Original Investigation

New Clinical Subtypes of Parkinson Disease and Their Longitudinal Progression

A Prospective Cohort Comparison With Other Phenotypes

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IMPORTANCE There is increasing evidence that Parkinson disease (PD) is heterogeneous in its clinical presentation and prognosis. Defining subtypes of PD is needed to better understand underlying mechanisms, predict disease course, and eventually design more efficient personalized management strategies.

OBJECTIVES To identify clinical subtypes of PD, compare the prognosis and progression rate between PD phenotypes, and compare the ability to predict prognosis in our subtypes and those from previously published clustering solutions.

DESIGN, SETTING, AND PARTICIPANTS Prospective cohort study. The cohorts were from 2 movement disorders clinics in Montreal, Quebec, Canada (patients were enrolled during the period from 2005 to 2013). A total of 113 patients with idiopathic PD were enrolled. A comprehensive spectrum of motor and nonmotor features (motor severity, motor complications, motor subtypes, quantitative motor tests, autonomic and psychiatric manifestations, olfaction, color vision, sleep parameters, and neurocognitive testing) were assessed at baseline. After a mean follow-up time of 4.5 years, 76 patients were reassessed. In addition to reanalysis of baseline variables, a global composite outcome was created by merging standardized scores for motor symptoms, motor signs, cognitive function, and other nonmotor manifestations.

MAIN OUTCOMES AND MEASURES Changes in the quintiles of the global composite outcome and its components were compared between different subtypes.

RESULTS The best cluster solution found was based on orthostatic hypotension, mild cognitive impairment, rapid eye movement sleep behavior disorder (RBD), depression, anxiety, and Unified Parkinson's Disease Rating Scale Part II and Part III scores at baseline. Three subtypes were defined as *mainly motor/slow progression*, *diffuse/malignant*, and *intermediate*. Despite similar age and disease duration, patients with the diffuse/malignant phenotype were more likely to have mild cognitive impairment, orthostatic hypotension, and RBD at baseline, and at prospective follow-up, they showed a more rapid progression in cognition (odds ratio [OR], 8.7 [95% CI, 4.0-18.7]; $P < .001$), other nonmotor symptoms (OR, 10.0 [95% CI, 4.3-23.2]; $P < .001$), motor signs (OR, 4.1 [95% CI, 1.8-9.1]; $P = .001$), motor symptoms (OR, 2.9 [95% CI, 1.3-6.2]; $P < .01$), and the global composite outcome (OR, 8.0 [95% CI, 3.7-17.7]; $P < .001$).

CONCLUSIONS AND RELEVANCE It is recommended to screen patients with PD for mild cognitive impairment, orthostatic hypotension, and RBD even at baseline visits. These nonmotor features identify a diffuse/malignant subgroup of patients with PD for whom the most rapid progression rate could be expected.

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Parkinson disease (PD) varies dramatically in its clinical manifestations and overall prognosis, suggesting it may be divisible into subtypes.[1] Recently, the National Institutes of Health delineated subtype identification as one of the top 3 clinical research priorities in PD.[2] Defining different subcategories is key to understanding the underlying disease mechanisms, predicting disease course, and eventually designing more efficient personalized management strategies.

Cluster analysis uses a hypothesis-free data-driven approach to divide patients according to clinical features. Several previous studies used cluster analysis to define clinical PD subtypes based on motor severity, motor complications, some nonmotor features, and age at onset.[3] The depth of phenotypic information was variable, most studies relied on cross-sectional analysis, and there was little longitudinal assessment to evaluate prognosis of subtypes.[3,4]

In 2005, we began collecting comprehensive data on a PD cohort, which included standardized motor testing, an extensive profile of nonmotor manifestations, neuropsychological assessment, and polysomnography. We continued to follow this cohort prospectively. This provides an opportunity to perform cluster analysis based on deep phenotyping followed by prospective testing of subtypes. Our aims were to (1) identify clinical subtypes of PD with cluster analysis, (2) compare rate of disease progression between different PD subtypes, and (3) compare the prognostic value of our clustering solution with previously published clustering solutions within the same cohort.

Methods

Recruitment of Participants

Participants were enrolled from the movement disorders clinics of the McGill University Health Centre and the Centre Hospitalier de l'Université de Montréal, in Montreal, Canada, during the period from 2005 to 2013. Patients were eligible for recruitment if they had parkinsonism (UK Brain Bank Criteria) and if idiopathic PD was deemed as the most likely cause.[5] Exclusion criteria consisted of baseline dementia, defined using Movement Disorder Society criteria,[6] and diagnosis of other causes of parkinsonism on baseline or follow-up assessments. The study protocol was approved by the ethics committee of the Hôpital du Sacré-Coeur de Montréal and Montreal General Hospital. Written informed consent was obtained from all participants, and the results are presented anonymously.

Baseline Assessments

Assessments were performed during the medication "on" state. Disease duration was defined as the time since first symptom/sign of a cardinal motor parkinsonism manifestation (patient self-report). The full description of these variables has been previously published.[7-9] Variables included the following:

Motor Severity and Subtypes
- Unified Parkinson's Disease Rating Scale (UPDRS) subscales I to IV.[10]
- Hoehn and Yahr staging.
- Motor impairment score:[11] "A" = sum of UPDRS-Part III items on facial expression, tremor, rigidity, and bradykinesia (dopamine-responsive), and "B" = sum of UPDRS-Part III items concerning speech and axial impairment (dopamine nonresponsive).

Motor Complications
- Dyskinesia: sum of UPDRS Part IV:32-34.
- Fluctuation: sum of UPDRS Part IV:36-39.

Motor Subtypes
- Postural-instability-gait-difficulty score.[12]
- Freezing-speech-swallowing score.[12]
- Predominance of each core parkinsonism manifestation.[13]
- Schiess ratio.[14]
- Side of onset.[7]
- Asymmetry Index.[15]
- Axial to limb ratio.[13]
- Presence of falls, freezing, choking, and drooling.

