ORIGINAL ARTICLE

Parkinson Disease: The Relationship Between Non-motor Symptoms and Motor Phenotype

Fang Ba, Mona Obaid, Marguerite Wieler, Richard Camicioli, W.R. Wayne Martin

ABSTRACT: ***Background:*** Parkinson disease (PD) presents with motor and non-motor symptoms (NMS). The NMS often precede the onset of motor symptoms, but may progress throughout the disease course. Tremor dominant, postural instability gait difficulty (PIGD), and indeterminate phenotypes can be distinguished using Unified PD Rating scales (UPDRS-III). We hypothesized that the PIGD phenotype would be more likely to develop NMS, and that the non-dopamine–responsive axial signs would correlate with NMS severity. ***Methods:*** We conducted a retrospective cross-sectional chart review to assess the relationship between NMS and PD motor phenotypes. PD patients were administered the NMS Questionnaire, the UPDRS-III, and the Mini-Mental State Examination score. The relationship between NMS burden and PD subtypes was examined using linear regression models. The prevalence of each NMS among difference PD motor subtypes was analyzed using chi-square test. ***Results:*** PD patients with more advanced disease based on their UPDRS-III had higher NMS Questionnaire scores. The axial component of UPDRS-III correlated with higher NMS. There was no correlation between NMS and tremor scores. There was a significant correlation between PIGD score and higher NMS burden. PIGD group had higher prevalence in most NMS domains when compared with tremor dominant and indeterminate groups independent of disease duration and severity. ***Conclusions:*** NMS profile and severity vary according to motor phenotype. We conclude that in the PD population, patients with a PIGD phenotype who have more axial involvement, associated with advanced disease and poor motor response, have a higher risk for a higher NMS burden.

RÉSUMÉ: **La relation entre les symptômes non moteurs et le phénotype moteur de la maladie de Parkinson.** ***Contexte:*** Il existe des symptômes moteurs et non moteurs dans la maladie de Parkinson (MP). Les symptômes non moteurs (SNM) précèdent souvent le début des symptômes moteurs et ils peuvent progresser pendant toute l'évolution de la maladie. On peut distinguer les phénotypes où dominent le tremblement, l'instabilité posturale et les troubles de la démarche (IPTD) et le phénotype indéterminé au moyen des Unified PD Rating Scales (UPDRS-III). Nous avons émis l'hypothèse que les SNM sont plus susceptibles de survenir chez le phénotype IPTD et que les signes axiaux qui ne répondent pas au traitement par la dopamine sont corrélés à la sévérité des SNM. ***Méthode:*** Nous avons effectué une revue transversale rétrospective de dossiers afin d'examiner la relation entre le phénotype SNM et le phénotype moteur de la MP. Des patients atteints de la MP ont été évalués au moyen du questionnaire SNM, des UPDRS-III et du mini-examen de l'état mental. Nous avons utilisé l'analyse de régression linéaire pour évaluer la relation entre le fardeau des SNM et les sous-types de MP. Nous avons analysé la prévalence de chaque SNM dans différents sous-types moteurs de MP au moyen du test du chi-carré. ***Résultats:*** Les patients atteints de la MP dont la maladie était plus avancée selon les UPDRS-III avaient des scores plus élevés au questionnaire SNM. La composante axiale des UPDRS-III était corrélée à la présence de plus de SNM. Il n'existait pas de corrélation entre les SNM et les scores de tremblement. Il existait une corrélation significative entre le score IPTD et un fardeau plus important à cause des SNM. Le groupe à phénotype IPTD avait une prévalence plus élevée dans la plupart des domaines des SNM par rapport aux groupes où le tremblement dominait ou au groupe à phénotype indéterminé, indépendamment de la durée de la maladie et de sa sévérité. ***Conclusions:*** Le profile SNM et la sévérité varient selon le phénotype moteur. Nous concluons que dans la population de patients atteints de la MP, les patients présentant le phénotype IPTD qui ont plus de problèmes axiaux associés à un stade avancé maladie et à une mauvaise réponse motrice au traitement ont un risque plus élevé de présenter un fardeau plus élevé de SNM.

