

## Side and Type of Motor Symptom Influence Cognition in Parkinson's Disease

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**Abstract:** It is well known that many patients with Parkinson's disease experience neuropsychological decline. However, the nature and extent of mental status change varies widely, with some patients showing mild or no cognitive impairments and others exhibiting frank dementia. Research has shown that several clinical disease parameters may differentially correlate with patterns of neuropsychological dysfunction. The present study examined side and type of motor symptom at disease onset and their relationship to cognition in idiopathic Parkinson's disease (PD). We identified 58 patients who initially presented with one of the following symptom profiles: right-side tremor onset (RSO-T;  $n = 15$ ), right-side bradykinesia/rigidity onset ( $n = 12$ ), left-side tremor onset ( $n = 19$ ), and left-side bradykinesia/rigidity onset ( $n = 12$ ). There were no differences between groups in disease duration, overall mental status, education, or depression severity. We administered a battery of neuropsychological measures to the four PD sub-

groups and a group of matched control subjects ( $n = 40$ ). MANCOVAs controlling for age revealed patients with RSO-T performed significantly better than the other three PD subgroups across the entire neuropsychological battery. Further, the RSO-T subgroup performed comparably to controls. In contrast, the other three PD subgroups showed widespread cognitive deficits. These findings suggest an intricate relationship between motor symptom and side of disease onset and it is the combination of these factors that may influence the disease course and extent of cognitive deterioration. Furthermore, patients who develop tremor on the right side of their body represent a distinct subgroup of PD patients who exhibit relative sparing of cognitive function. © 2006 Movement Disorder Society

**Key words:** Parkinson's disease; cognition; dementia; motor symptoms; side of onset

It is well known that patients with Parkinson's disease (PD) experience cognitive decline.<sup>1–4</sup> The nature and severity of the neuropsychological impairments vary widely, with some patients showing widespread deficits and others remaining relatively intact throughout the course of their illness. While progress has been made toward understanding the pathophysiology of PD motor symptoms, the etiology of cognitive decline remains poorly understood. Much of the research examining this issue has focused on correlating patterns of neuropsychological dysfunction with clinical disease parameters.

It is believed that this approach will yield valuable information regarding the underlying neural basis of cognitive decline in PD.

Predominant motor symptoms (bradykinesia, rigidity, and tremor) have been differentially linked to severity of intellectual decline in PD. Research has consistently demonstrated that bradykinesia and rigidity are correlated with cognitive impairment, whereas tremor is not.<sup>5–8</sup> Portin and colleagues<sup>5</sup> found that patients with predominant bradykinesia and rigidity were more likely than patients with tremor to show mental status decline. Huber and colleagues<sup>7</sup> compared patients with predominant tremor to those with predominant bradykinesia/rigidity and found only the latter group of patients exhibited deficits in memory, visuospatial, and executive skills. Iwasaki and colleagues<sup>8</sup> reported a negative correlation between bradykinesia and visuospatial tasks and rigidity and memory tasks in patients with idiopathic PD. These findings suggest that the pathophysiological mech-

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Received 1 August 2005; Revised 15 February 2006; Accepted 24 May 2006

Published online 21 September 2006 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mds.21105

anisms responsible for producing bradykinesia and rigidity may also underlie PD-related cognitive deficits. Accordingly, tremor may result from disruption of a distinct or unrelated pathway. This dissociation has also been supported by studies linking bradykinesia and rigidity to more rapid disease progression.<sup>9,10</sup> In addition, functional imaging data have consistently shown bradykinesia and rigidity, but not tremor, to be associated with underlying markers of disease severity.<sup>11–13</sup>

Research examining the relationship between symptom asymmetry and cognitive decline has been equivocal. Some investigators have shown a clear lateralized cognitive profile: patients with right-sided symptoms (left hemisphere dysfunction) perform more poorly on verbally mediated tasks<sup>14–19</sup> and patients with left-sided symptoms (right hemisphere dysfunction) perform worse on visuospatial tasks.<sup>14,17–19</sup> Others have found patients with left-sided symptoms demonstrate widespread cognitive deficits, while those with right-sided symptoms do not exhibit mental status decline.<sup>20</sup> There have also been studies showing no relationship between cognition and side of predominant motor symptoms.<sup>21</sup> These conflicting findings may be due in part to methodological differences, as many studies have failed to control for important variables such as disease duration and PD severity, and few have had adequate sample size.