Quantitative Motor Testing
- Purdue Pegboard test.[16]
- Timed Up-and-Go.[17]
- Alternate Tap test.[18]

Cognitive Status
- Mini-Mental State Examination.[19]
- Neuropsychological assessment to document mild cognitive impairment (MCI)[8,20]: MCI was defined at baseline according to the 2012 Movement Disorder Society Task Force guidelines using 5 cognitive domains.[21] This was also classified according to:
- single domain vs multiple domain;
- subtype[22]:
  1. frontal = either impaired attention or executive functions or episodic verbal memory (free recall) or a mix of these 3 domains, or
  2. posterior = impaired visuospatial abilities. Patients were grouped as frontal only, posterior only, or frontal plus posterior.

Autonomic Manifestations
- Unified Multiple System Atrophy Rating Scale.[13,23]
- Orthostatic hypotension (OH)[24]: drops in systolic and in diastolic blood pressure measured manually supine and after 1 minute of standing.

Psychiatric Manifestations
- Depression: Beck Depression Inventory II.[25]
- Anxiety: Beck Anxiety Inventory.[26]
- Apathy: UPDRS Part I-3.
- Hallucinations/Illusions: the hallucinations/illusions section from the Parkinson Psychosis Questionnaire.[27]
- Impulse control disorders: systematic interview on paranoia, compulsive gambling, hypersexuality, excessive spending, and punding.

Sleep Disorders
- Percentage density of tonic and phasic rapid eye movement (REM) muscle activity during overnight polysomnography (PSG).[28]
- REM sleep behavior disorder (RBD): evaluated by overnight PSG, defined with International Classification of Sleep Disorders-II diagnostic criteria[29] and PSG criteria.[28]

- Cardiac autonomic dysfunction: based on electrocardiogram from waking PSG, evaluating time domains (mean *RR* interval and *RR* standard deviation) and frequency domains (high, low, and very low frequency), assessed in a subset of patients, as previously published.[30]
- Insomnia: Insomnia Severity Index.[31]
- Daytime somnolence: Epworth Sleepiness Scale.[32]

Special Senses

- Olfaction: University of Pennsylvania Smell Identification Test (40-item version) (<80% age/sex-adjusted norms = hyposmia).[13]
- Color vision: Farnworth-Munsell 100 Hue test (error score of >125% age-adjusted norms = impaired color discrimination[33]).

Follow-up Assessments

After a mean follow-up period of 4.5 years, the same movement disorder specialist reassessed patients on the same variables as baseline. For neuropsychological assessment, the number of cognitive tests was reduced, and cognitive status was determined using a 3-domain definition.[9]

Overall Disease Severity and Global Composite Outcome

To examine overall severity and prognosis, we classified variables according to the most critical manifestations, summarized into 4 broad categories:

1. Motor symptoms: sum of UPDRS-Part II and UPDRS-Part IV scores.
2. Motor signs: UPDRS-Part III score.
3. Cognition: graded as normal (score = 0), single-domain MCI (score = 1), multiple-domain MCI (score = 2), mild-to-moderate dementia (score = 3), and severe dementia (score = 4).
4. Other nonmotor manifestations: equal weighting of standardized (0-4) scores of depression, anxiety, hallucinations, apathy, somnolence, insomnia, orthostatic dysfunction, urinary dysfunction, and constipation.

A global composite outcome (GCO) was created by merging the standardized scores for these 4 categories.[34] The total score was calculated by summing up the quintile values of different domains (range, 0-16). In assessment of progression, the same cutoff values for baseline quintiles were used to assess overall disease severity (except for cognition, which used the same 5-grade status).

Statistical Analysis

Multiple imputation algorithms using independent regression equations were performed to impute 124 individual missing values (1.3% of the total). We applied a 2-step cluster analysis on different combinations of both categorical and continuous (*z* scores) variables to improve the clustering performance. The most fitting solution (number of clusters and included variables) was selected based on Bayesian information criterion. In the second phase of the cluster analysis, solutions found by other groups, including Post et al,[11] Graham and Sagar,[35] Lewis et al,[36] Gasparoli et al,[37] Reijnders et al,[38] van Rooden et al,[12] and Erro et al,[4] were rerun using their corresponding variables in our cohort (eFigure 1 in the Supplement). The Pearson χ^2 test, 1-way analysis of variance, or the Kruskal-Wallis test with Tukey post hoc analysis were performed for univariate comparisons between clusters whenever appropriate. Ordinal univariate logistic regression was used to compare the quintiles of the main variables between the clusters at baseline, and their odds ratios (ORs) and 95% CIs were calculated. We used repeated-measures analysis of variance and generalized estimation equation modeling to compare the trend of change in numeric and ordinal variables over the follow-up period. A 2-tailed $P < .05$ was considered statistically significant. Further details of all statistical methods are explained in the eAppendix in the Supplement.

Table 1. Baseline Characteristics of Patients

Characteristic	Patients, No. (%) (n = 113)
Sex	
Male	73 (64.6)
Female	40 (35.4)
Age, mean (SD), y	66.7 (8.9)
Disease duration, mean (SD), y	5.7 (4.2)
Initial symptom at disease onset	
Tremor	46 (40.7)
Bradykinesia/rigidity	56 (49.6)
Gait disturbances	11 (9.7)
Hoehn and Yahr stage, mean (SD)	2.5 (0.9)
UPDRS score, mean (SD)	
Part I	2.3 (2.0)
Part II	10.8 (5.6)
Part III	23.8 (10.5)
Part IV	3.2 (3.1)
Total	39.0 (14.1)
Medication	
Levodopa treatment	93 (82.3)
Levodopa dose, mean (SD), mg/d	476.6 (364.1)
Dopamine agonist	39 (34.5)
Other antiparkinsonian medications	48 (42.5)
No treatment	9 (8.0)
Antidepressant	19 (16.8)
Antipsychotic	8 (7.1)

Abbreviation: UPDRS, Unified Parkinson's Disease Rating Scale.

