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Clinical Characteristics of Exacerbations in Parkinson Disease

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Abstract

Background—Episodes of subacute worsening of motor function occur commonly in Parkinson disease (PD), but there has been surprisingly little research about the clinical characteristics of these exacerbations in the outpatient setting.

Methods—Retrospective study of an established cohort of 120 outpatients with PD. Primary outcome measures were the frequency, causes, and outcomes of motor exacerbations. Statistical analysis was performed to compare baseline characteristics of subjects with subsequent exacerbations versus without subsequent exacerbations.

Results—Over an 18-month period, 43 exacerbations occurred, affecting 30 of 120 subjects (25.0%). Infection was the single most frequent underlying cause, accounting for 11 of 43 (25.6%) exacerbations. Other common etiologies were anxiety ($n = 8$), medication errors ($n = 6$), poor adherence ($n = 6$), medication side effects ($n = 3$), and postoperative decline ($n = 3$). Overall, 35 episodes (81.4%) were attributable to reversible or treatable causes. Most subjects recovered fully, but 10 (33.3%) experienced recurrent episodes, 5 (16.7%) suffered permanent decline, and 1 died. At baseline, subjects with exacerbations had a significantly longer median disease duration (7.8 vs. 5.7 y, $P = 0.003$), lower Mini-Mental State Examination scores (27.0 ± 3.3 vs. 28.6 ± 1.6 , $P = 0.02$), higher modified Hoehn and Yahr scores (2.2 ± 0.5 vs. 1.9 ± 0.5 , $P = 0.006$), greater dopaminergic medication use (median, 750.0 vs. 395.0 levodopa equivalents; $P = 0.009$), and a greater prevalence of motor complications (55.2% vs. 29.4%, $P = 0.01$) than subjects without exacerbations.

Conclusions—Exacerbations are common in PD, associated with more advanced disease, and usually attributable to treatable secondary causes such as intercurrent infection. Increased recognition of these underlying causes may help to decrease morbidity, reduce health care costs, and optimize quality of care in PD.

Keywords

quality of care; Parkinson disease; exacerbation; disability; health care utilization

Parkinson disease (PD) is a common neurodegenerative disorder with motor and nonmotor manifestations.^{1–5} As the disease advances, end-of-dose medication wearing off frequently

develops, such that the severity of symptoms fluctuates in relationship to medication timing (“ons” and “offs”).⁶ The overall progression of PD is slow, however, occurring gradually over the course of months to years.

Despite the insidious course of PD, it is not uncommon for patients to experience episodes of subacute worsening of their motor symptoms that may persist for days to weeks, and do not fluctuate with medication dosing. Such “motor exacerbations” are sometimes misinterpreted as an intrinsic worsening of the disease for which patients may request higher doses of PD medications. In reality, however, these exacerbations may be attributable to secondary factors such as intercurrent medical illness, surgery, trauma, medication changes, anxiety, or psychosocial stressors.⁷⁻⁹ Accordingly, optimal management of motor exacerbations requires the diagnosis and treatment of their underlying cause(s), rather than the adjustment of PD medications. Failure to recognize these secondary factors can lead to delayed diagnosis, with associated increases in patient distress, morbidity, and health care utilization.

Despite the clinical significance and societal impact of motor exacerbations in PD, there has been surprisingly little research investigating the causes, characteristics, and risk factors for such episodes. To our knowledge, only 1 other study in the literature has examined this issue in the outpatient setting—and that was a small case series completed in 1961, before dopamine replacement therapy was available.⁹ Thus, there is a paucity of information about the characteristics and precipitants of motor exacerbations in PD outpatients. Our goals were therefore to systematically evaluate the frequency, causes, and consequences of subacute motor deterioration in PD, and to identify clinical predictors of these exacerbations. Such information is of critical importance in reducing morbidity, decreasing health care costs, and optimizing quality of care in PD.

