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ORIGINAL COMMUNICATION

Benign versus malignant Parkinson disease: the unexpected silver lining of motor complications

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Abstract

Objective We sought to evaluate demographic, clinical, and habits/occupational variables between phenotypic extremes in Parkinson's disease (PD).

Methods Databases from nine movement disorders centers across seven countries were retrospectively searched for subjects meeting criteria for very slowly progressive, benign, PD (bPD) and rapidly progressive, malignant, PD (mPD). bPD was defined as Hoehn and Yahr (H&Y) stage ≤ 3, normal cognitive function, and Schwab and England (S&E) score ≥ 70 after ≥ 20 years of PD (≥ 10 years if older than 60 at PD onset); mPD as H&Y > 3, S&E score < 70, and cognitive impairment within 10 years from PD onset. We performed between-group analysis of demographic, habits/occupational, and clinical features at baseline and follow-up and unsupervised data-driven analysis of the clinical homogeneity of bPD and mPD.

Results At onset, bPD subjects ($n = 210$) were younger, had a single limb affected, lower severity and greater asymmetry of symptoms, and lower prevalence of depression than mPD ($n = 155$). bPD was associated with active smoking and physical activity, mPD with agricultural occupation. At follow-up, mPD showed higher prevalence of depression, hallucinations, dysautonomia, and REM behaviour disorder. Interestingly, the odds of mPD were significantly reduced by the presence of dyskinesia and wearing-off. Data-driven analysis confirmed the independent clustering of bPD and mPD, with age at onset emerging as a critical discriminant between the two groups (< 46-year-old vs. > 68-year-old).

Conclusions Phenotypic PD extremes showed distinct demographic, clinical, and habits/occupational factors. Motor complications may be conceived as markers of therapeutic success given their attenuating effects on the odds of mPD.

Keywords Parkinson · Epidemiology · Benign · Malignant · Aging · Motor complications

Introduction

Despite a consensus on the unifying pathological hallmark, α-synuclein-filled Lewy bodies and Lewy neurites, the clinical, pathological, and biological boundaries of Parkinson disease (PD) remain poorly defined [1]. At a clinical level, most patients with PD will eventually develop motor and non-motor disability milestones and levodopa-resistant symptoms such as dementia, dysphagia, postural instability, and falls [2], with a median survival time from motor onset of 15.8 years [3]. However, PD progression is heterogeneous [4–7]. On the malignant end, the phenotype includes rapidly progressive marked axial symptoms and cognitive

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impairment within 10 years from symptom onset (mPD); on the benign end, mild to moderate, very slowly progressive disability, with no dementia accruing after more than 20 years of disease (bPD) [8, 9]. The factors that lead to this variability remain undetermined.

Prior studies have identified a growing list of proposed multidimensional data-driven PD subtypes [10–12]. However, these subtypes lacked reproducibility in a well-characterized cohort of patients [13] and proved to be inadequate to predict postmortem severity or distribution of pathological findings [14]. Still, certain clinical phenotypes (e.g., young age at onset, tremor-dominant) are known to be associated with a benign PD subtype, while others (e.g., orthostatic hypotension, REM sleep behavior disorder (RBD), non-tremor dominant) correlate with early functional decline and reduced life-expectancy [6, 15, 16]. Last, epidemiological studies have demonstrated a complex interaction between PD and exposure to environmental factors such as pesticides, metals, or other toxins, emphasizing the importance of multiple environmental factors (exposome) in the cascade of pathological processes associated with neurodegenerative disorders [17].

We hypothesized that the phenotypic extremes bPD and mPD are associated with other demographic, clinical, response to therapy, and life habits/occupational variables beyond their slower and more rapid progression, respectively.

Methods

Definitions and eligibility criteria

Through the consensus of nine specialized movement disorders centers from seven countries (United States, Italy, Spain, Argentina, Germany, United Kingdom, and Canada), we designed a retrospective cohort study of idiopathic PD patients meeting UK PD Brain Bank definition [18] and the following criteria for bPD and mPD: (1) bPD was defined by the combination of a Hoehn and Yahr (H&Y) stage ≤ 3 (daily medication-ON condition), preserved cognitive function, defined as a Montreal Cognitive Assessment ≥ 26 or Mini Mental Status Examination Scale ≥ 24 [19, 20], and independence in activities of daily living (ADL) documented by a score ≥ 70 on the Schwab and England scale [21] after ≥ 20 years from symptom onset (or ≥ 10 years in patients with age at PD onset > 60 years-old). (2) mPD was defined as the combination of H&Y stage > 3 (daily medication-ON condition), significant ADL impairment documented by a score < 70 at the Schwab and England [21], and cognitive impairment or dementia (Montreal Cognitive Assessment < 26 and/or Mini Mental Status Examination Scale < 24 [19, 20]) appearing within 10 years from symptom onset. We excluded patients with atypical features suggestive of an alternative form of Parkinsonism, antidopaminergic drug exposure, and dementia and/or hallucinations within 12 months from symptom onset.