Results

Baseline Characteristics

A total of 113 patients with PD were included. The mean (SD) age was 66.7 (8.9) years, 73 (64.6%) were male patients, and the mean (SD) disease duration was 5.7 (4.2) years. Among the whole study population, RBD and MCI were found in 63 (55.8%) and 59 (52.2%) patients, respectively, at baseline. **Table 1** summarizes the baseline clinical characteristics of the patients.

Cluster Results on Baseline Evaluation

Seven variables were identified as the most informative in generating clusters, including UPDRS Part II, UPDRS Part III, RBD,

MCI, OH (systolic blood pressure drop >10 mm Hg), depression, and anxiety. A model with 3 clusters in which OH, MCI, and RBD contributed the most information was the best solution. Detailed characteristics of these 3 clusters are listed in **Table 2** and the heatmap (eFigure 2 in the Supplement).

The first cluster of 43 patients (cluster I, termed *mainly motor* based on baseline features) was characterized by the absence of OH and a low frequency of RBD, although MCI was seen in 19 patients (44.2%). Depression and anxiety were relatively mild, and motor signs/symptoms moderate. In terms of external variables, tremor was slightly more prominent than in other groups (14% of UPDRS Part III in cluster I vs 12% and 8% of UPDRS Part III in clusters II and III, respectively; $P = .05$). Falls (4 patients [9.3%]) and freezing (7 patients [16.3%]) were uncommon. Autonomic symptoms were generally mild (mean [SD] total Multiple System Atrophy Rating Scale score, 1.7 [1.4]), and hallucinations were uncommon (3 patients [7.0%]). Polysomnograms demonstrated little REM sleep muscle atonia loss (tonic REM% = 27% in cluster I vs 40% and 65% in clusters II and III, respectively).

At the other extreme, the second cluster of 40 patients (cluster II, termed *diffuse* based on baseline features) was characterized by the presence of both OH and MCI in all 40 patients, with a very high frequency of RBD (37 patients [92.5%]). These patients had more severe motor symptoms and signs, and more depression/anxiety. Among external variables, there was greater REM sleep muscle atonia loss among the patients in cluster III than among the patients in clusters I and II ($P < .05$).

On quantitative motor testing, cluster III had a significantly worse performance with regard to the Purdue Pegboard test (with a mean [SD] score of 5.8 [2.2] in cluster III vs 7.8 [3.2] and 7.7 [1.6] in clusters I and II, respectively; $P < .01$), the Alternate Tap test (with a mean [SD] score of 138.4 [25.9] in cluster III vs 154.7 [25.2] and 158.6 [22.9] in clusters I and II, respectively; $P = .004$), and Timed Up-and-Go (with a mean [SD] score of 8.9 [3.0] in cluster III vs 7.3 [1.2] and 7.9 [2.3] in clusters I and II, respectively; $P = .05$).

They had the most severe gait disturbance (with a mean [SD] percentage of UPDRS Part III of 11% [6%] in cluster III vs 8% [7%] and 7% [7%] in clusters I and II, respectively; $P = .02$) and the highest prevalence of falls (with a mean [SD] percentage of patients who fell of 36.8% in cluster III vs 9.3% and 16.7% in clusters I and II, respectively; $P = .01$). They had more severe autonomic symptoms (with a mean [SD] total Multiple System Atrophy Rating Scale score of 3.4 [1.9] in cluster III vs 1.7 [1.4] and 2.1 [1.6] in clusters I and II, respectively; $P < .001$), and evidence of greater cardiac denervation on electrocardiograms (reduced *RR* standard deviation and low-frequency component).

Hallucinations were relatively common (10 of 40 patients [25.0%]), and color discrimination loss was more severe (with a mean [SD] percentage of normative Farnworth-Munsell 100 Hue test scores of 165% [78%] in cluster III vs 127% [72%] and 129% [57%] in clusters I and II, respectively; $P = .03$). Regarding cognition, multiple-domain impairment (66.7% of patients in cluster III vs 0% and 20.9% in clusters I and II, respectively; $P < .001$) and both the frontal-only and frontal-plus-posterior subtypes of MCI were more common. The average daily levodopa dose was slightly higher, but differences were not statistically significant ($P = .22$). Patients were less likely to be receiving dopamine agonists and other antiparkinsonian agents. The patients in cluster II (ie, 30 patients who have the subtype of intermediate PD) all experienced an orthostatic drop in systolic blood pressure of more than 10 mm Hg, but none had MCI (according to the 5-domain criteria) at baseline, and RBD was moderately frequent (18 patients [60.0%]). Depression and anxiety scores were intermediate, but they had the lowest baseline severity of motor signs and symptoms.

To assess whether clusters could be identified early in the disease, we performed a secondary analysis, stratifying according to a disease duration of 3 years or less or of more than 3 years. The percentage of patients identified in each cluster did not significantly differ (35.0% at ≤3 years vs 39.7% at >3 years in cluster I, 30.0% at ≤3 years vs 24.7% at >3 years in cluster II, and 35.0% at ≤3 years vs 35.6% at >3 years in cluster III; $P = .82$ [eFigure 3 in the Supplement]).