METHODS

A cohort of nondemented outpatients with PD (N = 120) followed at a tertiary academic movement disorders center was recruited as part of a longitudinal study of motor and nonmotor manifestations of PD as previously described.¹⁰⁻¹² Inclusion criteria comprised a diagnosis of PD by United Kingdom Parkinson’s Disease Society Brain Bank criteria,¹³ capacity to provide informed consent, and ability to complete the research questionnaires. Exclusion criteria included a clinical diagnosis of dementia, modified Mini-Mental State Examination (MMSE) score < 25, neurodegenerative disease other than PD, use of a dopamine receptor blocking agent, life expectancy < 12 months, or prior PD neurosurgery. Written, informed consent was obtained from all subjects in accordance with the Weill Cornell Institutional Review Board.

All study subjects were evaluated by a movement disorders neurologist (M.J.N., C.H., or P.P.), who performed a detailed history and neurological examination, including a full Unified Parkinson’s Disease Rating Scale (UPDRS), modified Hoehn and Yahr scale (H&Y), and Schwab and England Activities of Daily Living Scale (S&E). The UPDRS consists of 4 subscales, with higher scores denoting greater impairment: (I) mentation, behavior, and mood (range, 0 to 16); (II) activities of daily living (ADL; range, 0 to 52); (III) motor function (range, 0 to 108); and (IV) complications of therapy (range, 0 to 23). The H&Y quantifies PD disease severity, ranging from stage I (unilateral symptoms only), to stage V (wheelchair-bound or bed-bound). The S&E is a patient-reported assessment of independence in activities of daily living, ranging from 0% (bedridden) to 100% (no functional deficits).

Subjects subsequently completed the following assessments under the supervision of a research assistant: MMSE, Beck Anxiety Inventory, Beck Depression Inventory-2, Obsessive Compulsive Inventory-Revised, and Parkinson's Disease Quality of Life Questionnaire. These data, along with baseline demographic information, past medical history, family history, and quantitative medication usage were recorded in a prospective clinical database (Microsoft Access; Microsoft Corp., Redmond, WA).¹⁰⁻¹² All PD medications were converted to levodopa equivalents using standard formulas, as previously described.^{10,12}

Comprehensive chart reviews, including data from all office visits and telephone encounters, were performed to identify and characterize all motor exacerbations that occurred in the cohort over an 18-month period beginning on December 1, 2008. Motor exacerbations were defined as patient-reported or caregiver-reported episodes of subacute worsening of PD motor function in 1 or more domains (bradykinesia, tremor, rigidity, or PD-related postural instability/gait disturbance) that caused a decline in functional status, developed over a period of < 2 months, did not fluctuate with medication timing, and were not caused by intentional adjustments of PD medications by the treating neurologist. The clinical manifestations, etiology, duration, and outcome were recorded for each of these episodes. Causes of motor exacerbations were determined based on a close temporal relationship between: (1) onset of the causative factor and development of the exacerbation; and/or (2) resolution of the causative factor and amelioration of the exacerbation. The duration of each exacerbation was defined as the amount of time elapsed between the onset and resolution of worsening motor symptoms. The term "motor complications" was defined as the presence of dyskinesias and/or "on/off" motor fluctuations related to PD medication timing. The term psychosis was used to denote hallucinations, illusions, or delusions with loss of insight.

Descriptive statistics (including mean, median, SD, minimum, maximum, frequency, percentage) were calculated for demographic and clinical variables of subjects in the cohort. Baseline characteristics of subjects with motor exacerbation(s) were compared with those of PD subjects without exacerbations (PD controls). Univariate statistical analysis was performed using the 2-sample *t* test (or Mann-Whitney test) for continuous variables and the χ^2 test (or Fisher exact test) for categorical variables. All *P* values were 2-sided with statistical significance evaluated at the 0.05 α level. Analyses were performed in SPSS Version 18.0 (SPSS Inc., Chicago, IL) and SAS Version 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