Keywords: motor subtype, non-motor symptoms, Parkinson's disease

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Parkinson disease (PD) is a neurodegenerative disorder of unknown aetiology that causes motor and non-motor symptoms (NMS) and signs. Motor symptoms of PD have long been the main focus in the diagnosis and the management of patients. However, most PD patients experience other symptoms including depression, anxiety, sleep disorders, bowel and/or bladder problems, other

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autonomic disturbances, and sensory complaints. Cognitive difficulties also occur and are associated with adverse outcomes such as nursing home placement and increased mortality. These symptoms have been termed NMS by Chaudhuri and others.[1] The NMS Questionnaire (NMS Quest) was developed[2] and validated[3] to screen for the presence of NMS.[4,5] The NMS Quest is a 30-item screening questionnaire to be used by the patient/caregiver as a screening tool. It contains ten domains to cover gastrointestinal symptoms, urinary tract symptoms, sexual functions, cardiovascular issues, apathy/attention/memory concerns, hallucinations/delusions, depression/anxiety, sleep problems/fatigue, pain, and miscellaneous complaints such as diplopia and weight loss.[2] In addition, effort has been made to update the Unified PD Rating Scale (UPDRS)[6] to better address non-motor features of PD.[7] Individual rating instruments and scales are available for specific domains. NMS have been underrecognized, undertreated, and are implicated in functional disability experienced by patients with PD.[4,5] The onset of these symptoms may precede the onset of the motor symptoms.[3] This phenomenon is consistent with the Braak staging of the pathology of PD, and possibly related to widespread Lewy body and Lewy neurite deposits, including the olfactory and autonomic systems as well as in other non-dopaminergic nuclei early in the disease process.[8,9]

NMS are very common in PD patients. Barone et al[10] have shown that 98.6% of patients with PD reported NMS in a large collaborative study. The frequency of NMS increased with the disease duration and severity. As the disease advances, NMS can become the most troublesome feature,[11] with a high impact on patients' prognosis and decreased quality of life.[12]

Motor phenotypes in PD can be divided into tremor dominant (TD) and postural instability gait difficulty (PIGD) types.[13] PIGD patients have predominant axial symptoms. Loss of postural reflexes is one of the characteristic features in the PIGD phenotype, along with freezing of gait. PIGD patients are particularly disabled in comparison to those who have predominantly limb manifestations such as tremor.[13,14] Bulbar dysfunction is also more common in the PIGD group,[14] raising the concern that NMS in general might be prominent in the PIGD subtype.

In spite of growing literature on NMS of PD, there are few data on the association between NMS and motor phenotypes of PD, and these usually focused only on specific domains of NMS, such as cognition, mood/anxiety issues, or sleep disorders.[15-18] A recent study by Herman et al[19] demonstrated the relationship between NMS and PD motor subtypes. The study revealed non-demented patients from the PIGD subtype experienced more NMS and poorer quality of life compared with the TD subtype.

In our study, we aimed to explore the relationship between motor subtypes and NMS. We performed a retrospective cross-sectional chart review to clarify the relationship between NMS and PD phenotypes. The two subscores of UPDRS-III, subscore A, which largely correlates with dopamine-responsive features and manifests as nonaxial impairment, and subscore B, which largely correlates to dopamine nonresponsive dysfunction,[20] were analyzed in relation to the PD subtypes and clinical features to determine whether subscore A or B or both subscores were independently associated with the NMS of PD. In addition, specific domains of NMS were examined in relation to PD subtypes and medication classes.

Methods

In this cross-sectional study, charts of all PD patients seen in the University of Alberta Movement Disorders Program in Edmonton between January 2009 and the end of 2012 were reviewed. The Movement Disorders Program is the only specialized PD clinic in northern Alberta. All patients were assessed and diagnosed by movement disorders neurologists. All patients with an established diagnosis of PD were given the NMS Quest form to fill out. The NMS Quest was prospectively completed at each clinic visit. When necessary, patients were instructed by a Movement Disorders Program staff member about how to complete the questionnaire before assessment by a movement disorders neurologist.