Disease Progression in Different Clusters

After a mean duration of 4.5 years, follow-up data were available for 76 patients (**Table 3**). Patients in cluster III had a dramatically worse prognosis, with more rapid progression in all domains, including cognition (OR, 8.7 [95% CI, 4.0-18.7]), other nonmotor symptoms (OR, 10.0 [95% CI, 4.3-23.2]), motor signs (OR, 4.1 [95% CI, 1.8-9.1]), motor symptoms (OR, 2.9 [95% CI, 1.3-6.2]), and the GCO (OR, 8.0 [95% CI, 3.7-17.7]). Of 27 patients in the diffuse cluster (ie, cluster III), 18 (66.7%) had developed dementia, and 20 (74.1%) had progressed to the worst quintile on both motor signs and symptoms. The intermediate cluster (ie, cluster II) had a medium progression rate, slightly higher than that in cluster I. On the GCO, 23 of 27 patients (85.2%) in the diffuse cluster progressed into the worst quintile compared with 7 of 20 patients (35.1%) in the intermediate cluster and 7 of 29 patients (24.1%) in the mainly motor cluster ($P < .001$). Based on this prognostic information, we updated the terminology of cluster III to *diffuse/malignant* and of cluster I to *mainly motor/slow progression*, leaving cluster II terminology unchanged (ie, intermediate).

Comparison With Other Clustering Solutions

At baseline, previously published cluster solutions had variable power in identifying differences in key outcomes (eTable in the Supplement). Most solutions found substantial differences in other nonmotor symptoms between their clusters. Similarly, motor symptoms were generally significantly different among cluster solutions, most notably among the solution of van Rooden et al,[12] with a 2-fold increase in the severe (all) phenotype. However, motor signs, as assessed by the UPDRS Part III, differed variably between clustering solutions. The baseline GCO scores were significantly different between the clusters in all solutions. Further assessment was also performed to check membership overlaps between our clusters and other solutions (eFigure 4 in the Supplement).

Table 2. Group Characteristics at Baseline in the 3 PD Subtypes[a]

Category, Characteristic	Mean (SD) Value			*P* Value[b]
	Cluster I (n = 43)	Cluster II (n = 30)	Cluster III (n = 40)	
Baseline features included in clustering				
Nonmotor				
SBP drop >10 mm Hg, No. (%)	0 (0)	30 (100)	40 (100)	<.001
MCI, No. (%)	19 (44.2)	0 (0)	40 (100)	<.001
RBD, No. (%)	8 (18.6)	18 (60.0)	37 (92.5)	<.001
Beck Depression Inventory II score	9.5 (5.3)	10.1 (6.2)	13.4 (7.1)	.01 (III vs I)
Beck Anxiety Inventory score	10.1 (6.1)	10.7 (7.8)	11.9 (10.5)	.60
Motor				
UPDRS-Part II score	9.7 (4.9)	9.4 (5.3)	13.1 (5.9)	.005 (III vs I, II)
UPDRS-Part III score	22.2 (9.4)	21.0 (8.6)	27.6 (11.9)	.01 (III vs I, II)
External validation (variables not included in clustering)				
General information				
Sex, No. (%)				
M	27 (62.8)	16 (53.3)	30 (75.0)	.16
F	16 (37.2)	14 (46.7)	10 (25.0)	
Age at onset, y	59.9 (8.9)	59.5 (12.7)	63.2 (10.9)	.27
Current age, y	65.2 (7.6)	65.8 (10.5)	68.8 (8.7)	.15
Disease duration, y	5.3 (3.4)	6.3 (5.1)	5.7 (4.2)	.62
Family history of PD, No. (%)	5 (11.9)	8 (29.6)	7 (18.9)	.19
Levodopa therapy, No. (%)	34 (79.1)	25 (83.3)	34 (85.0)	.77
Levodopa dose, mg/d	430.2 (342.4)	435.0 (302.5)	557.6 (419.6)	.22
Dopamine agonists, No. (%)	21 (48.8)	10 (33.3)	8 (20.0)	.02
Other antiparkinsonian drugs, No. (%)	22 (51.2)	17 (58.6)	9 (22.5)	.004
No treatment, No. (%)	3 (7.0)	1 (3.3)	5 (12.5)	.36
Antidepressant, No. (%)	7 (16.3)	6 (20.0)	6 (15.0)	.85
Antipsychotic, No. (%)	2 (4.7)	1 (3.3)	5 (12.5)	.25
Motor severity				
UPDRS-Total score	36.9 (13.3)	34.8 (12.4)	44.6 (14.9)	.04 (III vs II)
Hoehn & Yahr stage	2.4 (0.8)	2.3 (1.0)	2.7 (0.8)	.11
Motor Impairment				
Score A[c]	19.2 (7.8)	19.0 (7.7)	22.7 (9.5)	.10
Score B[d]	3.2 (2.1)	2.8 (2.4)	4.9 (3.1)	.002 (III vs I, II)
Motor complications				
Dyskinesia				
Positive history, No. (%)	11 (25.6)	6 (20.7)	11 (28.9)	.74
UPDRS-Part IV score	0.6 (1.3)	0.3 (0.8)	0.6 (1.5)	.60
Fluctuations				
Positive history, No. (%)	17 (41.5)	10 (35.7)	12 (32.4)	.70
UPDRS-Part IV score	1.0 (1.4)	0.9 (1.4)	0.8 (1.4)	.81
Motor subtypes				
Tremor, % of UPDRS-Part III	14 (15)	12 (13)	8 (9)	.05 (III vs I)
Rigidity, % of UPDRS-Part III	21 (13)	21 (14)	21 (10)	.98
Bradykinesia, % of UPDRS-Part III	46 (15)	47 (15)	48 (11)	.70
Gait, % of UPDRS-Part III	8 (7)	7 (7)	11 (6)	.02 (III vs II)
Schiess tremor predominance ratio	0.83 (1.18)	0.77 (1.06)	0.37 (0.45)	.07
Asymmetry Index, % of total	0.38 (0.39)	0.35 (0.21)	0.19 (0.18)	.01 (III vs I, II)
Onset side, No. (%)				
Unilateral onset	38 (88.4)	25 (83.3)	27 (67.5)	.05
Bilateral onset	5 (11.6)	5 (16.7)	14 (35.0)	
Freezing, No. (%)	7 (16.3)	7 (23.3)	14 (36.8)	.10
Falls, No. (%)	4 (9.3)	5 (16.7)	14 (36.8)	.01
Choking, No. (%)	9 (22.0)	6 (20.7)	14 (37.8)	.19
Drooling, No. (%)	24 (58.5)	13 (44.8)	25 (67.6)	.18
Axial to limb ratio	0.38 (0.23)	0.36 (0.19)	0.47 (0.21)	.07

