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Parkinson's disease with dementia: comparing patients with and without Alzheimer pathology

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Abstract

Subjects with Parkinson's disease (PD) frequently develop dementia with greater than one-third meeting neuropathologic diagnostic criteria for Alzheimer's disease (AD). The objective is to identify clinical and neuropathological differences between PDD (PD with dementia) subjects, with and without coexistent AD pathology. Neuropathologic examination was available on subjects diagnosed by clinicopathologic criteria with PDD-AD (N = 23) and PDD+AD (N = 28). A small subset of subjects with PDD-AD and PDD+AD had received at least one standardized neuropsychological assessment. PDD+AD subjects were significantly older at age of PD onset and death, progressed to onset of dementia in less time, and had a shorter duration of PD symptoms prior to the onset of dementia. Education, responsiveness of L-Dopa and dopaminergic medications, presence of cognitive fluctuations and hallucinations, mean MMSE, GDS, FAST and UPDRS scores did not differ significantly between the two groups. The PDD+AD group had significantly greater total plaques, neuritic plaques, total tangles, and Braak stages compared to PDD-AD. This study suggests that it is difficult to distinguish PDD+AD and PDD-AD on the basis of movement, clinical, and neuropsychological assessment. PDD-AD and PDD+AD have similar degrees of dementia and approximately half of PDD subjects have enough AD pathology to attain a neuropathological diagnosis of AD. PDD can develop in the absence of significant Alzheimer pathology.

Key Words and Phrases

Parkinson' disease with dementia; Alzheimer's Disease; Dementia with Lewy Bodies; assessment of dementia

Introduction

Dementia is common among patients with advanced Parkinson's Disease (PD). Estimates of its occurrence in PD patients vary from 27 to 78%.¹ PD subjects have been shown to have six-fold risk of developing dementia compared to those without PD. A recent comprehensive review has reported that Parkinson's disease with dementia (PDD) accounts for 3.6% of all elderly dementia cases, with a prevalence in the elderly population of 0.5%.² In recent studies it has been shown that 32 - 44% of PDD subjects have neuropathological findings consistent with intermediate to high probability of AD.³ With such a high proportion of PDD subjects with concurrent AD, it would be valuable, from a therapeutic standpoint, to identify earlier those with AD. Determining whether PDD with AD (PDD+AD) cases had a different prognosis or whether treatment could slow disease progression are important clinical outcomes to measure. In this study, we have analyzed and compared the clinical and neuropathologic profiles of neuropathologically defined PDD without AD (PDD-AD) and PDD+AD subjects.

Methods

All subjects were recruited from a longitudinal clinicopathologic study of aging and neurodegenerative disease. All subjects with a clinical diagnosis of dementia and a neuropathologic diagnosis of PD were included in the study. Extracted data from subject assessments include medical and family history questionnaire, neuropsychiatric features, neurological examination, Mini-Mental State Examination (MMSE), movement disorders assessment including the Unified Parkinson's Disease Rating Scale III (UPDRS III), functional assessment, including the Global Deterioration Scale (GDS), and Functional Assessment Staging (FAST).

Dementia was diagnosed according to DSM-IV criteria. The clinical diagnosis of PD was made with UK brain bank criteria and when two of the three cardinal features of Parkinson's disease (tremor, bradykinesia, and rigidity) were present. The distinction between PDD and dementia with Lewy bodies (DLB) was made clinically, on the basis of relative time of appearance of motor and cognitive signs.⁴ A small subset of subjects received at least one standardized neuropsychological assessment. The cognitive assessments were performed blinded to the functional and global scores. Exclusion criteria included DLB, progressive supranuclear palsy, mild cognitive impairment (MCI), PD non demented, non-idiopathic parkinsonism including parkinsonism or dementia from vascular causes.

Neuropathologic procedures

All subjects received a standardized neuropathologic examination after death. Cases with dementia were rated according to National Institute on Aging (NIA)-Reagan criteria. All cases were also classified according to the Consortium to Establish a Registry for Alzheimer's Disease criteria for the diagnosis of AD, and all cases are assigned a Braak neurofibrillary stage.⁵ The defined regions to be counted and the method of developing a Lewy body score and stage were as described in the original report of the DLB consortium.⁴ Neuritic plaque and neurofibrillary tangle abundance was estimated semi-quantitatively (none, sparse, moderate or frequent.) Total plaque density (diffuse and neuritic) was also estimated in this manner. All semi-quantitative scores for plaques, tangles, Lewy bodies and white matter rarefaction were converted to numerical scores for statistical analysis. The score and stage used were done with established criteria.⁴ The scores from all brain regions were summed to give a total score.