The diagnosis of PD was based on UK Brain Bank Criteria.[21] Age of onset was defined as the age of the first motor symptom of PD. Duration of PD was defined as the period between the first motor symptom of PD and the clinical evaluation by a movement disorders neurologist. Cognitive function was assessed with the Mini-Mental State Examination (MMSE) during the same clinic visit. Motor function was evaluated by a movement disorders neurologist, using the UPDRS-III score.[22] The motor phenotype was divided into TD, indeterminate. or PIGD types[13] based on the UPDRS. The TD group was defined by a ratio of mean tremor score/mean PIGD score ≥ 1.5 and the PIGD group was defined by a ratio of ≤ 1, as described previously.[13] If the ratio was between 1 and 1.5, the patient was placed in the indeterminate type group. PIGD score is composed of falling, freezing, walking, gait, and postural stability representing axial symptoms from UPDRS-II and -III. Individual medication and dosage were systematically recorded, and dosage of PD medications was adjusted to levodopa equivalent dose (LED) by using a conversion formula, as previously reported.[23]

Differences in demographic characteristics, disease severity, disease duration, and NMS severity were first analyzed with one-way analysis of variance (ANOVA). To determine whether NMS burden varied according to PD subgroup, we compared the TD, indeterminate, and PIGD groups. The primary outcome measure of interest was the relationship between NMS and PD motor subtype. Groups were compared using one-way ANOVA for continuous variables and chi-square tests for categorical variables. Analyses were carried out in a stepwise manner. Disease duration and disease severity were added as covariates in analyses involving group comparisons predicting NMS in analyses of covariance.

The contribution of disease severity to NMS was examined next. The correlation between NMS severity and UPDRS-III scores was evaluated using regression models. The UPDRS-III is divided into six motor domains (tremor, rigidity, bradykinesia, facial expression, speech, and axial impairment) and two subscores, subscore A (tremor, rigidity, bradykinesia, and facial expression), and subscore B (speech, arising from chair, gait, and posture stability),[20] thus allowing for analysis of the entire cohort. Patients with more axial symptoms tend to be the PIGD type, with a higher subscore B. Analyses were performed to determine whether subscore A or B or both subscores were independently associated with the NMS of PD in the overall group. Subgroup analysis for relationship between the PD motor subtype and the NMS was then further analyzed using linear regression models. Standardized estimated regression coefficients (β) and coefficients of multiple determination (R^2) were calculated, with $p < 0.01$ chosen to be significant. The lower p value was

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determined to correct for increased type 1 error rate because there were multiple comparisons in the linear regression model. The prevalence of each NMS among different PD motor subtypes was analyzed using chi-square test. The difference was then adjusted for disease severity (UPDRS-III) and disease duration in binary logistic regression models. All analyses were performed with GraphPad Prism6 and SPSS, version 21.

Results

A total of 398 charts were reviewed and 274 were analyzed. Charts were excluded due to missing components of the NMS Quest, MMSE, or UPDRS. Demographic data are shown in Table 1. There were more males than females. Young onset PD (age of onset, ≤45 years) composed 11.3% of the sample. Among the cohort, 145 patients were TD type (52.9%) and 104 were PIGD type (38.0%), with the remaining 25 patients (9.1%) falling into the indeterminate group. The average age of disease onset was 59.7 ± 10.9 years, and average age at the time of assessment was 65.4 ± 10.0 years. The majority of the patients were in the early to mid-stage of the disease with an average Hoehn and Yahr (H&Y) stage of 2.1 ± 0.5. For the 124 charts that were excluded, disease duration, average age at disease onset, gender distribution, MMSE, H&Y staging, total UPDRS-III, and the LED daily dose were did not differ significantly from the patients included in the analysis (data not shown).

Comparing the TD, indeterminate, and PIGD groups (Table 2), PIGD patients had longer disease duration ($p = 0.0006$), more advanced disease ($p < 0.0001$ for H&Y staging; $p = 0.0001$ for UPDRS-III total score), higher subscore B ($p < 0.0001$), worse NMS profile ($p = 0.0006$), and a higher dose of PD medications ($p = 0.0007$). In the analyses of covariance, the covariates, disease duration, and severity were significantly related to the NMS profile in PD patients ($F = 4.56$, $p < 0.001$ and $F = 4.90$, $p < 0.001$, respectively). The total NMS Quest score was significantly higher in the PIGD group when compared with the TD and indeterminate groups after controlling for disease duration and severity (UPDRS-III).

To determine whether the NMS in PD were affected by age, disease duration, severity of PD, cognitive status, or the impact of levodopa treatment, univariate analyses (Table 3) were performed in the overall group. The univariate analyses showed that age, gender, and MMSE did not correlate with NMS. In contrast, disease duration and disease severity (UPDRS-III) were significant predictors of NMS ($p = 0.009$ and $p = 0.0001$, respectively). LED dose ($p = 0.009$, $R^2 = 0.07$) also correlated with a higher NMS.