(continued)

Table 2. Group Characteristics at Baseline in the 3 PD Subtypes[a] (continued)

Category, Characteristic	Mean (SD) Value			*P* Value[b]
	Cluster I (n = 43)	Cluster II (n = 30)	Cluster III (n = 40)	
Quantitative motor testing				
Purdue Pegboard test, No. of pegs	7.8 (3.2)	7.7 (1.6)	5.8 (2.2)	.01 (III vs I, II)
Alternate Tap test, No. of taps	154.7 (25.2)	158.6 (22.9)	138.4 (25.9)	.004 (III vs I, II)
Timed Up-and-Go, s	7.3 (1.2)	7.9 (2.3)	8.9 (3.0)	.06 (III vs I)
Autonomic manifestations				
Unified Multiple System Atrophy Rating scale				
Orthostatic	0.4 (0.5)	0.6 (0.8)	1.0 (0.9)	.001 (III vs I, II)
Urinary	0.6 (0.8)	0.6 (0.7)	1.0 (1.0)	.06
Constipation	0.8 (0.9)	1.0 (0.8)	1.4 (1.0)	.02 (III vs I)
Erectile dysfunction (men only)	1.7 (1.4)	2.1 (1.6)	2.0 (1.4)	.60
Total score	1.7 (1.4)	2.1 (1.6)	3.4 (1.9)	<.001 (III vs I, II)
Orthostatic drop in blood pressure, mm Hg				
Systolic	−0.3 (7.5)	24.3 (12.4)	25.9 (13.1)	<.001 (II vs I, III vs I)
Diastolic	−2.6 (7.1)	7.0 (10.9)	7.0 (9.4)	<.001 (I vs II, III)
Psychiatric manifestations, No. (%)				
Hallucinations	3 (7.3)	4 (13.8)	10 (25.6)	.07
Illusions	4 (9.5)	4 (14.3)	11 (28.2)	.08
Impulse control disorder	7 (16.3)	6 (20.7)	10 (26.3)	.54
Special senses				
Olfaction				
% of normative UPSIT score	52 (21)	58 (20)	51 (19)	.36
Hyposmic (<80% of normal), No. (%)	36 (83.7)	26 (86.7)	38 (95.0)	.26
Color vision				
% of normative FM-100	127 (72)	129 (57)	165 (78)	.03 (III vs I)
Abnormal FM-100 (>125% normal), No. (%)	17 (39.5)	14 (46.7)	25 (62.5)	.11
Cognitive assessments				
MCI status, No. (%)				
None	25 (58.1)	27 (96.4)	2 (5.6)	
Single domain	9 (20.9)	1 (3.6)	10 (27.8)	<.001
Multiple domain	9 (20.9)	0 (0)	24 (66.7)	
MCI subtype, No. (%)				
None	25 (58.1)	27 (96.4)	2 (5.6)	
Frontal only	12 (27.9)	1 (3.6)	25 (69.4)	<.001
Frontal plus posterior	6 (14.0)	0 (0)	9 (25.0)	
MMSE score	28.7 (1.3)	28.8 (1.4)	28.1 (1.5)	.12
Sleep analysis				
REM, %				
Tonic	27.2 (31.1)	40.1 (34.6)	65.8 (31.5)	<.001 (III vs I, II)
Phasic	20.2 (18.0)	24.5 (18.1)	31.2 (21.0)	.05 (III vs I)
Beat-to-beat *RR* variability				
RR interval, ms	979.0 (155.5)	988.3 (125.8)	904.6 (99.7)	.13
RR standard deviation, ms	24.1 (16.2)	35.2 (13.9)	18.3 (8.9)	.003 (III vs II)
HF component, ms^2	166.9 (324.2)	257.5 (334.3)	100.1 (141.5)	.26
LF component, ms^2	187.3 (280.1)	234.6 (247.7)	53.6 (76.1)	.04 (III vs II)
Very LF component, ms^2	85.1 (133.7)	321.9 (493.5)	169.4 (313.8)	.25
LF to HF ratio	1.3 (1.4)	2.1 (4.0)	0.8 (0.8)	.28
Epworth score	9.6 (4.2)	8.7 (5.4)	9.7 (4.9)	.68
Insomnia Severity Index	8.6 (7.3)	12.6 (7.7)	10.6 (7.1)	.07

Abbreviations: FM-100, Farnworth-Munsell 100 Hue test; HF, high-frequency; LF, low-frequency; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; OH, orthostatic hypotension; PD, Parkinson disease; RBD, REM sleep behavior disorder; REM, rapid eye movement; SBP, systolic blood pressure; UPDRS, Unified Parkinson's Disease Rating Scale; UPSIT, University of Pennsylvania Smell Identification Test.

[a] The 3 subtypes were defined as *mainly motor/slow progression* (cluster I), *diffuse/malignant* (cluster II), and *intermediate* (cluster III). All data are presented as mean (SD) values unless otherwise indicated. In some cases, the percentages do not correspond to the total number of patients in each cluster because of missing data.

[b] Determined by use of Tukey post hoc analysis; between-group comparisons were performed using the Pearson χ^2 test, 1-way analysis of variance, or the Kruskal-Wallis test whenever appropriate.

[c] The sum of UPDRS–Part III items concerning facial expression, tremor, rigidity, and bradykinesia that are considered relatively responsive to levodopa.