Data collection

Between November 2018 and May 2019, patients were screened during their scheduled follow-up visit in each of the centers involved. Then, medical records were reviewed for demographic information on gender, age, age at onset, ethnical background, working activity (Dictionary of Occupational Titles (DOT) codes [22]), and family history of movement disorders, as well as the following clinical data collected during the first neurological evaluation within 5 years from symptom onset (baseline visit), and at the last follow-up available:

Motor symptoms Disease duration, handedness, body side and segment (upper vs. lower limbs) affected at onset, Unified PD Rating Scale (UPDRS) part III [23] score in the ON medication state, H&Y stage in the ON state, Schwab and England score in the ON state. Also, clinical charts and UPDRS parts II, III, and IV scores were reviewed for presence and severity of wearing-off, freezing of gait, dyskinesia, and postural abnormalities including camptocormia and Pisa syndrome.

Non-motor symptoms Depression, hallucinations, autonomic dysfunction, including orthostatic hypotension, drooling, bladder dysfunction, and sexual dysfunction (data retrieved from the reviews of systems available on clinical notes); and RBD, diagnosed according to the "single question screen" [24].

Therapeutic regimen The total levodopa equivalent daily dose (LEDD) was calculated according to a validated conversion table [25] including the daily dose of levodopa (immediate release and extended release formulations), dopamine agonists, monoaminoxidase-B inhibitors (iMAO-B), catechol-O-methyltransferase inhibitors (i-COMT), and amantadine.

We included in the analyses age-related comorbidities (hypertension, myocardial infarction, peripheral arterial disease, diabetes, stroke, vascular encephalopathy, hypercholesterolemia).

The annual progression rate was computed using the following formula: (UPDRS-III at the last follow-up—UPDRS-III at baseline)/(age at last follow-up—age at baseline). In addition, data on smoking and alcohol intake and physical activity, defined as a minimum of 30 min 5 days/week and/or 20 min of vigorous physical activity on at least 3 days/week [26] were obtained for the baseline evaluation. Missing data or discordant information were acquired/clarified with a telephone or in-person clinical interview.

Standardized form of data collection and instruments were used to minimize biases in data recording and interpretation. Patients with incomplete records, or for whom a precise collection of data was not possible were excluded from the study. A third reviewer verified the random data to ensure the validity of different diagnosis or symptom characteristics across different countries/practices.

Data analysis

Comparisons of baseline characteristics between bPD and mPD groups were carried out using Chi square/Fisher's exact test for categorical variables and unpaired *t*-test for quantitative variables. All the significant characteristics were compared according to each age group at onset compared to the rest of age-groups using Fisher's exact test. A multivariable logistic regression analysis was used to determine adjusted associations of cofactors with mPD compared to bPD. The backward stepwise procedure with the probability of removal at 15% was applied for selecting appropriate factors in multivariable analysis. The results of logistic regression analysis were summarized using the odds ratio (OR), 95% confidence interval (CI), and *p*-value. Further, the results of the logistic regression model were validated after imputing missing data using multiple imputation (MI) method. In the imputation analysis, 10 datasets were imputed. Each dataset was analyzed using logistic regression analyses, and results from each model were pooled to obtain model estimates. Separate adjusted analyses were carried out for differentiating mPD from bPD using baseline and follow up variables. The association of covariates with the rate of UPDRS III score progression was determined using linear regression analysis and results were presented with regression coefficients (RC) and *p*-values.