It has been proposed that patients with greater left-sided disease are also more likely to exhibit bradykinesia and rigidity.<sup>6</sup> Zetuský and Jankovic<sup>6</sup> argue that motor symptom, not the asymmetry of disease, accounts for PD-related cognitive impairment. Others have refuted this notion by demonstrating an association between symptom asymmetry and cognition in patients with similar degrees of bradykinesia and rigidity.<sup>20</sup>

Some investigators have chosen to study the relationship between cognition and the laterality of symptoms at the time of disease onset, rather than the relationship with an individual's current symptoms.<sup>22</sup> This approach may prove useful in understanding the relationship between cognition and motor symptoms for several reasons. First, as the disease progresses, patients develop increasingly complex symptoms; therefore attempts to classify subjects with more advanced disease into "predominant" symptom groups oversimplifies the clinical picture while minimizing the other motor signs. Second, it has been demonstrated that dopaminergic decline continues to show disproportionate depletion in the initially affected hemisphere, even if there is bilateral progression in clinical symptomatology. Third, neurological ratings typically employ Likert-type scales that are not necessarily comparable across symptom subtypes, making it difficult to equate the severity of each motor sign in order

to determine which is predominant. Lastly, medication is known to affect individual motor symptoms differentially. Thus, evaluation of clinical symptom severity after initiation of pharmacological intervention may not accurately reflect the underlying neuropathology.

Tomer and colleagues<sup>22</sup> found evidence supporting the importance of examining symptom asymmetry at the time of disease onset. After controlling for symptom asymmetry at the time of the assessment, patients with right-side symptom onset showed significantly better cognitive functioning compared to patients who developed symptoms on the left side of their body. It was concluded that the clinical motor symptom profile at the time of disease onset may be a more critical determinant of cognitive change than current motor symptomatology.<sup>22</sup> No research to date has focused on the relationship between the predominant motor symptom at disease onset and cognition. The purpose of the current study was to examine the complex relationship between symptom lateralization and type of motor symptom at disease onset.

## PATIENTS AND METHODS

### Subjects

Fifty-eight patients with idiopathic PD were referred from the Movement Disorders Clinic at the University of Miami. Each patient underwent a neurological examination and received a diagnosis of PD from a movement disorders specialist (W.W.). Patients with a history of drug or alcohol abuse, a major psychiatric disorder, cardiovascular disease, insulin-dependent diabetes, head injury, or other neurological illness, as well as patients who underwent neurosurgical operation, were excluded. Patients were also excluded if the neurological evaluation revealed signs or symptoms not consistent with a diagnosis of idiopathic PD, including lack of responsiveness to levodopa, a rapidly progressing dementia, or evidence suggestive of another movement disorder. A sample of 40 control participants were included, consisting of either patients' spouses or senior citizens recruited from an adult retirement community.

### Procedures and Data Collection

Written informed consent was obtained and each patient underwent a 3-hour comprehensive interview and neuropsychological evaluation. Subjects were tested in the Division of Neuropsychology at the University of Miami. The examiners were graduate and postdoctoral students in clinical neuropsychology and were fully trained in the administration and scoring of the neuropsychological test battery.