[d] The sum of UPDRS–Part III items concerning speech and axial impairment (arising from chair, posture, postural stability, and gait) that are considered relatively nonresponsive to levodopa.

We then examined progression over time (eTable in the Supplement and **Figure**). After 4.5 years, the mean GCO score significantly increased in most of the clusters; however, differences in the progression rate were significant only between the clusters found in our study ($P = .01$) and those of Lewis et al[36] ($P = .01$). The diffuse/malignant cluster of our model and the nontremor cluster identified by Lewis et al[36] showed significantly more progression in the mean GCO score after follow-up. The remaining clustering solutions could not identify significant between-clusters differences in the GCO change.

Table 3. Progression of Major Manifestations of Disease in 76 Patients in the 3 Clusters, Presented in Quintiles[a]

	Patients, No. (%)					
	Cluster I (n = 29)		Cluster II (n = 20)		Cluster III (n = 27)	
Characteristics	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
Cognition						
Normal	19 (65.5)	20 (69.0)	16 (80.0)	12 (60.0)	6 (22.2)	4 (14.8)
MCI						
Single domain	6 (20.7)	5 (17.2)	4 (20.0)	3 (15.0)	10 (37.0)	3 (11.1)
Multiple domain	4 (13.8)	2 (6.9)	0 (0.0)	1 (5.0)	11 (40.7)	2 (7.4)
Dementia						
Mild	0 (0.0)	2 (6.9)	0 (0.0)	2 (10.0)	0 (0.0)	10 (37.0)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	2 (10.0)	0 (0.0)	8 (29.6)
OR (95% CI) [*P* value]						
At baseline[b]	1 [Reference]		0.4 (0.1-1.6) [.20]		6.1 (2.1-17.9) [.001]	
For progression[c]	1 [Reference]		0.9 (0.4-2.1) [.85]		8.7 (4.0-18.7) [<.001]	
Other nonmotor						
1st quintile	10 (34.5)	5 (17.2)	4 (20.0)	3 (15.0)	4 (14.8)	0
2nd quintile	8 (27.6)	11 (37.9)	5 (25.0)	5 (25.0)	1 (3.7)	1 (3.7)
3rd quintile	4 (13.8)	5 (17.2)	5 (25.0)	5 (25.0)	5 (18.5)	4 (14.8)
4th quintile	6 (20.7)	4 (13.8)	5 (25.0)	3 (15.0)	4 (14.8)	5 (18.5)
5th quintile	1 (3.4)	4 (13.8)	1 (5.0)	4 (20.0)	13 (48.1)	17 (63.0)
OR (95% CI) [*P* value]						
At baseline[b]	1 [Reference]		1.7 (0.6-4.5) [.30]		8.1 (2.8-23.3) [<.001]	
For progression[c]	1 [Reference]		1.6 (0.7-3.7) [.26]		10.0 (4.3-23.2) [<.001]	
Motor signs						
1st quintile	6 (20.7)	4 (13.8)	4 (20.0)	0 (0.0)	5 (18.5)	1 (3.7)
2nd quintile	7 (24.1)	6 (20.7)	5 (25.0)	4 (20.0)	5 (18.5)	1 (3.7)
3rd quintile	8 (27.6)	4 (13.8)	3 (15.0)	4 (20.0)	3 (11.1)	0 (0.0)
4th quintile	4 (13.8)	10 (34.5)	5 (25.0)	7 (35.0)	6 (22.2)	5 (18.5)
5th quintile	4 (13.8)	5 (17.2)	3 (15.0)	5 (25.0)	8 (29.6)	20 (74.1)
OR (95% CI) [*P* value]						
At baseline[b]	1 [Reference]		1.2 (0.4-3.2) [.75]		1.9 (0.7-4.9) [.19]	
For progression[c]	1 [Reference]		1.4 (0.7-3.0) [.36]		4.1 (1.8-9.1) [.001]	
Motor symptoms						
1st quintile	9 (31.0)	5 (17.2)	6 (30.0)	3 (15.0)	5 (18.5)	1 (3.7)
2nd quintile	4 (13.8)	3 (10.3)	3 (15.0)	1 (5.0)	6 (22.2)	1 (3.7)
3rd quintile	7 (24.1)	2 (6.9)	4 (20.0)	3 (15.0)	2 (7.4)	0 (0.0)
4th quintile	5 (17.2)	10 (34.5)	5 (25.0)	4 (20.0)	7 (25.9)	5 (18.5)
5th quintile	4 (13.8)	9 (31.0)	2 (10.0)	9 (45.0)	7 (25.9)	20 (74.1)
OR (95% CI) [*P* value]						
At baseline[b]	1 [Reference]		1.0 (0.4-2.8) [.97]		1.9 (0.7-4.9) [.18]	
For progression[c]	1 [Reference]		1.2 (0.5-2.6) [.72]		2.9 (1.3-6.2) [<.01]	
Global composite outcome						
1st quintile	9 (31.0)	4 (13.8)	4 (20.0)	1 (5.0)	2 (7.4)	0 (0.0)
2nd quintile	10 (34.5)	4 (13.8)	7 (35.0)	2 (10.0)	3 (11.1)	1 (3.7)
3rd quintile	2 (6.9)	10 (34.5)	4 (20.0)	7 (35.0)	6 (22.2)	1 (3.7)
4th quintile	6 (20.7)	4 (13.8)	3 (15.0)	3 (15.0)	5 (18.5)	2 (7.4)
5th quintile	2 (6.9)	7 (24.1)	2 (10.0)	7 (35.0)	11 (40.7)	23 (85.2)
OR (95% CI) [*P* value]						
At baseline[b]	1 [Reference]		1.4 (0.5-4.0) [.47]		6.6 (2.4-18.4) [<.001]	
For progression[c]	1 [Reference]		1.5 (0.7-3.3) [.27]		8.0 (3.7-17.7) [<.001]	