The study population consisted of 120 subjects (57 female), with a mean age of 69.1 ± 9.7 years (range, 40.8 to 91.0 y), and a median disease duration of 6.1 years (range, 1 to 30.2 y). During the 18-month study period, 43 PD motor exacerbations occurred, affecting 30 of 120 subjects (25.0%) in the cohort (Table 1). These episodes persisted for a median duration of 30 days (range, 1 to 188 d). The most common causes for exacerbations were: (1) medical/surgical problems (16 of 43, 37.2%) such as infection, other intercurrent illness, or postoperative decline; (2) medication problems (15 of 43, 34.9%); and (3) anxiety (8 of 43, 18.6%). Four exacerbations (9.3%) were unexplained, but each of those episodes resolved without intervention.

Intercurrent infection was the single most frequent cause of motor exacerbations, accounting for 11 of 43 (25.6%) of the total episodes and for 11 of 16 (68.8%) of those attributed to medical/surgical problems (Table 1). Medication problems included prescribing/dispensing errors by outside health care professionals and poor patient adherence, each of which caused 6 (40.0%) of the medication-related motor exacerbations. Less frequently, medication-related exacerbations occurred as a side effect of a non-PD medication (3 of 15, 20.0%).

Types of motor deterioration included tremor alone (12 of 43, 27.9%), gait alone (9 of 43, 20.9%), bradykinesia alone (1 of 43, 2.3%), or, most commonly, a decline in more than one of these categories (21 of 43, 48.8%). All episodes that involved a decline in multiple (≥ 2) PD motor symptoms were attributable to medical/surgical problems (12 of 21, 57.1%) or medication problems (9 of 21, 42.9%). In contrast, tremor alone was usually due to anxiety (8 of 12, 66.7%) or a side effect of a non-PD medication (2 of 12, 16.7%). Deterioration of gait alone was the most difficult presentation to diagnose, with 4 of 9 episodes (44.4%) remaining unexplained.

Motor exacerbations were frequently associated with increased health care utilization, including emergency department visits and/or hospitalization in 6 of 43 cases (14.0%). One-third of subjects (10 of 30) with motor exacerbations experienced ≥ 2 episodes. Most subjects returned to baseline after the underlying cause was addressed, but 6 (20.0%) experienced a persistent decline in motor function, including 1 subject with a urinary tract infection who died 3 months later of refractory urosepsis. Episodes characterized by tremor alone had a consistently excellent prognosis; all subjects with this presentation eventually made a full clinical recovery. In contrast, those with multiple motor manifestations recovered fully in only 18 of 21 cases (85.7%).

Baseline demographic and clinical characteristics of study subjects with and without motor exacerbations are shown in Table 2. Subjects with exacerbations had a longer median disease duration than those without (7.8 vs. 5.7 y, respectively; $P = 0.003$) and were more likely to be retired (86.7% vs. 58.9%, respectively; $P = 0.005$). Subjects with and without exacerbations were similar in other baseline demographic features, including age, age of PD onset, race, sex distribution, educational level, and marital status. Subjects were almost always examined in the “on state” (while their PD medications were in effect) or had no history of “on” and “off” motor fluctuations (Table 2).

Compared with PD control subjects, those with exacerbations had higher baseline impairment in ADL on the UPDRS part II (mean, 12.2 ± 6.2 vs. 8.2 ± 4.5 , respectively; $P = 0.003$), a more advanced disease stage on the H&Y (mean, 2.2 ± 0.5 vs. 1.9 ± 0.5 , respectively; $P = 0.006$), greater total use of dopamine replacement therapy (median, 750.0 vs. 395.0 levodopa equivalents, respectively; $P = 0.009$), an increased prevalence of motor complications (55.2% vs. 29.4%, respectively; $P = 0.01$), and a trend towards greater motor impairment on the UPDRS part III (mean, 25.0 ± 11.3 vs. 20.9 ± 10.6 , respectively; $P = 0.07$) (Table 2).