A latent profile analysis (LPA) was used to determine the number of latent groups which can differentiate unknown slow or rapidly progressive PD groups irrespective of the a priori definition of bPD and mPD, based on demographic and clinical characteristics of patients. The number of clustering was determined using Voung–Lo–Mendell–Rubin likelihood ratio test (LRT) and adjusted LRTs. A significant *p*-value of LRTs indicates the best fit for a model with *k*-classes compared to a model with *k*–1 classes. The posterior class probabilities from the developed model were used to classify individuals in different latent classes and compared with the previously obtained PD groups. The LPA results were further validated after multiple imputations for missing data with 10 datasets as described above.

p-Values less than or equal to 5% were considered statistically significant. All analyses were conducted using STATA 15 while the LPA was conducted using MPLUS 7.4.

Sample size considerations and handling of missing data

We used published data for the sample size calculation. Although with methodological differences, Fereshtehnejad et al. [10] demonstrated 5 disease characteristics (with moderate effect size, odds ratio varying from 1.41 to 2.45) associated with rapid PD progression compared to benign/average PD progression with 17% prevalence of benign and rapid PD prevalence. We also expected some disease characteristics moderately associated (OR = 1.4) with mPD compared to bPD. Using this information, we estimated that a total sample size of 340 was sufficient to detect significant factors moderately associated with bPD and mPD with 80% power using a logistic regression analysis with 15% variance explained by other factors at 5% level of significance. Further, we estimated that this sample size was sufficient to test 25 predictors assuming 10–15 subjects per predictor [27]. This sample size was also powered (80%) to determine 2–4 latent classes using 9–15 variables with moderate effect size using a latent profile analysis [28]. Data with > 30% of missing values were excluded from the analyses.

Ethics

The study received IRB/ethics committee approval at all participating centers and was conducted in accordance with the Good Clinical Practice and the International Conference on Harmonization guidelines and any applicable national and local regulations. All General Data Protection Regulation requirements for data collection were met.

Results

Patients

Screening of available databases resulted in the identification of 428 patients meeting criteria for bPD ($n = 264$) or mPD ($n = 164$): 365 (210 bPD and 155 mPD) were included in the analysis and 63 excluded due to incomplete clinical data (Online Resource 1).

Demographics The two groups were comparable in sex, ethnicity, handedness, and family history of neurological disorders (Table 1). Age at onset differed between groups (Fig. 1): 60% bPD vs. 1.9% mPD had an onset under 50 years ($p < 0.001$); 26.2% bPD vs. 12.3% mPD between 51 and 60 years ($p = 0.001$); 11.9% bPD vs. 38.1% mPD between 61 and 70 years ($p < 0.001$); and 1.9% bPD vs. 47.7% mPD after 70 years ($p < 0.001$).

Table 1 Baseline differences between benign and malignant Parkinson's disease

	bPD ($n=210$)	mPD ($n=155$)	p value
Male Sex	128 (61.0%)	90 (58.1%)	.578
Ethnical background			.803
Caucasian	201 (95.7%)	146 (94.2%)	
African American	7 (3.3%)	7 (4.5%)	
East Asians	2 (1.0%)	2 (1.3%)	
Handedness (right)	204 (97.1%)	149 (96.1%)	.591
Family history of neurological disorders	36 (17.1%)	34 (21.9%)	.250
Age at onset (years)	48.7 ± 10.6 *(22–78)*	69.2 ± 7.8 *(47–87)*	< .001
Time from onset to baseline visit (months)	18.7 ± 13.0 *(3–60)*	16.2 ± 13.5 *(2–60)*	.427
Profession			.002
Professional, technical, managerial	61 (44.5%)	21 (36.8%)	
Clerical, sales	56 (40.9%)	15 (26.3%)	
Service	6 (4.4%)	5 (8.8%)	
Agricultural	2 (1.5%)	9 (15.8%)*	
Machine trades	3 (2.2%)	2 (3.5%)	
Benchwork	1 (0.7%)	0 (0.0%)	
Structural work	7 (5.1%)	3 (5.3%)	
Miscellaneous	1 (0.7%)	2 (3.5%)	
Side of symptoms onset			< .001
Asymmetric [right/left]	194 (96.0%) [111/83]	120 (78.9%) [69/51]	
Symmetric	8 (4.0%)	32 (21.1%)	
Area affected at onset			< .001
Single limb [upper/lower]	166 (86.9%) [131/35]	75 (59.1%) [63/12]	
Both arm and leg	25 (13.1%)	52 (40.9%)	
Depression			< .001
No	133 (70.7%)	56 (40.0%)	
Yes	55 (29.3%)	4 (60.0%)	
UPDRS-III score (ON condition)	9.83 ± 5.10 *(3–30)*	22.94 ± 10.70 *(2–71)*	< .001

Results are reported as average ± standard deviation (*range*) or absolute values (percentage), as appropriate. Profession is coded following the dictionary of occupational titles (DOT) codes

bPD benign Parkinson's disease, *mPD* malignant Parkinson's disease, *UPDRS* Unified Parkinson's disease rating scale

*$p<0.05$ at the post-hoc pairwise comparison

Baseline

At disease onset, bPD was associated with higher asymmetry of symptoms ($p<0.001$), greater prevalence of single limb (arm or leg) involvement ($p<0.001$), lower UPDRS-III scores ($p<0.001$), and lower prevalence of depression ($p<0.001$) (Table 1).