UPDRS-III total score and H&Y staging correlated with a higher NMS Quest score ($p = 0.0001$, and $p < 0.0001$, respectively). Subscores A and B also correlated with a higher NMS burden (Table 3; $p = 0.003$ and $p < 0.0001$, respectively).

Table 1: Demographic and clinical characteristics of patients

Variable	No. (%) of patients (N = 274)
Gender	
Male	188 (68.4)
Female	86 (31.6)
Average age of onset (years)	59.7 ± 10.9
Average age at examination (years)	65.4 ± 10.0
Age at onset (years)	
>45 (late onset of PD, LOPD)	243 (88.7%)
≤45 (young onset of PD, YOPD)	31 (11.3%)
Duration of PD (years)	5.7 ± 4.9
H&Y stage	
I	40 (14.6)
II	210 (76.6)
III	23 (8.4)
IV	1 (<0.1)
PD medication treatment	
Levodopa	207 (75.3)
Dopaminergic agonists	72 (26.2)
Selegiline or rasagiline	23 (8.4)
Amantadine hydrochloride	22 (8.0)
Anti-cholinergics	11 (4.0)
Levodopa equivalent dosage (mg/day)	768.3 ± 649.4
	Mean ± SD
H&Y staging	2.1 ± 0.5
UPDRS motor score (total range, 0-108)	17.2 ± 9.4
Subscore A* (total range, 0-88)	14.2 ± 8.0
Subscore B† (total range, 0-20)	2.8 ± 2.2

H&Y = Hoehn and Yahr; LOPD = late onset PD; PD = Parkinson disease; UPDRS = Unified Parkinson's Disease Rating Scale; YOPD = young onset PD.
*Subscore A: tremor, rigidity, bradykinesia, and facial expression.
†Subscore B: speech and axial impairment.

Table 2: Demographic characteristics of TD, indeterminate, and PIGD groups

		Mean ± SD		
Variable	TD 145 (52.9%)	Indeterminate 25 (9.1%)	PIGD 104 (38.0%)	p value
Age at onset (years)	59.1 ± 10.9	61.9 ± 10.6	60.0 ± 11.0	0.08
Gender (male %)	65.3	76.0	70.5	0.07
PD duration (years)	4.9 ± 4.0	6.0 ± 3.7	7.0 ± 5.9	0.009*
H&Y staging	1.9 ± 0.4	2.2 ± 0.4	2.3 ± 0.4	<0.0001*
UPDRS III	15.0 ± 8.1	20.06 ± 9.8	19.3 ± 9.8	0.0001*
Subscore A	13.1 ± 7.4	16.9 ± 7.6	15.2 ± 8.3	0.024
Subscore B	1.8 ± 1.3	3.4 ± 2.2	4.1 ± 2.4	<0.0001*
LED (mg/day)	644.8 ± 601.9	665.8 ± 726.3	952.5 ± 662.7	0.0007*
NMS	6.5 ± 4.7	6.7 ± 3.7	8.9 ± 5.1	0.0006*

*Statistically significant.
H&Y = Hoehn and Yahr; LED = levodopa equivalent dose,
NMS = non-motor symptoms; PIGD = postural instability gait difficulty,
PD = Parkinson disease, SD = standard deviation, TD = tremor dominant,
UPDRS = Unified Parkinson's Disease Rating Scale.
Subscore A: tremor, rigidity, bradykinesia, and facial expression.
Subscore B: speech and axial impairment.

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Table 3: Correlation between multiple determinants with NMS and motor measures of pd using univariate linear regression models in the overall PD group

	NMS	
	R^2	p value
Gender	<0.01	0.18
Age at onset	<0.01	>0.5
PD duration	0.05	<0.01*
UPDRS III	0.05	0.0005*
Subscore A	0.04	0.003*
Subscore B	0.10	<0.0001*
MMSE	<0.01	>0.5
LED	0.03	0.009*

*Statistically significant.
LED = levodopa equivalent dose; MMSE = Mini-Mental State Examination; NMS = non-motor symptoms, PD = Parkinson's disease, UPDRS = Unified Parkinson's Disease Rating Scale.
Subscore A: tremor, rigidity, bradykinesia, and facial expression.
Subscore B: speech and axial impairment.