All PD patients were evaluated by a neurologist and stage of illness was rated.<sup>23</sup> A total disability score was obtained using a modified version of the Northwestern University Disability Scale (NUDS).<sup>24</sup> Side of disease onset (left and right) and type of initial motor symptom (bradykinesia and/or rigidity at onset and tremor only at onset) were obtained from subject report during clinical interview and then subsequently confirmed through retrospective medical chart review. Patients were not included if medical record was not available for review; self-report was inconsistent with the clinical chart; there was evidence of a history of bilateral symptom onset or bilateral disease within 1 year; or there was evidence that tremor developed with bradykinesia or rigidity within the first year of disease onset. Four groups were ultimately identified: 15 right-side tremor onset (RSO-T), 12 right-side bradykinesia/rigidity onset (RSO-B/R), 19 left-side tremor onset (LSO-T), and 12 left-side bradykinesia/rigidity onset (LSO-B/R). All patients underwent neuropsychological evaluations while in the *on* drug condition.

**Measures**

The neuropsychological battery consisted of tests shown to be clinically and empirically sensitive to the spectrum of cognitive functions known to be compromised in PD.<sup>25</sup> The following domains were assessed: language: Boston Naming Test (BNT; odd-numbered items),<sup>26</sup> Controlled Oral Word Association Test (COWA; FAS and animals)<sup>27</sup>; memory: California Verbal Learning Test (CVLT)<sup>28</sup>; visuospatial: Ghent Embedded Figures Test,<sup>29</sup> Hooper Visual Orientation Test (HVOT; 10-item version),<sup>30</sup> Judgment of Line Orientation Test (JLO; 15-item version)<sup>31</sup>; and executive func-

tioning: Wisconsin Card Sorting Test (WCST; modified version).<sup>32</sup>

**RESULTS**

Simple analysis of variance (ANOVA) revealed that the four PD subgroups were equivalent with respect to age, age of disease onset, disease duration, education, stage of illness, overall degree of disability, level of depression, and overall mental status. Correlational analyses revealed that age was strongly correlated with performance on all the cognitive measures and was therefore selected as a covariate for the main analyses. Demographic and clinical data for each of the four PD subgroups and the subset of controls are presented in Table 1. PD patients and controls did not differ with respect to age, gender, and years of education, but PD patients performed worse than controls on a measure of overall mental status and exhibited more depressive symptoms on the Beck Depression Inventory (BDI) (Table 1).

Four separate two-way factorial MANCOVAs with age as the covariate were calculated for each of the cognitive domains (language, visuospatial, memory, executive). Adjusted means and standard errors of the cognitive data for each of the four PD groups are presented in Table 2.

Results revealed a main effect for side of onset within the memory domain ( $F(3,51) = 5.23; P = 0.003$ ), with the RSO patients performing better than those with LSO. Univariate tests showed this to be true for the immediate ( $F(1,53) = 6.06; P = 0.017$ ) and delayed recall ( $F(1,53) = 5.98; P = 0.018$ ) of the CVLT. On the executive tasks, there was a trend toward a main effect

**TABLE 1.** Demographic and clinical data for each of the four PD groups and control subjects

	Right-sided onset (n = 27)		Left-sided onset (n = 31)		Significance	Control subjects (n = 40)
	T only (n = 15)	B/R (n = 12)	T only (n = 19)	B/R (n = 12)		
Age (yr)	67.07 ± 5.27	59.75 ± 14.14	65.47 ± 9.91	67.92 ± 8.17	NS	68.30 ± 6.06
Sex (M/F)	11/4	7/5	10/9	5/7	NS	29/21
Handedness (R/L)	10/5	10/2	17/2	12/0	NS	35/5
Education (yr)	13.07 ± 3.15	14.17 ± 2.89	14.16 ± 2.29	14.08 ± 1.98	NS	13.50 ± 2.26
BDI	9.20 ± 5.78	13.58 ± 7.35	9.16 ± 7.57	11.33 ± 10.72	NS	5.63 ± 4.09 <sup>a</sup>
MMSE	25.54 ± 2.32	24.92 ± 2.61	24.79 ± 2.04	23.42 ± 3.00	NS	26.72 ± 0.94 <sup>a</sup>
Age of onset (yr)	58.07 ± 6.14	50.25 ± 13.23	59.21 ± 10.67	59.67 ± 9.25	NS	
Duration (yr)	9.07 ± 5.93	9.50 ± 5.40	6.32 ± 5.24	7.42 ± 4.70	NS	
PD stage	2.00 ± 0.85	2.75 ± 1.06	2.42 ± 0.84	2.50 ± 0.80	NS	
Stage I	3	2	2	1		
Stage II	9	2	9	5		
Stage III	2	5	6	5		
Stage IV	1	3	2	1		
Stage V	0	0	0	0		
PD disability	18.00 ± 12.82	19.00 ± 9.70	21.11 ± 12.54	19.08 ± 8.03	NS	