There was a significant difference in occupational exposure and habits between the two groups: mPD was associated with higher prevalence of agricultural occupations ($p<0.05$; Table 1), bPD with higher prevalence of active smokers ($p=0.046$) and with regular physical activity ($p<0.001$; Fig. 2). In multivariable analysis, mPD was associated with older age at onset (OR: 1.326; 95%CI: 1.196–1.470; $p<0.001$); involvement of both upper and lower limbs (OR: 11.059; 95%CI: 2.079–58.819; $p=0.005$); lack of physical activity (OR: 8.621; 95%CI: 1.140–66.667; $p=0.037$); depression (OR: 6.140; 95%CI: 1.567–24.061; $p=0.009$); and higher UPDRS-III score (OR: 1.228; 95%CI: 1.125–1.340; $p<0.001$). In validation analyses after imputing missing data, older age at onset, lack of physical activity, depression, and higher UPDRS-III remained significant (Online Resource 1).

Follow-up

By design, at the last follow-up there were significant differences in disease duration: bPD patients had accrued a mean disease duration of 20.8 ± 4.2 years, whereas mPD patients of 9.2 ± 3.2 years ($p<0.001$). Validating the

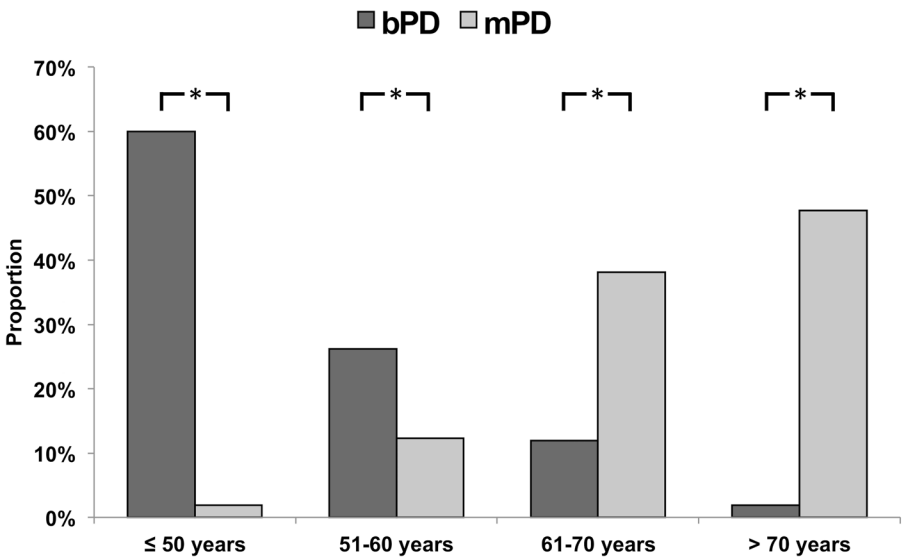

Fig. 1 Distribution of benign and malignant Parkinson's disease according to age at onset. bPD: benign Parkinson disease ($n=210$); mPD: malignant Parkinson disease ($n=155$). *Significant difference between bPD and mPD ($p<0.01$)