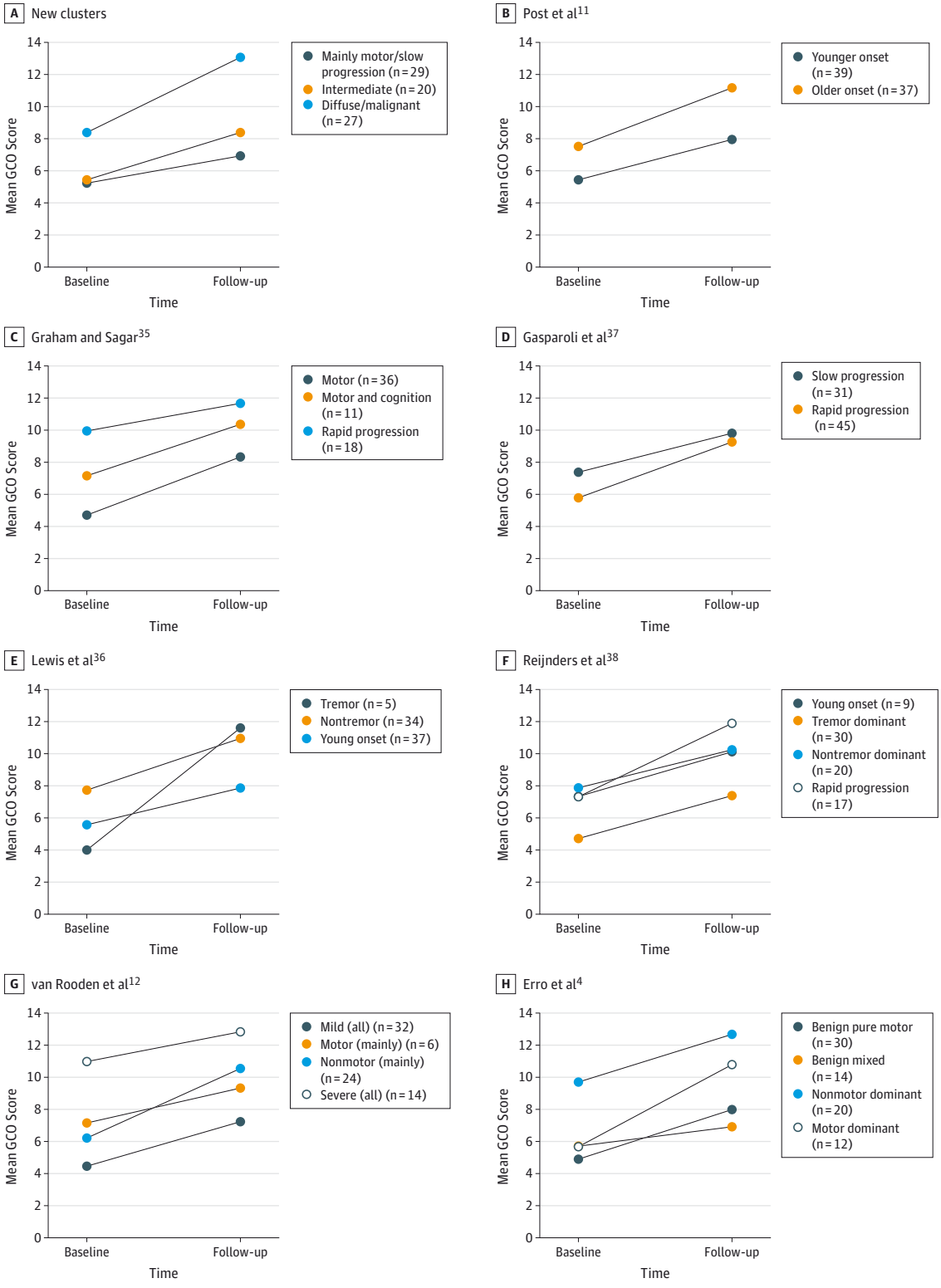
Abbreviations: MCI, mild cognitive impairment; OH, orthostatic hypotension; OR, odds ratio.

[a] The 3 subtypes of Parkinson disease were defined as *mainly motor/slow progression* (cluster I), *diffuse/malignant* (cluster II), and *intermediate* (cluster III).

[b] Ordinal logistic regression model.

[c] Generalized estimation equation analysis using ordinal logistic modeling on repeated response variables.

Figure. Progression of Global Composite Outcome (GCO) Scores in Previously Published Clustering Solutions



Using previously published clustering solutions, we simulated different phenotypes in our single database and compared the progression in the GCO scores between the clusters of each solution in each of the line graphs. The larger slope illustrates a more rapid progression into a higher GCO score (worse prognosis) in that cluster. The smaller slope shows phenotypes with a more stable condition and a better prognosis after follow-up.

Discussion

Our study has found that the most critical determinants of PD subtype and prognosis are nonmotor, especially cognitive status, RBD, and OH. Three subgroups were found: mainly motor/slow progression, diffuse/malignant, and intermediate. Identification of these subtypes at baseline was a strong predictor of prognosis. The mainly motor/slow progression cluster represents patients with PD who have predominantly motor manifestations; MCI and depression might be present but are milder than those present in the third cluster. These patients had the most favorable disease course with the least worsening of the GCO score after 5 years. On the other end of the spectrum, the diffuse/malignant subtype had OH, MCI (mostly multiple domain), and RBD at baseline. These patients also had more severe motor symptoms and more prominent nonpsychiatric disorders and color discrimination disturbances. This subgroup showed the most rapid and malignant progression rate in the GCO and also in all of its motor and nonmotor components. In between these 2 extremes, the intermediate subgroup was defined as having OH, but without MCI. Other nonmotor symptoms were moderate, whereas motor features were broadly similar to the mainly motor/slow progression phenotype. This subgroup experienced moderate progression, with prognosis generally closer to that of cluster I.