Values are mean ± SD.

<sup>a</sup> $P < 0.01$  (PD vs. control).

**TABLE 2.** Adjusted means and standard errors of the cognitive data for each of the four PD groups

	Right-sided onset (n = 27)		Left-sided onset (n = 31)	
	T only (n = 15)	B/R (n = 12)	T only (n = 19)	B/R (n = 12)
Language				
FAS	42.34 ± 3.44	36.66 ± 3.96	33.03 ± 3.04	35.95 ± 3.86
Animal <sup>a</sup>	16.77 ± 1.15	14.05 ± 1.33	13.09 ± 1.02	13.26 ± 1.29
BNT	25.69 ± 0.97	23.72 ± 1.11	23.79 ± 0.86	23.51 ± 1.09
Visuospatial <sup>b</sup>				
HVOT <sup>a</sup>	7.09 ± 0.59	5.18 ± 0.68	5.35 ± 0.52	6.33 ± 0.66
Ghent	32.64 ± 1.31	30.44 ± 1.50	29.83 ± 1.16	30.03 ± 1.47
JLO <sup>a</sup>	10.76 ± 0.92	9.33 ± 1.05	7.61 ± 0.81	9.00 ± 1.03
Memory <sup>c</sup>				
CVLT: fifth recall <sup>a</sup>	10.46 ± 0.73	8.56 ± 0.84	8.88 ± 0.65	9.72 ± 0.82
CVLT: immediate recall	8.13 ± 0.76	7.81 ± 0.87	5.67 ± 0.67	6.38 ± 0.85
CVLT: delayed recall <sup>a</sup>	8.98 ± 0.77	8.32 ± 0.89	5.89 ± 0.68	7.46 ± 0.87
Executive <sup>d</sup>				
WCST: categories <sup>a</sup>	4.92 ± 0.43	3.21 ± 0.50	4.03 ± 0.38	3.85 ± 0.49
WCST: perseverations <sup>a</sup>	3.37 ± 1.13	8.02 ± 1.30	7.31 ± 0.96	7.70 ± 1.26

<sup>a</sup> $P < 0.05$ : univariate comparisons (RSO-T > [RSO-B/R, LSO-T, LSO-B/R]); <sup>b</sup> $P = 0.068$ : side × symptom; <sup>c</sup> $P = 0.003$ : side of onset (RSO > LSO); <sup>d</sup> $P = 0.068$ : symptom of onset (T > B/R).

for symptom at disease onset ( $F(3,51) = 2.83$ ;  $P = 0.068$ ), with the subjects with tremor achieving a greater number of categories on the WCST ( $F(1,53) = 4.67$ ;  $P = 0.035$ ) and making fewer perseverative errors ( $F(1,53) = 4.37$ ;  $P = 0.041$ ) as compared to subjects with bradykinesia and rigidity. There was a trend toward an interaction between side and symptom of disease onset within the visuospatial domain ( $F(3,51) = 2.61$ ;  $P = 0.068$ ). Follow-up analyses revealed the RSO-T group performed better on the visuospatial tasks than the LSO-T group ( $F(3,29) = 3.29$ ;  $P = 0.034$ ) and univariate tests showed this to be true for the Hooper ( $F(1,31) = 5.03$ ;  $P = 0.032$ ) and JLO ( $F(1,31) = 7.17$ ;  $P = 0.012$ ). No significant effects were observed within the language domain.