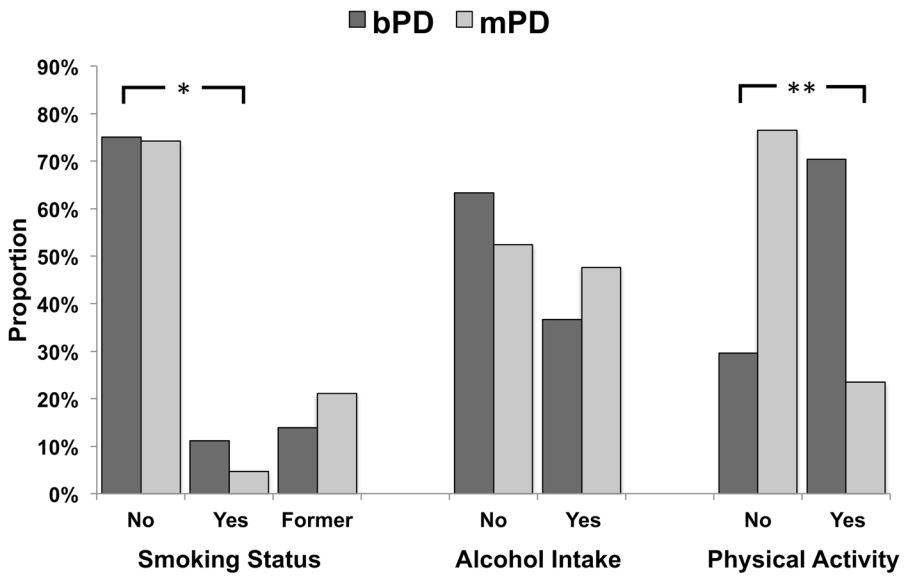

Fig. 2 Smoking status, alcohol intake, and physical activity. Smoking status, use of alcoholic beverages, and physical activity in bPD ($n=210$) and mPD ($n=155$) at baseline. bPD: benign Parkinson disease; mPD: malignant Parkinson disease. Significant difference between groups: *$p<0.05$; **$p<0.001$

separation between groups, the annual rate of UPDRS-III progression differed between the groups, slower in bPD and faster in mPD ($p<0.001$).

bPD was associated with greater prevalence of wearing-off ($p<0.001$) and dyskinesia ($p<0.001$), lower prevalence of freezing of gait ($p<0.001$) and postural abnormalities ($p<0.001$), and higher dosages of dopaminergic medications ($p<0.001$) (Table 2). While none of the mPD patients underwent subthalamic nucleus deep brain stimulation (DBS), 52/210 bPD patients (24.7%) did. Their mean duration of post-surgical follow-up was 7.2 ± 3.8 years. There was a similar prevalence of age-related comorbidities in the two groups (45.2% for bPD vs. 47.1% for mPD; $p=0.794$).

mPD was associated with a higher proportion of depression ($p<0.001$), hallucinations ($p<0.001$), autonomic dysfunction ($p<0.001$), and RBD ($p<0.001$). In multivariable analysis, the odds of mPD increased with freezing of gait (OR: 6.221; 95%CI: 1.621–21.132; $p=0.006$), trunk posture alterations (OR: 5.334; 95%CI: 1.901–15.116; $p=0.001$), depression (OR: 14.412; 95%CI: 3.259–65.321; $p<0.001$), hallucinations (OR: 49.243; 95%CI: 13.312–179.876; $p<0.001$) and autonomic dysfunction (OR: 6.034; 95%CI: 1.897–23.545; $p=0.004$). These odds were reduced by the presence of dyskinesia (OR: 0.175; 95%CI: 0.048–0.603; $p=0.005$) and wearing-off (OR: 0.221; 95%CI: 0.058–0.742; $p=0.015$) both before and after adjusting for UPDRS progression. In the validation analysis, after imputing missing data, all

Table 2 Follow-up differences between benign and malignant Parkinson's disease

	bPD	mPD	*p* value
Motor features			
Wearing-off in between L-dopa doses bPD (*n* = 210) mPD (*n* = 142)	77.6%	54.2%	< .001
Moderate to severe dyskinesia bPD (*n* = 208) mPD (*n* = 149)	19.2%	10.7%	.038
OFF-time > 25% of the waking day bPD (*n* = 200) mPD (*n* = 144)	29.5%	27.1%	.720
Occasional to severe freezing of gait bPD (*n* = 210) mPD (*n* = 151)	22.9%	51.0%	< .001
Moderate to severe trunk posture alterations bPD (*n* = 186) mPD (*n* = 152)	29.0%	81.6%	< .001
UPDRS-III score (ON condition) bPD (*n* = 196) mPD (*n* = 147)	23.6 ± 9.3 *(7–60)*	38.3 ± 11.5 *(16–76)*	< .001
UPDRS-III annual progression rate bPD (*n* = 196) mPD (*n* = 147)	0.8 ± 0.7 *(0.05–2.60)*	3.0 ± 3.5 *(0.14–16.00)*	< .001
Total LEDD (mg) bPD (*n* = 205) mPD (*n* = 148)	1001.8 ± 524.2 *(200–2985)*	769.4 ± 443.9 *(100–2500)*	< .001
Non motor features			
Depression bPD (*n* = 210) mPD (*n* = 151)	59.5%	87.4%	< .001
Hallucinations bPD (*n* = 210) mPD (*n* = 154)	21.0%	81.8%	< .001
Autonomic dysfunction bPD (*n* = 208) mPD (*n* = 153)	52.4%	83.7%	< .001
RBD bPD (*n* = 201) mPD (*n* = 115)	45.8%	60.0%	0.019