Until recently, classic PD subtypes were defined based on age at onset and tremor predominance. A review[3] showed that most studies consistently identify 2 distinct clusters of "old age at onset and rapid disease progression" and "young age at onset and slow disease progression." However, most studies lacked actual longitudinal follow-up to track progression. The most recently published study[4] on naive early diagnosed patients with PD recommended 4 different subtypes based on both motor and nonmotor features and progression rate. However, the follow-up duration was relatively short (2 years), and only a few motor-related characteristics were assessed at follow-up.[4]

Having collected data on a broad list of motor and nonmotor features, we were able to directly compare 7 different clustering solutions and proposed phenotypes on our single database. As expected, baseline differences in motor and nonmotor symptoms could be seen between the clusters from different models. However, our solution was only 1 of 2 that could demonstrate differences in disease progression between subtypes. This is notable when we consider that only baseline characteristics were used to define the clusters in our analysis. Interestingly, our model did not find large baseline differences in motor signs and symptoms, yet it strongly predicted motor progression on follow-up. The likely explanation for the enhanced predictive ability of our model was the inclusion of 3 critical nonmotor variables: MCI, RBD, and OH.

When comparing across subtype solutions, we found that the overlap was modest. However, patients with PD who had a diffuse/malignant phenotype were mostly clustered in the "severe" subtype of the van Rooden et al[12] model and in the "nonmotor-dominant" subtype of the Erro et al[4] model. Of note, the "rapid-progression" subtypes recommended by many models failed to predict actual progression during longitudinal follow-up among our patients.

The worst PD course was observed in patients with a combination of MCI, RBD, and OH. Previous studies[24,39] consistently found that these variables are correlated. Because they are related to dysfunction of very different anatomical systems, their simultaneous impairment may mark a relatively diffuse neurodegenerative process.

However, the relationship is more complex than a simple "pure" vs "diffuse" dichotomy. Although cluster II also had several nonmotor symptoms, progression was mostly of the diffuse/malignant subtype. Even among autonomic disorders, there were different prognostic implications; while cardiac autonomic dysfunction (OH and electrocardiographic abnormality) was an important determinant in subtype definition, sexual dysfunction and urinary disturbances were not significantly different between the phenotypes (note that erectile dysfunction and urinary complaints are common in the general population, which impair power to detect differences directly caused by synucleinopathy). This suggests that different mechanisms of action should be sought for different nonmotor features.

Of note, no significant differences were observed in disease duration between the clusters, and we found a similar proportion of patients in the diffuse/malignant cluster with a disease duration of 3 years or less. This indicates that these phenotypes can be identified early in the disease course and that they are true subgroups rather than different stages of the same pathophysiologic entity.

The mechanism for subtype differences is unclear. Potential explanations include the variability in comorbid pathology (eg, subtle Alzheimer pathology interacting with synuclein in the cortex), the relative vulnerability of substantia nigra (if "mainly motor" patients have more vulnerable nigral neurons, then they may present earlier with pure motor symptoms), or perhaps even the variable propensity for synuclein pathology to spread from region to region.

We found that multiple-domain cognitive impairment is related to rapid progression, whereas the significance of single-domain MCI is less clear. We found a higher prevalence of both frontal-only and frontal-plus-posterior MCI in the diffuse/malignant cluster, and the subtypes did not differ in the relative proportion of MCI type. Mild cognitive impairment also appears to be a more important determinant of prognosis when coexistent with other nonmotor features, particularly OH and RBD. Interestingly, both RBD and cognitive decline have been shown to correlate with thalamic and cortical cholinergic deficits in positron emission tomography studies.[40]

Some limitations should be noted. Although our study was relatively comprehensive, additional variables (ie, neuroimaging markers and other biomarkers) may be able to further refine clusters. Second, this remains a study of a single cohort of patients, and our findings should be externally validated on an independent database. One practical obstacle, however, would be the difficulty of finding another PD cohort in which MCI, OH, and RBD all have been measured using validated methods. Our cohort was originally collected from a study of sleep in PD; patients with subjective sleep prob-

lems may have been more likely to enroll in our study, and these patients may have distinct characteristics (eg, the diffuse/malignant subtype associated with RBD may be overrepresented). This necessitates caution in generalizing our findings to the whole PD population. Measuring orthostatic blood pressure was performed as a bedside maneuver only once; further studies documenting a more detailed picture of OH may be able to further delineate clusters.

On the other hand, our study had some notable strengths. Most critically, we had a comprehensive database on a broad spectrum of motor and nonmotor characteristics. Some of these features, including the most powerful classifiers, were included in cluster analysis for the first time. Another strength is the objective measurements for the main variables; for example, orthostatic blood pressure and olfaction were directly measured rather than relying on questionnaires, overnight PSG was used to diagnose RBD, and neuropsychologic assessment defined MCI (the Mini-Mental State Examination is notably insensitive for detecting MCI in PD).[41] The GCO score allowed for a broad assessment of clinically relevant motor and nonmotor outcomes rather than relying on a potentially biased single outcome. Finally, our study was unique in having a prolonged follow-up, allowing direct estimation of prognosis in clusters defined at baseline.

Conclusions

To summarize, using a data-driven cluster analysis on a broad spectrum of motor and nonmotor features, we found 3 distinct phenotypes of PD consisting of mainly motor/slow progression, intermediate, and diffuse/malignant subtypes. This remains a first step toward a successful evidence-based personal management approach for PD. Further pieces of the puzzle are required to understand the clinicopathophysiologic clustering of PD, to identify differences in underlying disease mechanisms, and to better target neuroprotective strategies.

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Study concept and design: Fereshtehnejad, Gagnon, Postuma.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Fereshtehnejad.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Fereshtehnejad, Anang.
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