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Motor Symptoms at Onset of Parkinson Disease and Risk for Cognitive Impairment and Depression

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Abstract

Objective—To determine if side and type of initial motor symptoms in Parkinson disease predict risk for later development of cognitive impairment or depressive symptoms.

Methods—We recruited 124 nondemented patients with Parkinson disease to participate in a cohort study of cognitive function and depressive symptoms that used validated neuropsychological tests and a depressive symptom inventory. We first reviewed the patients' charts to determine their initial motor symptom and side of onset, and then classified the patients into 4 groups: right-side onset tremor, right-side onset bradykinesia/rigidity, left-side onset tremor, and left-side onset bradykinesia/rigidity. We excluded patients with bilateral symptom onset. We used analysis of variance on neuropsychological test performance and depressive symptoms to determine if group classification affected risk of cognitive impairment or depressive symptoms. We controlled our analyses for disease duration and motor severity as measured by the Unified Parkinson Disease Rating Scale Part III motor score.

Results—There were no differences in any cognitive measure by side and type of initial motor symptoms. The right-side onset tremor group had the lowest depressive symptom scores, and no patient in any group reported severe depressive symptoms.

Conclusion—Our findings suggest that patterns of nigral cell loss correlating to the initial side and type of motor symptoms in Parkinson disease are not related to the risk of later cognitive impairment. By contrast, patients with right-side onset of tremor appear to have a lower risk of depressive symptoms than patients with other presentations.

Parkinson disease (PD) is the second most common neurodegenerative disease, after Alzheimer disease, and results in both motor and nonmotor dysfunction. Dementia is one of the most disabling nonmotor features. It has been found in an estimated 80% of patients followed longitudinally for 8–20 years,^{1, 2} and it predicts mortality.³ Depression is twice as common in patients with PD as in healthy controls,⁴ affecting 31% of patients⁵; it may predate the onset of motor impairment.⁶ Counseling about prognosis is an important aspect of care for newly diagnosed patients. Given the importance of dementia and depression to

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the ultimate disease burden, it is worthwhile to try to correlate presenting motor features with risk of cognitive impairment and depressed mood.

Most previous research (31 of 36 studies reviewed by Verrejt et al)⁷ on the relationship between cognition and the distribution of motor symptoms in PD has evaluated location of the predominant symptoms at the time of the study. However, the type and distribution of symptoms at disease onset are of greater interest because any relationship established between onset site and risk of cognitive impairment can be used to counsel patients when they are first diagnosed.

Previous studies suggested a higher risk of cognitive impairment with bilateral onset of symptoms,⁸ but no difference in risk between right-side and left-side onset.^{8,9} Studies looking at the type of symptoms at onset found that in patients with tremor as their first symptom, dementia was less common and more delayed than in those with bradykinesia as their presenting feature.¹⁰

Further, cognitive function was found to be better preserved when first symptoms appear on the right side of the body than on the left.¹¹ Katzen et al, for example, studied motor symptom type and laterality at disease onset by evaluating neuropsychological test results in 58 patients and controls.¹² The patients whose presenting feature was an isolated tremor in the right hand had fully intact cognitive function, but patients with left-sided onset of any motor symptom or right-sided onset of bradykinesia and/or rigidity had impaired neuropsychological performance.

Studies evaluating the link between laterality of PD symptoms and depressed mood have also shown conflicting results. Of 3 studies considering predominant involvement at the time of the study, 1 found that right-side-predominant symptoms were associated with a greater number of depressive symptoms,¹³ 1 found a strong association between left-sided symptoms and more severe depression,¹⁴ and 1 showed no difference.¹⁵ In 2 studies that assessed the relationship between depression severity and laterality of symptoms at disease onset, both found that right-sided onset was associated with more severe depressive symptoms.^{16,17}

In this study, we sought to determine whether side and type of motor symptoms at onset were associated with later cognitive function and depressive symptoms in a high-functioning, nondemented cohort of patients with PD.

METHODS

Participant Recruitment

We recruited 124 patients with PD who were being followed by a movement disorders specialist at the Clinical Center for Movement Disorders at the University of Texas Southwestern Medical Center. We invited the patients during their routine clinic visits from February 2010 to April 2011. Inclusion criteria were:

- Age younger than 90 years
- A clinical diagnosis of PD, defined as asymmetric motor features including bradykinesia plus resting tremor and/or rigidity, treated with and responsive to dopamine agonist or levodopa therapy for at least 30 days
- English as the primary language

Exclusion criteria were:

- Any other known or suspected cause of parkinsonism

- Significant features suggesting atypical parkinsonism
- Lifetime *Diagnostic and Statistical Manual of Mental Disorders*, 4th Ed., text revision Axis I psychiatric diagnosis other than major depressive disorder
- Alcohol abuse or dependence within the past 6 months
- Substance abuse or dependence within the past 6 months
- Any unstable or clinically significant condition that could impair the person's ability to comply with study procedures
- History of mental retardation
- Current diagnosis of delirium

Patients provided written informed consent to participate, and the investigation was approved by the local institutional review board.