Subjects with motor exacerbations also had greater baseline impairment in several nonmotor domains compared with PD controls, including lower MMSE scores (mean, 27.0 ± 3.3 vs. 28.6 ± 1.6 , respectively; $P = 0.02$), a higher prevalence of symptomatic orthostatic hypotension (42.9% vs. 19.5%, respectively; $P = 0.01$), a greater lifetime prevalence of psychosis (20.0% vs. 5.6%, respectively; $P = 0.03$), and trends towards higher anxiety scores on the Beck Anxiety Inventory and lower quality of life scores on the Parkinson's Disease Quality of Life Questionnaire. In contrast, baseline Beck Depression Inventory-2, Obsessive Compulsive Inventory-Revised scores, and prevalence of sleep disorders were similar in both groups (Table 2).

DISCUSSION

Motor exacerbations are of major importance in the management of outpatients with PD, but to our knowledge this is the first study to systematically evaluate their causes, consequences, and predictors. We show that motor exacerbations in PD are common, frequently protracted, and associated with considerable morbidity and increased health care utilization. They

affected at least 25% of subjects in the cohort, lasted for a median duration of 30 days, and were associated with increased medical visits and hospitalizations. Almost all of these episodes were attributable to identifiable secondary causes. The majority of these underlying causes were reversible or treatable, but recognition of these causes was frequently delayed.

Causes of motor exacerbations fell into 3 categories—medical/surgical problems, medication problems, and anxiety—with the first 2 groups accounting for more than two-thirds of episodes. Overall, intercurrent infection was the single most frequent cause of motor exacerbations, accounting for >25% of cases; of these, respiratory tract and urinary tract infections were most common. Medication-related exacerbations were most often attributable to medication errors (prescribing errors, administration errors, pharmacy dispensing errors) or to poor patient adherence. Anxiety accounted for 19% of motor exacerbations—including some of the most protracted episodes in the cohort—but had an excellent prognosis, with all cases fully reversing after treatment of anxiety and/or alleviation of underlying psychosocial stressors.

Most of the underlying medical/surgical issues were either readily apparent (eg, postoperative decline) or associated with systemic clinical manifestations such as fatigue or urinary frequency. These systemic manifestations were often subtle, however, and difficult to distinguish from baseline nonmotor symptoms of PD. Thus, even when subjects were cognizant of systemic symptoms, these were often overshadowed by the concomitant worsening of PD motor symptoms, and therefore remained unrecognized. Motor exacerbations without concomitant systemic symptoms were sometimes attributable to underlying medical illness (eg, “silent” urinary tract infection), but were more commonly related to medication problems or errors.

Consequences of PD motor exacerbations in the cohort included increased morbidity, mortality, and health care utilization, often aggravated by delayed diagnosis of the underlying cause. The occurrence and potentially life-threatening consequences of delayed diagnosis underscores the need for better education of both patients and physicians about the differential diagnosis of PD motor exacerbations. As our center is aggressive not only in identifying motor exacerbations and treating their underlying causes but also in educating patients about this issue, the incidence of morbidity and mortality observed in this study likely underestimates that in the general PD population.^{7,8}

Clinical predictors of motor exacerbations included several markers of advancing disease: longer disease duration, greater baseline impairment of ADLs, higher H&Y scores, increased use of dopaminergic medications, an increased prevalence of motor complications, and a trend towards greater UPDRS motor impairment. Nonmotor predictors of motor exacerbations included lower MMSE scores (despite the exclusion of demented patients), an increased prevalence of symptomatic orthostatic hypotension, and a higher lifetime prevalence of psychosis, all of which are additional markers of disease severity.¹⁴⁻¹⁸ Dementia and psychosis, in particular, have also been associated with increased mortality in PD.¹⁹ Further investigation is therefore warranted to determine the extent to which various causes of motor exacerbations may contribute to this increased mortality.