Results are reported as mean ± standard deviation (*range*) or absolute values (percentage)

LEDD Levodopa equivalent daily dose, *bPD* benign Parkinson's disease, *mPD* malignant Parkinson's Disease, *RBD* rapid eye movement behavior disorder, *UPDRS* unified Parkinson's disease rating scale

variables remained statistically significant except for wearing-off (Online Resource 2).

Motor fluctuations were associated with younger age at PD onset and higher LEDD in both groups and with an asymmetric PD onset in mPD. No associations were observed between gender, UPDRS-III at onset and at follow-up, or UPDRS-III annual progression rate and motor fluctuations (Table 3).

Clustering based on clinical and demographic characteristics of patients

The unsupervised data-driven analysis confirmed an independent clustering of bPD and mPD according to baseline clinical characteristics, with age at onset emerging as a critical discriminant between the two groups (< 46-year-old in bPD and > 68-year-old in mPD; Online Resource 2). Patients with age at onset between 60 and 70 years showed partial overlap in baseline clinical features, followed by divergent clinical evolutions over follow-up (Fig. 3). bPD was associated with an asymmetric clinical presentation involving the upper or lower limb, UPDRS-III at onset < 10, and physical activity. mPD was associated with a symmetric clinical presentation involving both upper and lower limbs, UPDRS-III at onset > 20, agricultural occupation, and history of depression (Online Resource 3).

Table 3 Clinical and demographic differences: fluctuating vs. non-fluctuating patients

	bPD			mPD		
	fluctuating ($n=182$)	Non-fluctuating ($n=28$)	p value	fluctuating ($n=88$)	Non-fluctuating ($n=54$)	p value
Age at onset (years)	47.6 ± 9.8	56.4 ± 12.9	.001	67.7 ± 7.2	71.4 ± 7.4	.001
Gender (males, %)	60.4	64.3	.698	59.1	57.4	.843
Asymmetric onset (%)	95.5	100.0	.301	75.9	81.1	.466
Single limb (upper or lower) involvement at onset (%)	86.8	87.5	.927	50.7	69.8	.044
UPDRS-III score at onset (ON condition)	9.6 ± 4.7	11.6 ± 7.6	.613	22.8 ± 11.7	22.9 ± 8.7	.641
UPDRS-III score at follow-up (ON condition)	23.4 ± 8.9	24.7 ± 11.9	.742	37.7 ± 11.9	39.6 ± 10.8	.197
UPDRS-III Annual progression rate	0.8 ± 0.7	0.8 ± 0.6	.976	3.0 ± 3.4	2.9 ± 3.2	.794
Total LEDD at follow-up (mg)	1054.5 ± 524.3	693.5 ± 372.5	< .001	859.6 ± 461.2	553.4 ± 244.5	< .001

Results are reported as mean ± standard deviation or percentage

LEDD Levodopa equivalent daily dose, *bPD* benign Parkinson's disease, *mPD* malignant Parkinson's Disease, *UPDRS* unified Parkinson's disease rating scale

Discussion

Several conclusions from this analysis confirmed prior observations regarding the differential features of benign versus malignant ends of the phenotypic spectrum. The benign phenotype of PD was associated with a younger age at onset, asymmetric clinical presentation in one limb, and a greater prevalence of regular physical exercise and active smoking; the malignant phenotype with freezing of gait, postural abnormalities, hallucinations, and autonomic dysfunction, and a greater prevalence of depression and agricultural occupation. The novelty of the analysis is in revealing a "silver lining" to aspects about therapy usually feared: higher dopaminergic dose as well as greater wearing off and dyskinesia were significantly more common in bPD than mPD. In addition, since the presence of motor fluctuations were associated with higher dosage of dopaminergic medications and lower odds of mPD, it is conceivable that a "malignant" course in PD may be contributed to, at least in part, by under-dopaminergic replacement.

