaques [64]. The largest amyloid imaging study with postmortem correlation to date did not analyze the striatum but confirmed that amyloid imaging is a sensitive and valid marker of postmortem Aβ amyloid deposits [36]. One study found the degree of uptake of PiB in putamen was closely associated with cognitive performance in AD [65]. Large antemortem-postmortem correlative studies are needed to determine whether a positive striatal amyloid imaging

signal would be a sensitive and specific marker of concurrent PD and AD and their clinical severities. As approximately 48 to 78% of PD cases will develop dementia sometime during the course of their illness [11,14], the ability to determine the cause of this is a crucial objective if effective treatments are to be developed.

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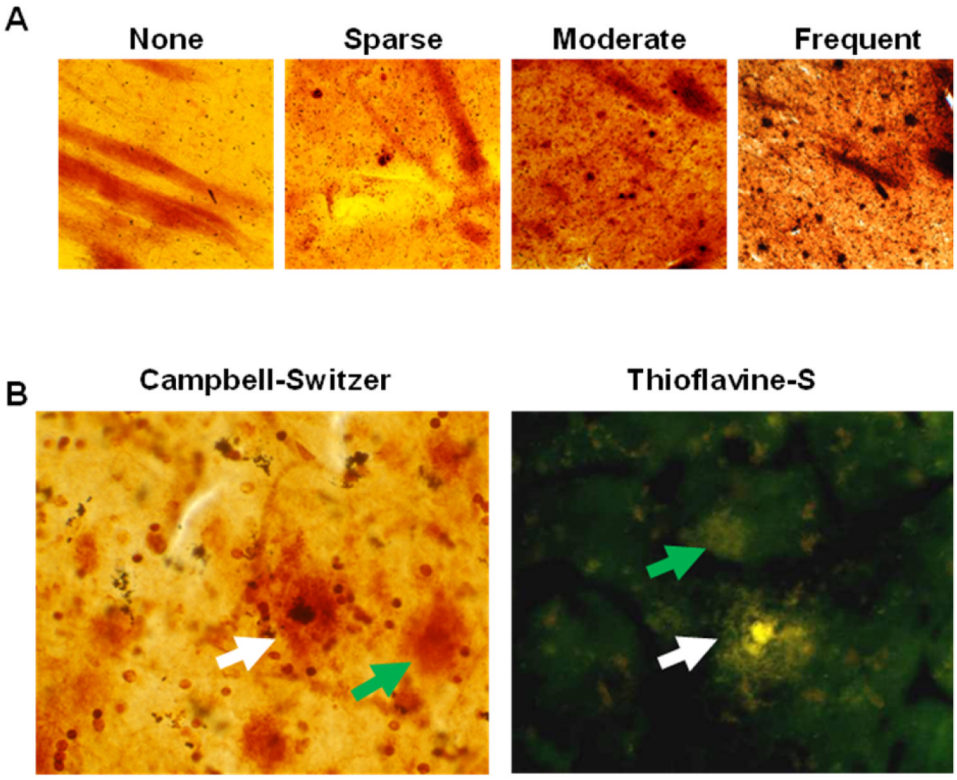

Figure 1.

A) Representative images taken at 10× magnification of plaque density scores in the putamen of none (0), sparse (1), moderate (2) and frequent (3), according to the published CERAD criteria [1]. **B)** Representative images taken at 40× magnification of neuritic (white arrow) and diffuse plaques (green arrow) with Thioflavine-S and Campbell-Switzer staining.