Study strengths include the prospective collection of baseline clinical data, including detailed quantitative motor, and nonmotor assessments, as well as the availability of a comparison group of PD control subjects who did not experience motor exacerbations. Limitations include the retrospective collection of data regarding motor exacerbations, which may have resulted in underestimation of the frequency of exacerbations, incomplete characterization of their clinical features, and/or disproportionate representation of more severely affected patients. In addition, the study sample consisted of nondemented subjects

from a single academic practice that may not be representative of the overall PD population. Larger, prospective, multicenter, or populationbased studies are therefore warranted to confirm and expand upon our findings.

In summary, we have shown that motor exacerbations in PD are common, associated with more advanced disease, and usually attributable to treatable secondary causes. Although most subjects eventually make a full recovery, some experience permanent motor decline or death. Improved recognition and aggressive treatment of the underlying causes of these motor exacerbations may help to reduce morbidity, decrease health care costs, and improve quality of care in PD.

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TABLE 1

Causes and Characteristics of PD Motor Exacerbations

Cause	Cases, n (%)	Motor Manifestations, n	Duration (d) Median (Range)	Full Recovery, n (%)
Medical/Surgical Problems	16 (37.2%)		30 (4-105)	13 (81.3%)
Infection				
Respiratory tract (6) [*]		Multiple, 9		
UTI (2)	11	Tremor, 1		
Multiple (1) [†]		Gait, 1		
Other (2) [‡]				
Other medical conditiony [§]	2	Multiple, 1 Gait, 1		
Surgery (postoperative decline)	3	Multiple, 2 Bradykinesia, 1		
Medication problems	15 (34.9%)		15 (1-90)	12 (80.0%)
Medication error				
Prescribing error (3) [¶]	6	Multiple, 5		
Administration error (2)		Tremor, 1		
Pharmacy error (1)				
Poor adherence	6	Multiple, 3 Gait, 3		
Medication side effect [#]	3	Multiple, 1 Tremor, 2		
Anxiety	8 (18.6%)	Tremor, 8	40.5 (1-188)	8 (100.0%)
Idiopathic	4 (9.3%)	Gait, 4	49 (5-90)	4 (100.0%)
Total	43 (100.0%)	Multiple-21 (48.8%) Tremor-12 (27.9%) Gait-9 (20.9%) Bradykinesia-1 (2.3%)	30 (1-188)	36 (83.7%)

^{*} Three cases of upper respiratory tract infection, 2 cases of pneumonia, and 1 case of bronchitis. The case of bronchitis was complicated by a subsequent reduction of PD medications by hospital staff.

[†] UTI, cellulitis, bronchitis, and pneumonia.

[‡] One case of shingles (in the setting of undiagnosed lymphoma), and 1 of dental abscess.

[§] One case of congestive heart failure and 1 case of stroke.

^{||} One partial hip replacement, 1 total knee replacement, and 1 bunionectomy.

[¶] All were due to the erroneous reduction of PD medication doses by outside providers.

[#]Bupropion, amlodipine, and asthma inhalers (1 case attributed to each).

PD indicates Parkinson Disease; UTI, urinary tract infection.

TABLE 2

Baseline Demographic and Clinical Characteristics of Subjects With and Without Subsequent Motor Exacerbations