Statistical Methods

Comparison of continuous data, including age, MMSE, GDS, UPDRS, brain weight and Lewy body counts, was done with unpaired, 2-tailed t-tests. Comparison of discontinuous data (eg.

semiquantitative neuropathologic scores) was done with the Mann-Whitney U-test. The significance level for all tests was set at $p < 0.05$.

Results

The sample included a total of 51 patients diagnosed as having Parkinson's disease with dementia (PDD). Of that group, 28 were diagnosed neuropathologically as PDD+AD using CERAD AD neuropathologic criteria and 23 were diagnosed as PDD-AD. PDD+AD subjects were significantly older at death and age of PD onset as well as shorter duration of PD disease (table 1). The time to onset of dementia was shorter in PDD+AD. The mean MMSE, FAST, GDS and UPDRS scores were not significantly different. Other factors such as the presence of hallucinations, cognitive fluctuations, and l-dopa responsiveness did not significantly differ between the groups.

The neuropsychological profile between PDD+AD and PDD-AD was indistinguishable as there were no significant differences on individual neuropsychological measures. These data should be interpreted with caution as there is limited statistical power with small sample sizes for the neuropsychological data and subjects with both hallucinations and fluctuations. Demographic and clinical data are summarized in Table 1.

The total and neuritic plaque scores, tangle scores, Braak stage, and white matter scores are summarized in Table 2. As expected, the PDD+AD had significantly greater total plaques, neuritic plaques, total tangles, and Braak stages compared to PDD-AD. The white matter score did not differ significantly among the groups.

The Lewy body counts, scores and stages are summarized in Table 2. The PDD+ AD group showed no significant differences for LB counts, scores and stages compared to the PDD-AD group.

Discussion

In this clinical and neuropathologic study of PDD, there are several findings. First, PDD-AD and PDD+AD have similar degrees of dementia but PDD+AD are older at death and age of PD onset, have a shorter duration of PD and progress to the onset of dementia in less time than PDD-AD. Second, PDD+AD cannot be clinically distinguished from PDD-AD in a small prospective subset of the entire sample. Third, in this series of 51 cases of PDD more than half the subjects have enough AD pathology to attain a neuropathological diagnosis of AD. These data suggest that the pathological substrate of dementia cannot be explained simply by the presence of plaques or tangles.

The development of dementia in PD is likely to be due to several underlying processes. These include the presence of accompanying AD and/or vascular lesions, spread of α -synuclein aggregation into limbic and neocortical brain regions and progressive neurotransmitter deficits, especially acetylcholine and dopamine,⁶ and the spread of LB's into the limbic system and cerebral cortex. It has been reported that about 40% of all PDD cases meet neuropathologic diagnostic criteria for AD,⁷ and cognitive function in PD subjects correlates not only with Lewy bodies but also with measures of both A β deposition and neurofibrillary tangles.⁸ Nevertheless, other studies found less marked AD changes in PDD⁹. One probable reason for discrepancies is that most studies have been based on only a small number of subjects. Contrary to our findings, it has been shown that as neocortical LB counts increase, there is a significant increase in senile plaques and neurofibrillary tangles. Given the differences between groups in terms of AD pathology but not differences in terms of LB pathology, one might infer that LB's are a contributor to the dementia in PDD. It has been demonstrated that there is no

relationship between the clinical stages of dementia and neuropathologic findings in PDD, PDD with LB, and PDD with AD.³

Non-demented PD patients with abnormal neuropsychological testing have an increased risk for the development of dementia. Abnormalities in executive function, memory and visuospatial function have all been shown to be predictive of dementia development. From a longitudinal perspective, distinguishing features between PDD and AD are cognitive fluctuations, visual and auditory hallucinations, depression, and sleep disturbances. We did not compare PDD and AD groups clinically, but our results show no difference between PDD+AD and PDD-AD with respect to the presence of hallucinations or cognitive fluctuations. The indistinguishable characteristics could be the result of a limited sample size. Functional assessments between PDD+AD and PDD-AD did not differ either based on UPDRS, GDS, and FAST. However, it has been previously found that PD and AD have similar degrees of functional decline and in PD, early functional decline may be due to motor impairments while later functional declines may be due to cognitive impairments.⁹ Also, other studies have corroborated our finding that PDD+AD have a shorter time from onset of PD symptoms to dementia¹⁰.