Examination of the cell means revealed that one of the tremor subgroups (RSO-T) actually obtained the highest mean performance scores across all cognitive variables (Table 2). Therefore, additional exploratory analyses were conducted comparing the RSO-T group with the other three PD subgroups combined (RSO-B/R, LSO-T, LSO-B/R). One-way MANCOVAs indicated that the RSO-T group demonstrated superior performance on tests of visuospatial abilities ( $F(3,49) = 3.82$ ;  $P = 0.015$ ) and executive functioning ( $F(2,51) = 5.64$ ;  $P = 0.006$ ). Univariate test results indicated that the RSO-T group exhibited better performance on the animal fluency task ( $F(1,52) = 6.86$ ;  $P = 0.012$ ), JLO ( $F(1,51) = 6.27$ ;  $P = 0.016$ ), HVOT ( $F(1,51) = 7.42$ ;  $P = 0.009$ ), number of categories on the WCST ( $F(1,52) = 4.19$ ;  $P = 0.046$ ), number of perseverations on the WCST ( $F(1,52) = 11.47$ ;  $P = 0.001$ ), the fifth trial of the CVLT ( $F(1,52) = 6.18$ ;  $P = 0.016$ ), and delayed recall of the CVLT ( $F(1,52) = 5.39$ ;  $P = 0.024$ ).

A second group of exploratory follow-up analyses was conducted to determine whether the superior performance of the RSO-T subgroup reflected intact cognitive functioning or simply less decline relative to the other PD groups. First, the RSO-T group was compared to a subset of control subjects ( $n = 40$ ). No significant differences were observed between the RSO-T group and controls across any of the cognitive measures. Second, the other three PD subgroups (RSO-B/R, LSO-T, LSO-B/R) were combined and compared to the subset of controls. The combined patient group performed more poorly across all cognitive domains assessed, including language ( $F(3,87) = 3.31$ ;  $P = 0.024$ ), visuospatial ( $F(3,87) = 7.76$ ;  $P \leq 0.001$ ), memory ( $F(3,87) = 7.97$ ;  $P \leq 0.001$ ), and executive domains ( $F(3,87) = 8.05$ ;  $P = 0.001$ ). Univariate tests indicated that the combined patient group (RSO-B/R, LSO-T, LSO-B/R) exhibited poorer performance than controls on phonemic fluency ( $F(1,89) = 6.98$ ;  $P = 0.01$ ), animal fluency ( $F(1,89) = 8.04$ ;  $P = 0.006$ ), Ghent ( $F(1,89) = 15.90$ ;  $P \leq 0.001$ ), HVOT ( $F(1,89) = 18.98$ ;  $P \leq 0.001$ ), trial 5 of the CVLT ( $F(1,89) = 22.70$ ;  $P \leq 0.001$ ), immediate recall of the CVLT ( $F(1,89) = 18.66$ ;  $P \leq 0.001$ ), delayed recall of the CVLT ( $F(1,89) = 15.95$ ;  $P \leq 0.001$ ), number of categories on the WCST ( $F(1,89) = 14.73$ ;  $P \leq 0.001$ ), and number of perseverations on the WCST ( $F(1,89) = 10.63$ ;  $P = 0.002$ ).

## DISCUSSION

This study examined the influence of lateralization and type of motor symptom at disease onset on cognition in PD. Our findings argue against a straightforward association between cognition and either disease parameter.

Rather, the relationship is complex. Patients who develop bradykinesia or rigidity as their initial sign demonstrate cognitive deficits regardless of the laterality of their symptoms, while patients who present with tremor demonstrate neuropsychological impairments only when the tremor begins on the left side of their body.

The one subgroup of patients who remain free of cognitive decline is the group that develops right-side tremor at disease onset. These findings suggest an intricate relationship between motor symptom and side of disease onset and it is the combination of these factors that may influence the disease course and extent of cognitive deterioration.