In multiple regression analyses, only disease duration, subscores A and B, and LED were included; age at disease onset, gender, and MMSE were not included because univariate analysis showed no correlations. Two models were used. Model 1 analyzed the correlations between the subscore A, subscore B, and LED with NMS severity; this model was significant with an R^2 of 0.142. Subscore A did not show any correlation, but subscore B ($p < 0.001$) and LED ($p < 0.001$) were both significantly associated with higher NMS burden. Model 2 examined the subscore A, subscore B, and duration of disease in relation to NMS severity. The model was significant ($R^2 = 0.152$). Duration of disease and subscore A did not correlate with NMS. Subscore B was associated with a higher NMS score in the multiple regression analysis ($p = 0.001$).

Further subgroup analyses showed that in the TD and indeterminate groups, neither the total tremor score nor the ratio of mean tremor score/mean PIGD score correlated with NMS. In contrast, in the PIDG type, the total PIGD score was a significant predictor of worse NMS profile ($p < 0.0001$, $R^2 = 0.064$), and the ratio of mean tremor score/mean PIGD score also correlated with a higher NMS quest score ($p = 0.01$, $R^2 = 0.055$). In addition, in the TD and indeterminate groups, no significant correlation was observed between NMS Quest score and UPDRS-III total score, subscore A, or subscore B. In the PIGD group, there was significant correlation between NMS Quest score and UPDRS-III total score ($p = 0.0022$), subscore A ($p = 0.0034$), and subscore B ($p = 0.0012$) in linear regression models.

Concerning the prevalence of NMS in each motor subtype group, the percentage of patients presenting with each symptom of NMS is summarized in Table 4. The PIGD group had higher proportions of patients endorsing all NMS on the NMS-Quest than TD group, except for nausea, fecal incontinence, weight loss, and leg swelling after adjustment for disease severity and duration (Table 4).

PD medication use is summarized in Table 5 for each PD subtype. The relationships between NMS and different PD medications were analyzed because some PD medications can produce and exacerbate many of the NMS. Levodopa (including the CR formulation and Stalevo, with dose conversion to LED) correlated with total NMS burden ($p = 0.003$) and with gastrointestinal symptoms ($p = 0.001$), urinary symptoms ($p < 0.001$), sensory complaints ($p = 0.004$), neuropsychiatric issues ($p = 0.01$), sexual dysfunction ($p = 0.005$), orthostatic hypotension ($p = 0.004$), and sleep difficulties ($p = 0.001$). Dopamine agonists (adjusted and converted to LED) also correlated to the severity of NMS ($p = 0.007$). Among all domains of symptoms, dopamine agonist usage correlated with neuropsychiatric symptoms ($p = 0.003$), orthostatic symptoms ($p = 0.006$), sexual dysfunction ($p = 0.01$), and pain ($p = 0.005$). The use of amantadine and anticholinergic agents, however, did not show any correlations to NMS severity in any group (data not shown), likely because of the very low percentage of patients on these agents.

Discussion

NMS are common in PD. These symptoms often contribute to disability and impact negatively on quality of life even in early-stage disease.[24] They are frequently underrecognized and undertreated. These symptoms are diverse and may reflect dysfunction in non-dopaminergic systems, though dopaminergic transmission dysfunction may play a role. In spite of growing literature focusing on NMS of PD in the past few decades, there are limited data on the association between NMS and motor phenotypes of PD. Identifying patient groups at risk might be of clinical value because treating such patients may have a positive impact on quality of life.

In the current study, we showed that PIGD patients had longer disease duration, more advanced disease, and a poorer NMS profile. After adjusting for disease duration and severity (UPDRS-III), this group of patients still had a significantly higher NMS Quest score, and the difference of NMS prevalence was evident in 26/30 domains. The only domains not differentially affected included nausea, fecal incontinence, weight loss, and leg swelling. In the overall group, disease duration, UPDRS-III score and total LED were significant predictors of NMS. These observations are in agreement with previous reports that long disease duration and more severe disease, as reflected by H&Y stage, are associated with a higher number of NMS.[25]

Subscore A correlated with NMS in the whole cohort (Table 3); however, it was not significant in the two multiple regression models we examined. Subscore B, on the other hand, strongly correlated with a higher NMS burden and remained significant in the multiple regression model. These results suggest that in the PD population, those with more axial symptoms as demonstrated by a higher subscore B have a higher NMS burden.