Limitations of this study include the small number of subjects who underwent neuropsychological evaluation and the method of collecting clinical information retrospectively from chart review. Unfortunately, the neuropsychological findings are far too limited to draw clear conclusions. One might speculate that addition of AD pathology to alpha-synuclein pathology do not appear to grossly alter the pattern of deficits based on the limited neuropsychological testing. Without enough data to formally analyze rate of cognitive decline, this study cannot estimate whether there are longitudinal differences in psychometric performance between the PDD+AD and PDD-AD groups.

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Table 1
Demographic and Clinical Features of PDD with and without AD^a

	PDD-AD		PDD+AD		p-value
	n	Mean	n	Mean	
Age at Death	23	75.7	28	80.6	0.005
Age at PD onset	23	57.3	28	68.2	<0.001
Age at first evaluation	22	67.7	26	71.9	0.05
Duration of PD Disease (yrs)	23	18.7	28	12.5	0.003
Time to Dementia (yrs)	23	15.0	23	10.3	<0.05
Education (yrs)	15	15.3	17	15.1	0.85
UPDRS III	20	41.6	12	50.7	0.23
First MMSE	14	23.1	9	23.6	0.88
Last MMSE	18	19.1	15	17.4	0.57
GDS	11	4.8	7	4.9	0.96
FAST	7	5.4	5	6.0	0.63
Mos. between last follow-up and death	21	13.5	25	14.6	0.72
No. of clinical follow-ups	22	7.2	25	6.1	0.29
AVLT (total)	9	24.0	5	21.8	0.76
AVLT (A7)	8	2.1	5	1.8	0.84
Stroop (cw)	3	14.7	2	13.0	§
COWA	9	23.3	4	15.5	0.34
Animals	9	10.8	5	7.8	0.37
Trails A (time; secs)	6	100.0	2	20.5	§
Trails B (time; secs)	4	272.0	1	143	§
Gender (%F)	35		20		
Presence of Cognitive Fluctuations	4/7		1/5		
Presence of Hallucinations	19/23		16/19		
Positive response to L-Dopa and dopaminergic medications	14/16		7/10		

PD: Parkinson's Disease
PDD: Parkinson's Disease with Dementia
MMSE: Mini Mental State Examination
GDS: Global Deterioration Scale
COWA: Controlled Oral Word Association

FAST: Functional Assessment Staging
AVLT: Rey Auditory Verbal Learning Test
Stroop (cw): Stroop color-word score
UPDRS: Unified Parkinson's Disease Rating Scale

* unless otherwise stated, each evaluation is the last prior to death
 δ_i insufficient data to perform means comparison
 α_i levels of significance set at p-value<0.05

Table 2
Comparison of AD histopathology, brain weight and white matter rarefaction, Lewy body counts, scores and stages ^a

	PDD-AD		PDD+AD			p-value
	n	Mean	SD	n	Mean	
Total Plaques	23	2.2	3.7	27	9.6	2.7 <0.0001
Neuritic Plaques	23	0.4	0.5	28	2.2	0.4 <0.0001
Total Tangles	23	3.1	1.5	27	4.7	2.3 0.005
Braak Stage	23	2.3	0.6	28	3.1	1.1 0.003
White Matter Score [§]	23	1.2	2.3	28	2.3	3.1 0.16
Trans LB count	16	21.6	31.3	16	42.3	43.3 0.14
Cing LB count	18	55.9	67.7	17	48.6	37.1 0.70
MFG LB count	18	5.1	9.1	17	5.7	5.9 0.82
MTG LB count	18	7.9	14.4	17	11.5	20.9 0.55
PAR LB count	18	3.7	7.7	17	7.0	12.1 0.34
Total LB count	17	95.2	128.7	16	114.9	93.1 0.62
LB stage [§]	20	2.4	0.7	20	2.7	0.6 0.15
LB score [§]	18	6.1	3.2	17	7.0	2.8 0.39

Trans: Transentorhinal cortex,
Cing: Cingulate gyrus,
MFG: Mid Frontal Gyrus
MTG: Medial Temporal Gyrus
PAR: Parietal Lobe

[§]described in methods

^alevels of significance set at p-value<0.05