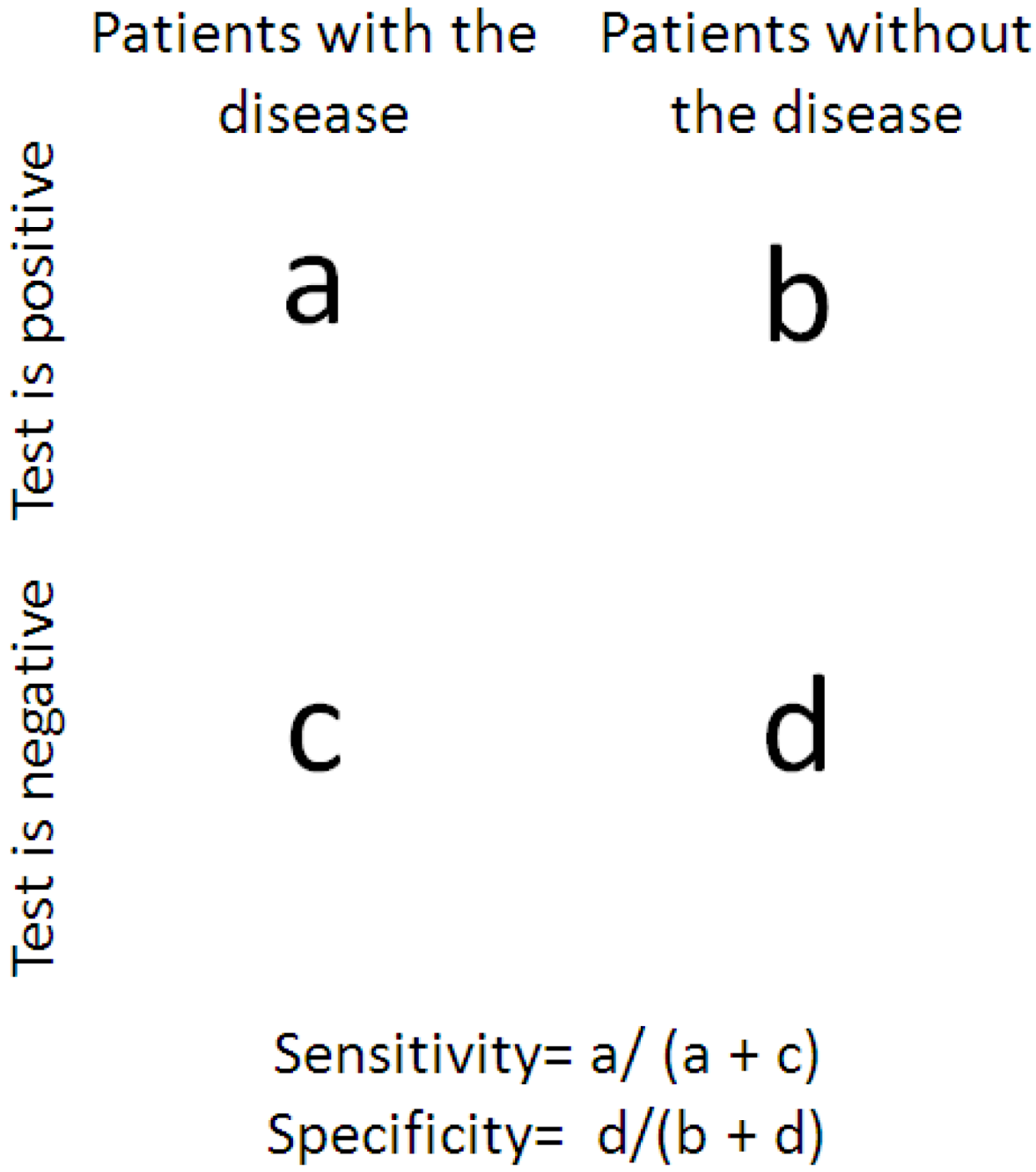

Figure 2.
Diagram of how sensitivity and specificity were determined. Sensitivities were calculated by dividing the number of cases containing a positive test (i.e. specified plaque measure) and patients with the disease (i.e. AD or dementia) - a in the figure above) by the total number of cases having the disease diagnosis regardless of test outcome (a + c). Specificities were calculated by dividing the number of cases having a negative test (i.e. lacking the specified plaque measure) and without the disease (i.e. no AD or dementia) - d in the figure above and by the total number of cases lacking the disease regardless of test outcome (b + d).