We showed that NMS severity varies according to motor phenotype. Subscore B correlated with higher NMS burden in overall group and predicted worse NMS profile in the PIGD group, but not in the TD or indeterminate group. There was a significant correlation between PIGD score and higher NMS burden in the PIGD group, but no correlation between tremor score and NMS in the TD group. It is well-documented that the TD group has slower disease progression and a more favourable prognosis.[26,27] For PIGD type, patients often present with more axial symptoms, or develop them over time, represented by a higher subscore B. This group usually responds poorly to

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Table 4: Chi-square analysis of patient proportions endorsing each of the NMS symptoms in different PD motor subtypes

Symptom of NMS	Whole group N = 274 (%)	TD N = 145 (%)	Indeterminate N = 25 (%)	PIGD N = 104 (%)	p value	p value (adjusted for disease severity)	p value (adjusted for disease duration)
Drooling	20.7	14.7	14.3	23.6	<0.001*	0.001*	<0.001*
Anosmia	11.3	13.8	5.8	23.6	<0.001*	<0.001*	<0.001*
Dysphagia	20.7	14.7	19.0	25.0	0.007*	0.01*	0.009*
Nausea	8.5	8.6	9.6	13.9	0.01*	0.04	0.03
Constipation	29.1	22.4	23.8	37.2	0.008*	0.01*	0.01*
Fecal incontinence	4.2	3.4	4.7	5.1	0.01*	0.05	0.04
Poor bowel empty	16.9	11.2	19.0	18.0	0.007*	0.01*	0.009*
Urinary urgency	44.6	31.9	23.8	51.3	<0.001*	<0.001*	<0.001
Nocturia	56.8	39.7	42.9	62.8	<0.001*	0.003*	0.001*
Pain	32.4	25.0	23.8	41.0	<0.001*	0.004*	0.001*
Weight loss	9.4	10.0	9.5	9.0	>0.05	>0.05	>0.05
Memory decline	36.6	28.4	23.8	47.4	<0.001*	0.005*	0.002*
Apathy	16.4	16.4	9.5	28.2	<0.001*	<0.001*	<0.001*
Hallucination	8.9	7.8	9.5	12.8	<0.001*	0.004*	0.003*
Poor concentration	25.9	20.7	23.8	33.3	<0.001*	<0.001*	<0.001*
Depression	31.9	22.4	21.4	37.2	<0.001*	0.001*	<0.001*
Anxiety	27.7	17.2	23.8	28.2	<0.001*	0.003*	0.002*
Hyposexuality	23.1	17.2	28.6	26.9	<0.001*	0.01*	0.008*
Sexual dysfunction	33.8	26.7	28.6	42.3	<0.001*	<0.001*	<0.001*
OH	31.0	21.6	14.3	37.2	<0.001*	<0.001*	<0.001*
Fall because of OH	12.1	10.3	9.5	14.1	0.008*	0.03	0.01*
Hypersomnolence	13.2	8.6	9.5	16.7	<0.001*	0.003*	0.001*
Insomnia	44.1	31.0	47.6	50.0	<0.001*	<0.001*	<0.001*
Vivid dreams	23.0	14.7	14.3	23.1	<0.001*	<0.001*	<0.001*
REMBD	26.2	19.0	19.0	30.8	<0.001*	0.001*	<0.001*
RLS	30.8	22.4	23.8	35.9	<0.001*	<0.001*	<0.001*
Leg swelling	13.5	9.5	9.5	15.4	0.03	>0.05	>0.05
Sweating	18.0	14.7	14.3	24.4	<0.001*	0.001*	<0.001*
Diplopia	11.7	11.2	4.7	19.2	<0.001*	<0.001*	<0.001*
Delusion	4.4	4.3	0	9.0	0.01*	>0.05	0.03

* Statistically significant.

NMS = non-motor symptoms; OH = orthostatic hypotension; PD = Parkinson disease; PIGD = posture instability gait difficulty type; REMBD = rapid eye movement behavior disorders; RLS = restless leg symptoms; TD = tremor dominant type.

dopaminergic treatment.[28] Between the two major motor subtypes, PIGD patients usually develop more disability than those of TD subtype,[13] with more bulbar dysfunction and gait and balance difficulties, reducing functional independence and an overall poorer prognosis.[13,29] This may be due, in part, to the poor responsiveness of subscore B signs to dopaminergic treatment. Our study is consistent with these observations, showing that the PIGD type, which has a higher subscore B, accumulates more NMS.