Our findings support the well-documented observation that PD patients exhibit memory impairments.<sup>19,33–37</sup> These data confirm an earlier study showing greater deficits in verbal learning and memory among patients with left-side symptom onset relative to patients whose initial motor symptoms are confined to the right side of the body.<sup>22</sup> Further, one subgroup of patients with right-sided onset, those with tremor as their initial sign, performed comparably to controls on memory tasks.

Impaired executive functioning has repeatedly been demonstrated in PD.<sup>25,38,39</sup> Patients with onset of bradykinesia and rigidity in this study exhibited a tendency to have greater difficulty on the card-sorting task compared to patients who develop tremor. As found in other domains, patients with right-side tremor onset performed comparably to controls on the executive measure, achieving more categories and making less perseverative errors than the other three PD groups.

This study also supports previous investigations documenting visuospatial impairments in PD.<sup>4,40–45</sup> While both laterality and symptom type have been linked to visuospatial deficits, the current investigation found a complicated relationship between these two variables. Patients with right-side tremor at onset not only perform better than patients who present with right- or left-side bradykinesia/rigidity or left-side tremor on visuospatial tasks, but they also were the only PD subgroup to show preservation of these skills compared to controls.

Although subtle changes in language abilities have been noted,<sup>46–48</sup> the majority of studies show that language remains relatively intact in PD.<sup>1,25,46</sup> The current findings support this view and demonstrate that PD patients as a group do not differ from controls on language tests. However, closer analysis reveals that only patients with right-side tremor at disease onset were truly free of deficits across all language tasks. Patients who presented with right- or left-side bradykinesia/rigidity or left-side tremor actually demonstrated impaired performance on measures of semantic and phonemic fluency. It is likely

that poor performance on the language measures in this subset of patients reflects difficulty handling the executive component of these tasks rather than a primary linguistic problem. This is consistent with more recent work showing executive dysfunction on language measures.<sup>47</sup> The fact that no deficits were observed in any of the PD subgroups on the confrontation-naming task further supports this notion.

It could be argued that the superior performance of patients with right-sided tremor onset reflects a sampling bias in that these patients have less advanced disease. This is a valid concern given that the intact PD subgroup did have slightly lower mean disease severity scores and fewer patients in this group showed evidence of bilateral disease. However, there were no significant differences between groups on either stage of illness or overall degree of disability. Furthermore, the right-sided tremor onset group had comparable disease duration when compared to patients with right-sided bradykinesia and rigidity onset and slightly longer disease duration as compared to both left-sided onset groups. Therefore, we do not believe that this argument can be used to explain the current findings.

It has been previously reported that patients with tremor show less functional impairment and fewer mental status changes compared to patients with bradykinesia and rigidity.<sup>23</sup> The current data lend support for this observation for patients who present with symptoms on the right side of their body. We propose that, at least early on, this subgroup may have a more benign disease course, characterized by slower progression in motor and cognitive symptoms. This may also apply to the preclinical phase, which in turn may reflect more gradual dopamine (DA) dropout within the nigrostriatal pathway.

It is well known that the striatal DA deficiency caused by loss of DA-containing neurons in the substantia nigra results in reduction in thalamocortical activation, which is primarily responsible for the development of parkinsonian symptoms.<sup>49,50</sup> Dopamine depletion within the basal ganglia alters the functioning of several distinct, parallel, topographically organized neuroanatomical pathways that connect the striatum with other subcortical nuclei and cortical regions.<sup>51,52</sup> Although the mechanisms that underlie bradykinesia, rigidity, and tremor remain poorly understood, it has been suggested that each of the cardinal motor signs develops independently and results from alterations in distinct subcircuits of the motor pathway.<sup>53</sup> Thus, the pathophysiology of tremor may involve a discrete pathway that does not directly impact basal ganglia systems linked to cognition.<sup>54–57</sup> In contrast, the basal ganglia circuitry disrupted in patients with bradykinesia or rigidity may be closely linked an-

atomically and neurochemically to other projections, including the dorsolateral prefrontal circuit that is known to be involved in cognitive processes.<sup>58,59</sup> This may explain why patients with bradykinesia or rigidity exhibit greater cognitive deficits.