The unsupervised data-driven analysis confirmed the validity of the a-priori clustering of bPD and mPD and identified age at onset, along with baseline motor severity, depression, and physical activity as critical distinguishing variables between these divergent clinical phenotypes [14, 29, 30]. bPD patients were more likely to have an onset under the age of 46 years, be engaged in regular physical activity, and present with an asymmetric onset, single limb involvement, and mild severity of motor symptoms. Conversely, mPD patients were more likely to have an onset after the age of 68 years, to have been employed in an agricultural profession, and present with depression, symmetric motor onset, moderate severity of motor symptoms, and involvement of both upper and lower limbs. Interestingly, bPD and mPD patients with age at PD onset in the seventh decade showed overlap in baseline clinical characteristics.

The data highlight the importance of age at onset as a critical factor differentiating the subtypes at the end of the phenotypic PD spectrum, as well as the risk for motor complications. Also, our findings suggest that a combination of modifiable environment and lifestyle factors contribute to their differential expression. Prior epidemiological studies have confirmed the beneficial effects of regular physical exercise [31, 32], although we cannot exclude that those in the mPD group reported lower physical activity at baseline due to their older age at PD onset or other selection biases. On the other end, detrimental effects associated with exposure to pesticide are well documented [33, 34], although ours stand in contrast with a reported association with tremor-dominant PD [35]. This might be partly explained by a recognition bias towards earlier and more accurate diagnosis in patients with tremor-dominant vs. akinetic-rigid PD, particularly in rural contexts with limited access to care.

The possibility exists that age-related compensatory mechanisms might have played a role on the observed results [36–38], but it seems also likely that the two divergent clinical phenotypes of bPD and mPD are manifestations of substantial biological divergence [39]. The bulk of differences between groups likely obey molecular, biological, and neuroanatomical factors. However, the positive association with motor complications, wearing off and dyskinesia, indicates preservation of cortico-striatal dopaminergic connections [40] with changes in synaptic plasticity [41, 42] maybe associated with younger age