Table 1

Demographics and pathologic descriptions of series. AD=Alzheimer's disease, PDAD= Parkinson's disease dementia with AD, PDD= Parkinson's disease dementia without AD, PD= Parkinson's disease, NC= non-demented normal control, NFT=neurofibrillary tangles, LB=Lewy bodies.

	AD	PDAD	PDD	PD	NC	P values
N (M:F)	50 (25:25)	40 (30:10)	31(22:9)	31(18:13)	62 (33:29)	0.07
age at death-mean (±stdev)	81±10	81±5	77±6	80±7	87±6*	<0.001
PD duration-mean (±stdev)	-	10±6	15±8#	14±8	-	0.01
Number of cases	-	37	31	25	-	
Dementia duration-mean (±stdev)	8±4*	3±2	4±5	-	-	<0.001
Number of cases	42	15	13	-	-	
Braak NFT stage-median (range)	V (II–VI)*	IV (I–V)**	II (I–IV)	III (I–IV)	III (I–IV)	<0.001
NIA Reagan-median	high**	intermediate**	not met	not met	not met	<0.001
APOE4 allele, N (%)	27 (54)**	17 (43)**	5 (16)	6 (19)	17 (27)	<0.001
Unified LB stage, N (%)						
lla. Brainstem Predominant	-	3 (8)	3 (10)	8 (26)	-	0.06
llb. Limbic Predominant	-	0	1 (3)	3 (10)	-	0.12
lll. Brainstem/Limbic	-	13 (33)	19 (61)#	16 (52)#	-	<0.001
lV. Neocortical	-	23 (59)†	9 (29)	4 (13)	-	<0.001

*significantly greater than all other groups,

**significantly greater than PDD, PD, and NC,

#significantly greater than PDAD,

†significantly greater than PDD and PD.

Table 2

Striatal and cortical plaque scores for all groups. All values are the median followed by the range in parentheses. The AD and PDAD groups had significantly higher plaque scores (both for total plaques and neuritic/cored plaques) in all areas analyzed. AD=Alzheimer's disease, CERAD= consortium to establish a registry for Alzheimer's disease, PDAD= Parkinson's disease dementia with AD, PDD= Parkinson's disease dementia without AD, PD= Parkinson's disease, NC= non-demented normal control, NP= neuritic/cored plaques.

	AD	PDAD	PDD	PDND	NC	P values
CERAD NP cerebral cortex score	3 (2–3)**	2 (2–3)**	0 (0–3)	0 (0–2)	0 (0–1)	<0.001
Total striatal plaque density	2.75 (0–3)**	1.5 (0–3)**	0 (0–2.5)	0 (0–2.5)	0 (0–3)	<0.001
NP striatal density	0.5 (0–2)*	0.25 (0–2)**	0 (0–0.5)	0 (0–0.5)	0 (0–1)	<0.001
Total cortical plaque density	3 (2–3)*	2.67 (1–3)**	0 (0–2.5)	0.5 (0–3)	1.5 (0–3)	<0.001
NP cortical density	3 (2–3)**	2.5 (1–3)**	1 (0–3)	1 (0–3)	1 (0–3)	<0.001

* significantly greater than all other groups,

** significantly greater than PDD, PD, and NC

Table 3

Percentage of all cases in specified group having any type of amyloid plaque (total) and cored/neuritic plaques (NP). AD=Alzheimer's disease, PDAD= Parkinson's disease dementia with AD, PDD= Parkinson's disease dementia without AD, PD= Parkinson's disease, NC= non-demented normal control.

	AD	PDAD	PDD	PDND	NC
Striatal Plaques present					
total	96%	80%	19%	23%	35%
NP	86%	48%	3%	13%	22%
Cortical Plaques present					
total	100%	100%	45%	58%	68%
NP	100%	100%	39%	55%	65%

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