As PD advances, patients can change from TD type to PIGD type, and develop more NMS subsequently. This is consistent with the observation that higher H&Y staging and UPDRS-III score correlate with a poorer NMS profile. NMS are often more disabling in PD population than motor symptoms. Hely et al[30] reported that 15 years after PD diagnosis, patients mainly suffered from non-dopaminergic–responsive features. The recent Profiling Parkinson's disease (PROPARK) study, which is a longitudinal cohort study, showed PD patients with more axial symptoms and NMS were associated with a significantly increased risk of mortality.[31] Higginson and et al[32] highlighted, in a longitudinal study with 82 patients, that a complex mix of motor and NMS exist in patients with late-stage PD. The disability from NMS identifies palliative care needs and suggests that subjects need early palliative assessment and interventions. As demonstrated by the current observations that poor axial symptoms correlate with higher NMS scores, one can postulate that the axial symptoms in PIGD and some domains of NMS may share common pathophysiology.

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Table 5: PD medication use in the motor subtypes

PD medication treatment	TD (n = 145)	Indeterminate (n = 25)	PIGD (n = 104)	p value
Levodopa	104 (71.7%)	16 (64.0%)	87 (83.7%)	<0.05*
Dopaminergic agonists	39 (26.9%)	4 (16.0%)	29 (27.9%)	0.08
Selegiline or rasagiline	14 (8.4%)	3 (12.0%)	6 (5.7%)	0.17
Amantadine hydrochloride	8 (5.5%)	1 (4.0%)	13 (12.5%)	0.31
Anticholinergics	6 (4.1%)	1 (4.0%)	4 (3.8%)	0.45
Levodopa equivalent dosage (mg/day)	644.8 ± 601.9	665.8 ± 726.3	952.5 ± 662.7	<0.001*

* Statistically significant.
NMS = non-motor symptoms; PD = Parkinson's disease; PIGD = posture instability gait difficulty type; TD = tremor dominant type.

Although NMS have been thought to reflect dysfunction in non-dopaminergic systems, there is evidence in the literature to suggest that dopaminergic pathologies may be associated with NMS.[33] Dopaminergic treatment has been shown to be beneficial for several NMS in previous studies.[34-36] These included pramipexole for the treatment of depressive symptoms,[36] and D1-receptor agonists for sleep-wake cycle-related symptoms.[34] In the current study, we demonstrated that levodopa dosage significantly correlated with a higher NMS Quest score, suggesting that NMS in general do not respond well to dopaminergic therapy. The correlation of levodopa dose with poorer NMS profile may reflect that patients at later stage PD or with more severe disease require higher dose of levodopa treatment and tend to have a higher NMS score.

There are some limitations with the current study. Many patient charts were excluded from the analysis, primarily because of missing components of the NMS Quest. We observed from the clinical history a tendency for patients without positive symptoms to leave the questions blank. There is no rationale to believe that differences exist between TD and PIGD patients when filling the NMS Quest. The parameters in the excluded patients showed no difference from those included in the analyses.

A previous report suggested that dementia was more likely to occur in the PIGD category of patient than in the TD type.[37] In our current study, we failed to demonstrate a direct correlation between MMSE and NMS, although the PIGD group had a significant lower MMSE score than the TD group. This might be due to the poor correlation between MMSE and dementia. Future studies using a better cognitive measure, such as the Montreal Cognitive Assessment[38] might provide more information. In this study, the old version of the UPDRS-III was used to keep the consistency of data collection through the study period. In the future studies, application of MDS-UPDRS would be helpful addition to the current findings.

Strength of our study includes the systematic collection of NMS in a representative clinical population. The relatively large sample allowed an examination of motor subtype in relation to NMS.

In conclusion, our current study has shown that in the PD cohort, NMS severity increases in more advanced disease and varies according to motor phenotype. The PIGD but not the TD subtype shows correlations with a worse NMS score. Patients with a PIGD phenotype who have more axial involvement, associated with advanced disease and poor motor response, are at risk for a higher NMS burden. In addition, we observed NMS in the TD group were not related to disease severity (UPDRS-III total score) or subscore B, supporting our hypothesis that NMS have a lower prevalence in patients with the TD subtype.

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Statement of Authorship

FB was involved in the manuscript preparation, writing of the first draft, and statistical analysis with design and execution. MO was involved in the initiation of the project, data collection, and review of the manuscript. MW was involved in organization and execution of the project, review and revision of the manuscript. RC was involved in the conception, planning and supervising the execution of the research project; planning and supervision of data analysis; and critical revision final review of the manuscript. WRWM was involved in the conception, planning and supervising the execution of the research project; and critical revision final review of the manuscript.

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