Research Procedures

Neurologic Examination—We performed a clinical neurologic exam to establish that the participant had at least 2 of the 3 cardinal features of PD, and, by history, had responded to dopaminergic medication. We obtained the Unified Parkinson Disease Rating Scale motor score (Part III) at the baseline clinical visit to determine disease severity.

Psychiatric Assessment—We used 2 separate depression symptom severity measures to quantify mood disturbance: the 16-item Quick Inventory of Depressive Symptomatology-Clinician Rated (QIDS-C₁₆) and the 16-item Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR₁₆). The QIDS-C₁₆ and QIDS-SR₁₆ are well-standardized measures of depressive symptoms that include core, melancholic, and atypical depressive items. They have good validity and reliability, are sensitive to change, and provide both objective and self-reported measures of depression severity.¹⁸

Neurocognitive Assessment—The neurocognitive assessment consisted of commonly used, psychometrically sound instruments that have available normative scores adjusted for demographics. We assessed the following neurocognitive domains with these measures and scores:

- Global cognitive function: Montreal Cognitive Assessment total score¹⁹
- Processing speed/attention: Trail Making Test Part A T-score²⁰
- Verbal memory: Rey Auditory Verbal Learning Test delayed recall T-score, Version AB²¹
- Nonverbal memory: Brief Visuospatial Memory Test-Revised delayed recall T-score, Form 1²²
- Working memory: Wechsler Adult Intelligence Scale, 3rd Ed. Letter-Number Sequencing subtest scaled score²³
- Executive function: Trail Making Test Part B T-score²⁰
- Language: Controlled Oral Word Association Test T-score (F-A-S)²⁴ (we added this test to the battery about 4 months after starting recruitment, so not all participants took it)

The Montreal Cognitive Assessment is a brief measure in which the participant answers questions about global cognitive functions such as simple attention, confrontation naming, and memory. In the Trail Making Test, the participant connects a series of numbers or a

series of numbers and letters in ascending order. The Rey Auditory Verbal Learning Test requires the participant to learn 15 nonrelated words across 5 learning trials, and then to recall those words after being presented with a distractor list. The Brief Visuospatial Memory Test-Revised requires the participant to learn 6 distinct geometric shapes across 3 trials and then to recall them. For the Wechsler Adult Intelligence Scale, 3rd Ed. Letter-Number Sequencing subtest, the participant is read aloud a string of combined numbers and letters, and then must repeat them in sequence, first the numbers and then the letters. On the Controlled Oral Word Association Test, the participant must generate as many words as possible within 1 minute starting with a specified letter (F, A, and S).

Assessment of Symptom Onset and Disease Duration—Because patients who have had PD for years may have difficulty remembering the type and side of their first symptom, we determined type, side, and year of symptom onset by chart review. In the notes from patients' first visit to our center, we combed the history of present illness for their report of the side and type of their first symptom. We then classified the patients into 4 groups: right-side onset tremor (RSO-T), right-side onset bradykinesia/rigidity (RSO-BR), left-side onset tremor (LSO-T), and left-side onset bradykinesia/rigidity (LSO-BR). We excluded 8 patients with mixed or bilateral presentations, and 3 patients whose side and type of onset were not clearly documented. We calculated disease duration as the year of study enrollment minus the year of symptom onset that the patients had reported in the history of present illness.

Statistical Design

We analyzed each of the 4 groups' neuropsychological and depression scores with a set of 1-way analyses of variance (ANOVAs). First, we compared the RSO-T group with the other 3 groups combined. Doing this let us test the hypothesis from Katzen et al¹² that the RSO-T group would have a more favorable neurocognitive profile. Next, we used the same data in a 2-way ANOVA with side of onset, type of onset, and their interaction as factors. This let us examine the more general hypothesis that side and type play a role in PD progression. We also performed analyses of covariance on these data, correcting for disease duration and severity as measured by the Unified Parkinson Disease Rating Scale motor score. We analyzed the demographic data by ANOVA for parametric items and by chi-square analysis for sex and medication use. On measures for which the ANOVA was statistically significant, we performed the Tukey-Kramer procedure to control for type I error in evaluating pairwise comparisons.