It has also been shown that there are neurochemical asymmetries among hemiparkinsonian patients who have been shown to persist throughout the disease course.<sup>60–62</sup> Tomer and colleagues<sup>22</sup> suggested that damage to the right hemisphere dopamine systems may play a disproportionately greater role in PD-related cognitive decline than comparable depletion within the left hemisphere. This study lends further support for that notion.

Animal studies have indicated that there is a neurochemical lateralization of the dopaminergic system with greater D1 and D2 receptor density and greater D2 receptor affinity within the right basal ganglia as compared to the left.<sup>63</sup> It would be reasonable to speculate that, if this asymmetry also exists in humans, the increased DA receptor density within the right basal ganglia may also involve a larger number of projections to the frontal lobes. It would then follow that damage to the right basal ganglia may have greater negative consequences in terms of cognition and behavior. To date, no such study has been conducted in humans.

**Acknowledgments:** We gratefully acknowledge Drs. Maria Llabre and Dr. Phillip McCabe for helpful advice and consultation.

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# Dementia in Parkinson's disease: a post-mortem study in a population of brain donors

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## SUMMARY

**Objective** To identify factors associated with dementia in a cohort of Parkinson's disease (PD) brain donors and determine whether its presence may influence the clinical phenotype of the disease.

**Methods** We included 67 consecutive patients with a clinical and pathological diagnosis of PD, who while alive, consented to donate their brains to the University of Miami Brain Endowment Bank<sup>TM</sup>. Dementia and psychiatric complications of PD were diagnosed according to established criteria. Case histories were abstracted and reviewed and comparisons between PD patients with (PD-D,  $n = 34$ ) and without (PD,  $n = 33$ ) dementia were made.

**Results** Age at death, age at disease onset and disease duration did not differ significantly between PD-D and PD patients. Other symptoms were similar in both groups. Visual hallucinations and bilateral symptoms at diagnosis were significantly higher in PD-D patients. No association between dementia and overall survival duration was found. Although the frequency of depression and psychosis was higher in the PD patients with dementia no statistical significance was reached. The overall lifetime prevalence of dementia in our group was 50.7%.

**Conclusion** Visual hallucinations and bilateral symptoms were associated with dementia in our cohort of PD brain donors. No association between dementia and survival duration was found. Understanding the influence of dementia on the clinical phenotype of the disease and predicting its development is essential for the successful management of PD. Copyright © 2005 John Wiley & Sons, Ltd.

KEY WORDS — Parkinson's disease; dementia; clinical phenotype; neuropathology; post-mortem; hallucinations; laterality

## INTRODUCTION

Idiopathic Parkinson disease (PD) is the second most common neurodegenerative disorder affecting 2%–3% of the population over 65 years (Moghal *et al.*, 1994; de Rijk *et al.*, 2000). Although motor symptoms that include rest tremor, rigidity and bradykinesia predominate in the initial stages, many patients will develop impairment of cognitive functions sufficient to fulfill the diagnosis of dementia. A prevalence of

40% was found in a systematic review of 27 studies from multiple points of origin (Cummings, 1988). Dementia is a significant burden to PD patients, as well as to caregivers (Korczyn, 1990), and has been shown to affect the severity of the disease (Papapetropoulos *et al.*, 2004).

In order to identify factors associated with dementia in PD and determine whether its presence may influence disease and survival duration, we performed a post-mortem comparison of demographic and clinical characteristics in patients with and without dementia in a cohort of PD brain donors.

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Contract/grant sponsor: National Parkinson Foundation; contract/grant number: NPF 662891.

## PATIENTS AND METHODS

We included 67 consecutive patients with a clinical and pathological diagnosis of PD, who while alive,