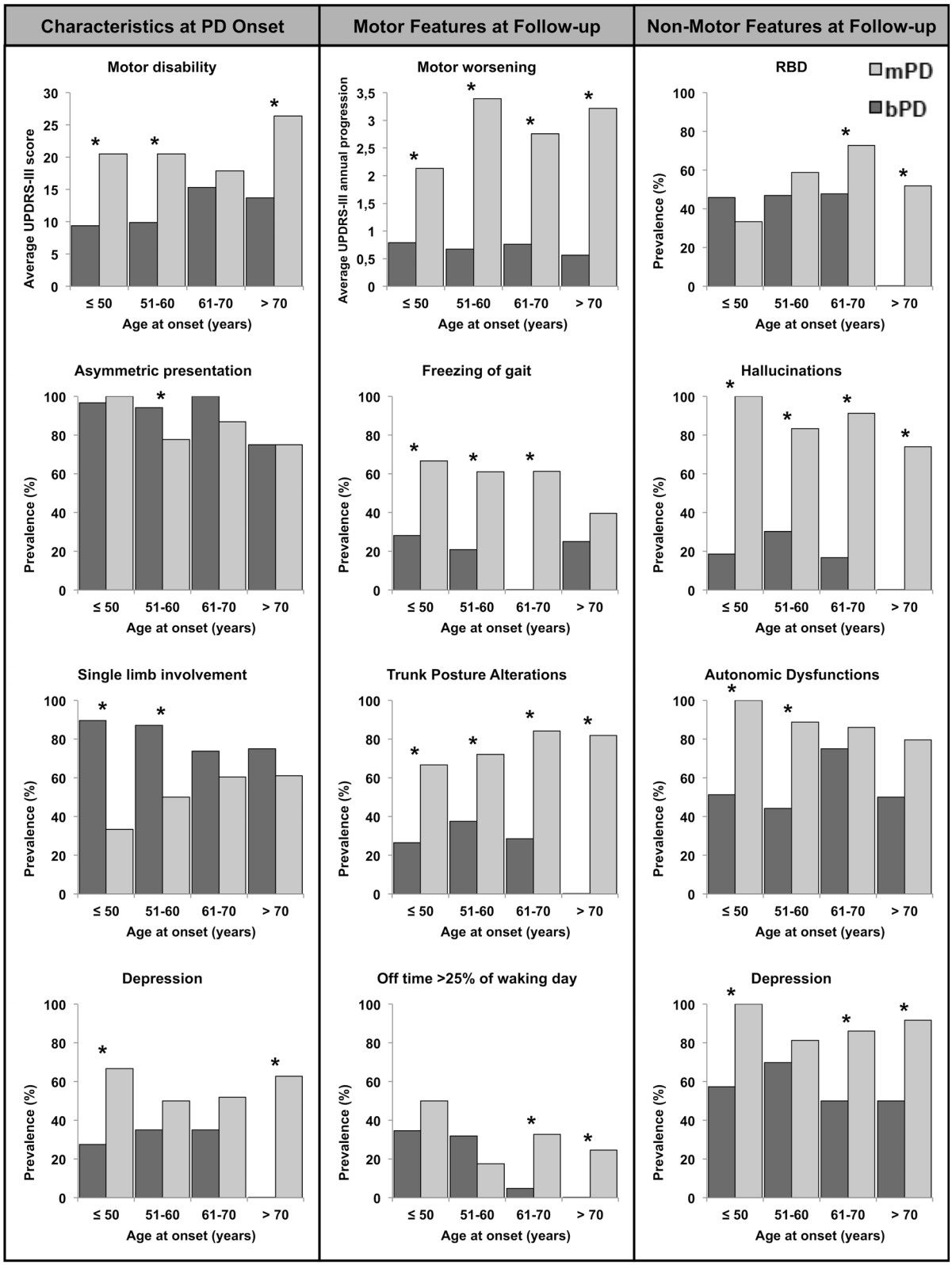

Fig. 3 Distribution of clinical features according to age at onset. *RBD* rapid eye movement behavior disorder, *bPD* benign Parkinson disease, *mPD* malignant Parkinson disease, *UPDRS* Unified Parkinson Disease Rating Scale. *Significant difference between bPD and mPD ($p < 0.05$). The numbers of patients considered in the analyses are reported in Tables 1 and 2

at PD onset [43]. Such effects are partly dependent on a therapeutic dose of levodopa and argue against aiming at low levodopa replacement [44, 45]. This may not be feasible in a subset of mPD patients in whom higher levodopa doses may induce or worsen hallucinations or autonomic dysfunction and response to treatment may be reduced to more widespread degeneration, well beyond the nigrostriatal system, including cholinergic [46], serotoninergic [47] and noradrenergic involvement [48]. Relatedly, our study confirms the strong association between RBD/OH and early cognitive impairment in mPD [49, 50].

These conclusions are tempered by several limitations. First, these retrospectively collected data may have been affected by recall and selection biases, which we aimed to minimize by involving several tertiary centers experienced in clinical research on PD. Second, the unequal lengths of follow-up duration, expected by virtue of the study design, precludes adjusting for disease duration or other age-dependent variables. Third, a minority of patients underwent the baseline evaluation after almost 5 years since the PD onset, although not surprisingly considering the delay frequently associated with the diagnosis of PD, especially in the akinetic-rigid phenotypes. Fourth, the clinical definition of bPD and mPD, although based on consensus from multiple international experts, are arbitrary. We opted for applying criteria based on the H&Y and MMSE/MoCA due to their wide diffusion and well-defined cut-offs. These criteria were further supported by the Schwab and England score, a validated instrument of daily living functional activities. Fifth, the lack of scales for assessing non-motor symptoms, which have only recently become available [51], were not administered at baseline. Sixth, the large majority of patients in both bPD and mPD group were Caucasian. Although the ethnic background was considered as a biological variable in the analyses, the disproportionate representation of Caucasian patients limits the generalizability of our results. Finally, the lack of genetic, neuroimaging, and pathological data partially limit the generalizability of our findings.

These limitations notwithstanding, our data showed that beyond anticipated differences in age at onset, susceptibility to occupational and lifestyle factors, clinical presentation, and functional systems involved, dyskinesia and wearing off emerged as motor complications of high prevalence in bPD exerting attenuating effects on the odds of mPD. These levodopa-dependent motor complications may be considered important markers of therapeutic success. Although these divergent clinical phenotypes may be mostly impacted by age-related mechanisms, the data suggests that an aggressive dopamine replacement strategy may attenuate the "malignant" end of the spectrum. Future research endeavors will need to examine molecular underpinnings, genetic variables, and gene-environment interactions underpinning the variability in phenotypes.

Data availability

A. Merola had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Compliance with ethical standards

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