RESULTS

We began the study with 124 patients who had provided written informed consent and completed the baseline neurologic exam and neuropsychological test battery. To maintain a non-demented sample, we had to exclude from analysis 10 patients who met criteria for dementia according to a consensus review of their neurocognitive data by 2 board-certified clinical neuropsychologists. Based on chart review, we classified the remaining 114 patients into 1 of the 4 groups by side and type of symptom onset: 47 patients to RSO-T, 12 to RSO-BR, 32 to LSO-T, and 12 to LSO-BR.

Table 1 lists demographic information for the 4 groups, along with the percentage of patients taking each class of dopaminergic medication. The only significant difference in demographic characteristics between groups was that both tremor groups were significantly older than the RSO-BR group. The groups had no significant differences in medication use.

Table 2 shows the analysis of cognitive function and depression by side and type of symptom onset. None of the neurocognitive measures showed any significant differences

between groups, or between the RSO-T group and the other 3 groups combined. Neither of the main effects nor their interaction was significant for any measure when we ran them as 2-way ANOVAS. Results of the analyses of covariance did not add to either the 1-way or 2-way ANOVA findings.

Both clinician-rated (QIDS-C₁₆) and self-reported (QIDS-SR₁₆) depressive symptoms were lower in the RSO-T group (3.0 ± 3.1 and 4.3 ± 3.2 , respectively) than in the average of the 3 other groups (5.2 ± 4.9 and 6.5 ± 4.9), $F(1,101) = 3.58$, $P = 0.008$ and $F(1,101) = 7.54$, $P = 0.007$. A further analysis compared all possible pairs of groups on both measures of depression. The overall F-ratios for the 2 measures were also significant, $F(3,99) = 3.58$, $P = 0.017$ and $F(3,99) = 5.09$, $P = 0.003$. Table 2 shows the group means. The only significant P values can be attributed to the low scores in the RSO-T group vs. the high scores in the LSO-BR group. These were the only Tukey-corrected significant pairwise differences for either depression measure. The results were unchanged when we controlled for disease duration and severity (data not shown). We also conducted a 2-way ANOVA, but our findings did not add to the results already presented.

Figure 1 shows our patients' self-reported depressive symptom scores.

Because antidepressant drugs can confound depressive symptom measures, we evaluated our participants' use of antidepressants. We found that 22 of our patients (21%) were taking antidepressants; of these, 15 (68%) had a QIDS-SR₁₆ total score of 5 or higher, indicating that these patients' depressive symptoms had reached clinical significance.

DISCUSSION

We found that side and type of PD symptom onset were not associated with impairment in any of the neurocognitive domains that we studied. Specifically, in contrast to the findings of Katzen et al.,¹² our RSO-T group did not perform better than the other groups. It is important, first, to show that the largely negative results that we found for our cognitive measures were not simply a function of sample size. In fact, our sample was nearly twice as large as Katzen's. For simplicity, the power analysis consisted of 2 groups of equal size, a power of 0.8, and an alpha level of 0.05. The smallest sample size per group under these conditions would have been 559 obtained with the Controlled Oral Word Association Test-TS, and the largest sample size per group would have been 110,432 obtained with the Trail Making Test Part B T-score. Clearly, our results cannot be attributed to lack of power.

There are several possible explanations for our discordant findings with Katzen et al.¹² First, because we excluded patients with dementia from our analysis, we studied a higher-functioning cohort. Second, Katzen's 4 groups were of roughly equal size, but our larger study had many more patients in the tremor groups than in the bradykinesia/rigidity groups. Third, we gave different neuropsychological tests for the domains that we evaluated, and we did not evaluate the visuospatial domain, an area in which Katzen's RSO-T group outperformed the LSO-T group.

Despite these methodological differences, our study was sufficiently powered to have detected a difference in neurocognitive domains between groups had one existed. Our finding that side and type of symptom onset do not directly influence the later development of cognitive impairment fits well with the Braak hypothesis of PD,²⁵ which maintains that cortical pathways important for cognition become involved by Lewy pathology only comparatively late in the disease course.

In contrast to our negative findings for cognition, those participants with right-side onset tremor had significantly milder depressive symptoms than those in the other groups.

Although this observation is statistically robust, our study population overall had quite mild depressive symptoms. Only 6 participants met research diagnostic criteria for major depressive disorder, and none of them had right-side onset tremor. These findings are unlikely to have been confounded by antidepressant use, given that most of the users exhibited some depressive symptoms on the QIDS-SR₁₆.