Subject Characteristics	Subjects With Exacerbations (n = 30)	Subjects Without Exacerbations (n = 90)	P
Demographics			
Age (y) (mean $\pm$ SD)	71.3 ($\pm$ 9.4)	68.3 ($\pm$ 9.7)	0.15
Age of PD onset (y) (mean $\pm$ SD)	61.7 ($\pm$ 11.9)	62.2 ($\pm$ 9.4)	0.81
Disease duration (y) (median, range)	7.8 (1.9-30.2)	5.7 (1.0-21.9)	0.003
Female sex, n (%)	15 (50.0%)	42 (46.7%)	0.75
Lifetime tobacco use (pack-years; median, range)	0.6 (0.0-110.0)	1.5 (0.0-99.0)	0.57
Married, n (%)	20 (66.7%)	59 (65.6%)	0.91
Retired, n (%)	26 (86.7%)	53 (58.9%)	0.005
White, n (%)	26 (86.7%)	79 (87.8%)	0.99
Educational level, college or higher, n (%)	22 (73.3%)	74 (82.2%)	0.30
Family history of PD, n (%)	10 (33.3%)	25 (28.1%)	0.59
Motor and disability scores[*]			
UPDRS ADL score (mean $\pm$ SD)	12.2 ($\pm$ 6.2)	8.2 ($\pm$ 4.5)	0.003
UPDRS motor score (mean $\pm$ SD)	25.0 ($\pm$ 11.3)	20.9 ($\pm$ 10.6)	0.07
Motor complications, n (%) [†]	16 (55.2%)	25 (29.4%)	0.01
Dyskinesias, n (%)	9 (33.3%)	13 (15.7%)	0.05
Wearing off, n (%)	14 (48.3%)	21 (24.4%)	0.02
Modified Hoehn and Yahr (mean $\pm$ SD)	2.2 ($\pm$ 0.5)	1.9 ($\pm$ 0.5)	0.006
Schwab and England disability (mean $\pm$ SD)	86.8 ($\pm$ 8.1)	88.8 ($\pm$ 11.2)	0.37
Nonmotor scores			
MMSE (mean $\pm$ SD)	27.0 ($\pm$ 3.3)	28.6 ($\pm$ 1.6)	0.02
Beck Anxiety Inventory score (mean $\pm$ SD)	11.3 ($\pm$ 7.1)	8.8 ($\pm$ 6.4)	0.09
Clinical diagnosis of anxiety, n (%)	11 (36.7%)	33 (36.7%)	0.99
Beck Depression Inventory-2 score (mean $\pm$ SD)	8.2 ($\pm$ 4.4)	6.8 ($\pm$ 5.6)	0.23
Clinical diagnosis of depression, n (%)	8 (26.7%)	33 (36.7%)	0.32
OCI-R score (median, range)	5.0 (0.0-23.0)	5.0 (0.0-43.0)	0.78
History of psychosis, n (%)	6 (20.0%)	5 (5.6%)	0.03
Symptomatic orthostatic hypotension, n (%)	12 (42.9%)	16 (19.5%)	0.01
Sleep disorder, n (%)	19 (65.5%)	50 (57.5%)	0.45
PDQL (median, range)	138.5 (100.0-175.0)	154.0 (92.0-181.0)	0.06
PD medication use			
On levodopa, n (%)	25 (83.3%)	62 (68.9%)	0.13
On dopamine agonist, n (%)	10 (33.3%)	32 (35.6%)	0.83
On levodopa and/or dopamine agonist, n (%)	26 (86.7%)	74 (82.2%)	0.57
Total PD medication dosage, in levodopa equivalents (median, range)	750.0 (0.0-3937.5)	395.0 (0.0-2715.0)	0.01

* Almost all subjects were either nonfluctuators or examined in the medication “on” state at the time of the baseline examination. This included 28 of 29 subjects (96.6%) with subsequent exacerbations and 85 of 86 subjects (98.8%) without exacerbations ($P = 0.99$). On-off status was not known for 1 subject in the exacerbation group and 4 subjects without exacerbations.

† Motor complications were defined as the presence of dyskinesias and/or wearing off. Data were unavailable for 5 subjects with exacerbations and 1 subject without exacerbations.

ADL indicates activities of daily living; MMSE, Mini-Mental State Examination score; OCI-R, Obsessive-Compulsive Inventory–Revised score; PD, Parkinson Disease; PDQL, PD Quality of Life Questionnaire score; UPDRS, Unified Parkinson’s Disease Rating Scale.