Our observation favors the endogenous over the reactive model of depression in PD because patients with dominant hand tremor (which would be expected to be more disabling than nondominant tremor) had the fewest depressive symptoms. That patients who have alpha-synuclein pathology beginning on the left side, with relatively healthy right brain function, are less prone to depression is concordant with previous reports that depression is associated with decreased activity in the right dorsolateral prefrontal cortex,²⁶ but is discordant with studies of depression and lateralized onset of PD symptoms.^{16, 17}

Limitations of our study include the retrospective collection of information about side and symptom of onset, the unequal numbers of patients in the 4 groups, few newly diagnosed patients in the cohort (only 4 participants had disease onset within 2 years of enrolling in the study), the lack of a measure of visuospatial function, and the lack of an analysis of our participants' handedness because too few were left-handed. Although our results cannot be generalized to apply to newly diagnosed patients, in light of our power calculations we think it is quite unlikely that our failure to find a link between side and symptom of onset and cognitive impairment represents a type II error.

Further study will be needed to sort out this complex and conflicting picture of the relationship among motor symptoms at onset, cognition, and depression. Given that we did not find a relationship between side and type of initial symptom and cognitive impairment, we think that all patients with PD should be carefully observed for cognitive impairment as a routine part of clinical care. At our center, we give patients the AD8^{27–29} at each follow-up visit to detect the start of dementia. When found, cognitive impairment prompts further evaluation and treatment. Although we believe that all patients with PD should also be carefully monitored for depression during routine follow-up, our results suggest that those with right-side onset tremor may be at lower risk for this disabling complication.

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Figure 1. Depressive symptom scores by side and motor symptom at onset of Parkinson disease. Error bars represent standard error of the mean.

TABLE 1

Demographic and Drug Information for Study Groups with Parkinson Disease

	Right-Side Onset Tremor (n=47)	Right-Side Onset Bradykinesia/ Rigidity (n=12)	Left-Side Onset Tremor (n=32)	Left-Side Onset Bradykinesia/ Rigidity (n=12)	P value
Age (y) *	66 ± 9.0	56 ± 14	67 ± 10	64 ± 8.4	0.02
Men/women	31/16	8/4	22/10	9/3	0.95
Education (y)	16 ± 1.8	15 ± 1.6	15 ± 1.9	15 ± 1.7	0.82
MoCA	24 ± 3.1	25 ± 2.5	23 ± 3.4	24 ± 3.6	0.23
Disease duration (y)	8.2 ± 4.9	7.2 ± 3.6	8.3 ± 5.3	9.1 ± 7.1	0.84
UPDRS motor score	10 ± 7.0	8.1 ± 5.3	13 ± 11	14 ± 9.6	0.18
Percent of patients taking dopaminergic medication:					
Levodopa	74.5	91.7	90.6	83.3	0.23
Dopamine agonist	68.1	66.7	53.1	75.0	0.45
MAO-B inhibitor	70.2	83.3	68.8	66.7	0.78
Entacapone	25.5	16.7	21.9	41.7	0.50

* Tukey's post-test showed that both groups with tremor onset were significantly older than the group with right-side onset bradykinesia/rigidity.

MoCA indicates Montreal Cognitive Assessment; UPDRS, Unified Parkinson Disease Rating Scale; MAO-B, monoamine oxidase type B.

TABLE 2

Neuropsychological Test and Depressive Symptom Scores

	Right-Side Onset Tremor (n=47)		Right-Side Onset Bradykinesia/Rigidity (n=12)		Left-Side Onset Tremor (n=32)		Left-Side Onset Bradykinesia/Rigidity (n=12)		P value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Rey Auditory Verbal Learning Test Delayed Recall T-score	47.0	11.4	53.3	10.5	44.7	12.8	48.1	11.9	0.911
Brief Visuospatial Memory Test- Revised Delayed Recall T-score	46.8	11.5	52.8	9.3	47.2	12.3	49.1	13.6	0.388
Wechsler Adult Intelligence Scale Letter-Number Sequencing Subtest Scaled Score	8.7	2.7	8.8	1.5	8.4	2.4	9.5	2.5	0.882
Trail Making Test Part A T-score	44.2	11.1	44.3	10.5	41.6	13.2	51.3	9.7	0.987
Trail Making Test Part B T-score	45.1	13.0	47.2	11.0	44.7	15.3	50.2	8.7	0.616
Controlled Oral Word Association Test T-score *	44.8 (n=29)	8.4	46.0 (n=10)	11.6	46.9 (n=19)	11.3	46.9 (n=8)	10.5	0.438
Quick Inventory of Depressive Symptomatology-Clinician Rated	3.0	3.1	5.3	5.6	4.5	3.8	7.1	6.5	0.008
Quick Inventory of Depressive Symptomatology-Self Report	4.3	3.2	5.3	5.9	5.9	4.0	9.3	5.2	0.007

*. Fewer patients took the Controlled Oral Word Association Test than took the other tests.